Research Project Portfolio

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SMART Rehab: Exploring the effects of Strengthening Mental Abilities with Relational Training on Cognitive Functioning for People with Multiple Sclerosis

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Doctorate in Clinical Psychology

"I must not fear.
Fear is the mind killer"

Frank Herbert, Dune

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Section I: Abstract

Background: Multiple Sclerosis (MS) is a progressive neurodegenerative disease that impacts on a range of both proximal and distal outcomes. People with MS commonly experience cognitive problems that have been shown to affect important aspects of life such as employment, mood, and quality of life. Whilst the disease is progressive, and the damage widespread, recovery from damage through neuronal plasticity does occur. There is growing evidence base in cognitive rehabilitation offerings but limited in quality to draw firm recommendations and studies not reporting a clear theoretical underpinning of their interventions hinders development. Training (SMART: Strengthening Mental Abilities with Relational Training) of Derived Relational Responding, a fundamental component of a well-established behavioural theory of cognition – Relational Frame Theory – has been shown to improve cognitive performance as measured by Intelligence Quotient tests. Studies have begun initial applications of relational responding training in cognitive rehabilitation studies.

Objectives: The primary objective was to explore the effects of SMART on both objective and subjective assessments of cognitive functioning for people with MS. Secondary objectives were to assess changes in secondary outcomes (mood, fatigue, quality of life), explore the relationship between relational responding and outcomes, and investigate the acceptability, practicality, and feasibility of the intervention.

Method: The study has a multiple baseline design with a feedback interview. The study aimed to recruit nine participants. Participants completed a battery of neuropsychological assessments in addition to secondary outcome measures. Participants then completed their respective baselines. They then began a 12-week intervention of 45-

minutes of training per week. Participants completed subjective assessments on a weekly basis and relational skills assessments every other week. The full battery was administered again at week six of the intervention, and again one week after the intervention had ended. A feedback interview, conducted by independent researchers, was delivered a week after the intervention ended. The full test battery was administered a final time at a three-month follow-up [1].

Results: A total of eight participants were enrolled into the study. Weekly measurements of subjective cognitive performance showed no phase contrasts. Objective measurements showed improvements. Processing speed outcomes improved in 87.5% of participants and this also represented a clinically significant improvement for 100% of participants who were in a clinically impaired range at intake. 50% of participants improved in the Repeatable Battery for the Assessment of Neuropsychological Status Total Score. Feedback interviews made recommendations to increase the intensity and duration of the intervention. Relational abilities improved in all but one participant. Secondary outcomes remained stable.

Conclusions: These preliminary findings on objective assessments are promising though are questioned by the lack of subjectively reported improvements. The relationship between relational skills and improved outcomes was inconclusive. The intervention appears to have been acceptable to participants, providing support for further development.

Portfolio Word Count: 31,992

[1] At the point of submission, three-month follow-up data had not yet been collected.

Section II: Statement of Contribution

The theoretical rationale of this project grew from initial discussions between the author, Dr Dave Dawson, and Dr Nima Moghaddam from October to November 2019. We were interested in recent developments in the application of Relational Frame Theory training to scholastic aptitude and were intrigued if such a program could be applied with those with neuropsychological clinical impairment, with the hope of improving outcomes. The first draft of the project, which had identified the clinical population as those with acquired brain injury, was presented at a panel discussion and then to a broader audience in the form of a presentation. At this presentation, Professor Roshan das Nair suggested that the clinical sample be changed to those diagnosed with MS. Professor das Nair agreed to co-supervise the project as we adapted the study for this new group. The methodology was fine-tuned over the coming months, drawing on feedback from a project presentation at a MS PPI group in March 2019, with a finalised protocol agreed upon in August 2019. Professor das Nair provided support and guidance in the ethical approval process.

Recruitment was facilitated by two local clinicians, Dr Nikos Evangelou and Dr Athanasios Papathanasiou, who recruited from their respective clinics, and Dr Gogum Topcu who disseminated study material to the PPI group.

All assessments, specific study material development, and analyses were completed by the author. Dr Bryan Roche facilitated access to the SMART program. The feedback interviews were delivered by two independent researchers, Kirandiph Badesha and Nathan Kerr.

Write up was conducted by the author between February and May 2021.

Section III: Research Paper

Journal Paper Title: Exploring the effects of derived relational responding cognitive rehabilitation in Multiple Sclerosis: A multiple baseline experimental design

Target Journal: Neuropsychological Rehabilitation

Author guidelines: See Appendix A

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Key words: multiple sclerosis, cognitive rehabilitation, multiple baseline, single case experimental design

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1. Abstract

Cognitive problems in MS are reported as one of the disease's most debilitating facet yet there is no strong evidence supporting a particular intervention option. This study aimed to explore effects of the Strengthening Mental Abilities with Relational Training (SMART) intervention for people with MS with a particular focus on objective and subjective assessments of cognitive functioning. Changes in secondary outcome measures (mood, fatigue, quality of life) and a proposed mechanism of therapeutic change (relational responding), were also explored. Participants provided feedback on the intervention, design, and subjective changes. A multiple baseline design was used with a feedback interview component. Eight participants were enrolled into the study, one withdrew during the intervention phase. The intervention duration was 12 weeks. Objective neuropsychological batteries showed improvements in processing speed (87.5% of participants), and this also represented a clinically significant improvement for 100% of participants who were in a clinically impaired range at intake. A general domain composite score improvement was observed in 50% of participants. Further improvements were observed in other domains. There were mixed results for subjective changes and the role of relational responding as a mediator of change. Feedback interviews, in addition to preliminary supportive outcome results, support the further development of this intervention.

2. Introduction

2.1. Epidemiology and Impact of Multiple Sclerosis

Multiple Sclerosis (MS) affects approximately 100,000 people within the UK, with 5,000 people diagnosed annually, resulting in MS being the highest cause of physical disability in the UK for working age adults (Mackenzie et al., 2014). There are myriad complex effects that MS can have on a person including issues with mental health,

motor, and cognition problems – the expression of all components unique – creating a heterogeneous disease profile (Chiaravalloti & DeLuca, 2008).

Between 40–70% of people with MS experience cognitive difficulties (Chiaravalloti & DeLuca, 2008). Within the cognitive domain, MS has been reportedly linked to deficits in executive functioning, memory, attention, processing speed, and visual perceptual functioning (Beatty & Monson, 1996; Diamond et al., 1997; Foong et al., 1997; Rao et al., 1993; Ruano et al., 2017). In addition to the primary effect these cognitive changes can have, secondary issues with employment, routine tasks, mental health, social activities, and independence have been reported (Rao et al., 1991; Staples & Lincoln, 1979). The aforementioned cognitive problems have been identified as the most debilitating facet of MS (Dorning et al., 2013). Therefore, unsurprisingly, finding treatments to improve cognition has been highlighted as one of the top 10 research priorities for people with MS (James Lind Alliance, 2019).

2.2. Cognitive Rehabilitation in MS

Recent reviews of cognitive rehabilitation in MS highlight a zeitgeist shift; studies are moving away from new learning and memory to interventions targeting processing speed, attention, and executive functioning (Goverover et al., 2018; Mitolo et al., 2015; O'Brien et al., 2008) – the more recent studies having shown improved outcomes and consistency (Filippi et al., 2012; Fink et al., 2010; Flavia et al., 2010; Parisi et al., 2014). In the wider field of cognitive rehabilitation of stroke and traumatic brain injury, Cicerone et al. (2019) report an intervention trend towards increased specificity and a movement towards identifying and manipulating a theoretical process of change (Hart et al., 2014). Their review also reports the increased application of computerised interventions. These

computerised interventions can benefit from increased precision, consistency, geographical accessibility, and participant performance scaled difficulty (Cicerone et al., 2019). The latter of which is paramount in supporting increased neuroplasticity and recovery (Cicerone et al., 2019; Cramer et al., 2011; Lovden et al., 2010).

Despite some preliminarily promising results for cognitive interventions in MS, intervention studies to date have not been predicated on robust theoretical foundations, nor have they sought to examine possible mechanisms of change. In the absence of a theoretical framework or process-based examination, it is difficult to synthesise across individual studies and understand or optimise intervention effects. Furthermore, in light of these preliminary findings of cognitive improvements, Mitolo et al. (2015) stress the need for measurements of participants' mood, fatigue, quality of life, and parallel subjective reports of cognitive functioning; the latter of which they state is paramount to people with MS due to neuropsychological assessments not always cohering with patient reported outcomes (Mantynen et al., 2014). Currently, only the modified Story Memory Technique (Allen et al., 1995) has reached the practice standard recommendation threshold, as it is supported by four Class I studies (Chiaravalloti et al., 2005; Chiaravalloti et al., 2020; Chiaravalloti et al., 2013; Krch et al., 2019). No evidenced-based recommendations or practice standards exist for other cognitive domains (Goverover et al., 2018). The lack of recommendations exposes the absence of a 'gold standard' intervention in this area and, given the impact of difficulties in these domains, it requires the development of an effective treatment.

2.3. Relational Frame Theory and SMART

Strengthening Mental Abilities with Relational Training (SMART) is a computerised training program that aims to improve cognitive

functioning (Cassidy et al., 2016). The program is based on theoretical developments in Relational Frame Training (RFT), an established theory of language and cognition based on operant learning principles (Hayes et al., 2001). RFT proposes that many cognitive processes are underpinned by our ability to 'relate' concepts together, and that this ability is learnt (starting in infancy) and develops over time as the individual interacts increasingly with their environment (Hayes et al., 2001). Derived relational responding, a key component of RFT, is classified as a specialised, and generalisable, operant behaviour which is learnt early in life (Hayes et al., 2001; Rehfeldt & Hayes, 1998). Relational responding is comprised of three main constituents: *direct training*, *mutual entailment*, and *combinatorial entailment*; an example will be used to explain these principles (shown in Figure 1). In direct training one is taught 'X is same as Y'. Mutual entailment is the bi-directional learning which occurs resulting in the additional derived relation of 'Y is same as X'. If we repeated the process with the new relation of 'Y is same as Z', one could derive 'X is same as Z' and 'Z is same as Y' without the need for direct training between X and Z; this is an example of combinatorial entailment.

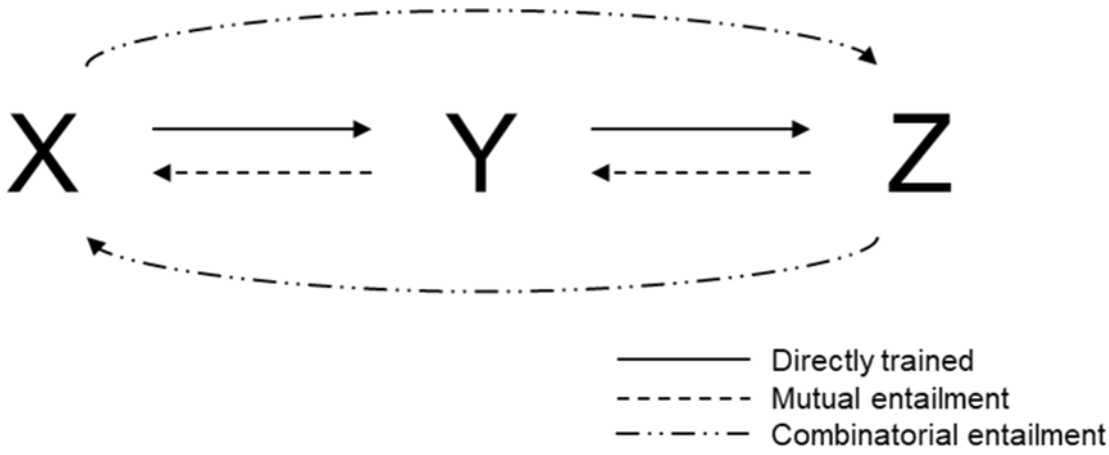

Figure 1: Graphical representation of derived relational responding (Törneke, 2010).

As these relational skills are learnt, through multiple exposures during normal development, they generalise and appear to underpin a variety of cognitive skills such as language, problem solving, and deductive reasoning (Cassidy et al., 2016; Cassidy et al., 2011; Hayes & Stewart, 2016). Building upon the concept of derived relational responding, the SMART program aims to train these relational skills (considered within RFT to be the building blocks of human cognition) to improve general cognitive functioning. SMART uses nonsense words, reducing the chance of prior learnt relations affecting training (Cassidy et al., 2016). Figure 2 shows two exemplar relations.

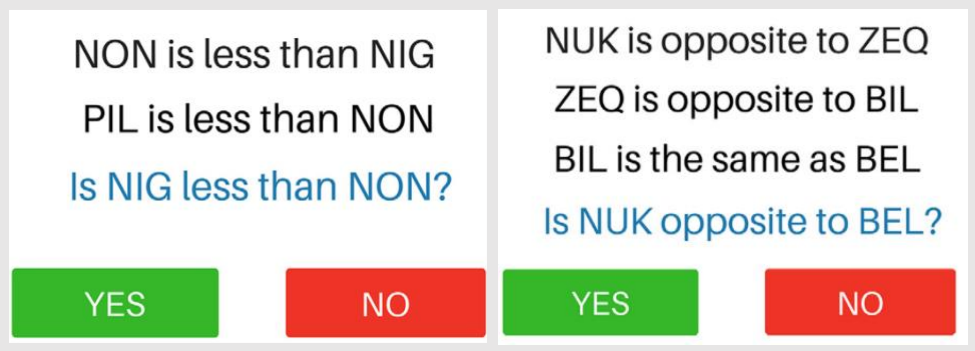

Figure 2: Screenshot of two different exemplars from the SMART program.

Whilst the majority of SMART research (see Amd & Roche, 2018; Cassidy et al., 2016; Colbert et al., 2018; Hayes & Stewart, 2016) has focused on increasing scholastic aptitude with school children, a recent RCT compared a combined SMART and pharmacological intervention against a pharmacological-only intervention for people with Alzheimer's disease (Presti et al., 2017). Significant small improvements in dementia assessment outcomes and attention were reported at three-month follow-up (Presti et al., 2017). Presti et al. (2017) have therefore made the initial steps of transposing this theoretical scholastic aptitude behaviour training into a clinical setting in an attempt to improve cognitive outcomes for those with

deficits and who are in decline. The results of Presti et al. (2017), along with previous SMART literature, are beginning to tentatively indicate that derived relational responding may play a role not only in scholastic non-clinical behaviours but also in relation to clinical domains.

2.4. Research Rationale

Despite being identified as a key concern for people with MS, no 'gold standard' recommended treatment for cognitive difficulties exists, thus there is a strong rationale for developing interventions in this area. The Medical Research Council (MRC) state complex interventions need to identify/develop an appropriate theory that will provide an understanding of change processes, enabling further development and improvement of the interventions (MRC, 2008). In the present study this will be achieved through testing an intervention that is based on RFT, identifying derived relational responding as the proposed process of change. Whilst a clinical study utilising SMART does exist and showed promising results, it did not track individual differences or process of change. The present study is a 'proof of concept' study that aims to explore the application of a theory-based intervention program that has shown to improve clinically relevant outcomes in another disease profile. An investigation into the mechanisms and feasibility of an intervention should be completed before assessing its efficacy against a control condition (MRC, 2008).

2.5. Study objectives and purpose

2.5.1. Purpose

The overall aim of the study is to examine the effect of SMART on multiple cognitive domains in a sample of people with MS and to explore the acceptability of the intervention.

2.5.2. Primary objective

1. Examine the impact of SMART on patient-reported measures and feedback and neuropsychological assessments of cognitive functioning.

2.5.3. Secondary objectives

1. To explore the acceptability, practicality, and feasibility of the SMART intervention for people with MS.
2. To explore individual changes in mood, fatigue, and Quality of Life following SMART intervention.
3. Examine the relationship between measures of relational responding and cognitive functioning.

3. Materials and Methods

3.1. Ethics

Ethical approval was granted by the Health Research Authority and the East Midlands – Nottingham 2 Research Ethics Committee on the 14th of April 2020.

3.2. Design

Refer to Table 1 for the design of the study. The study used a multiple baseline A-B design with two follow-up timepoints, following established procedures (Barlow et al., 2009; Carr, 2005). Participants were allocated sequentially, in order of consenting, to partake in the study to one of three baseline (A) conditions: three-, four-, or five-week baseline length. Utilising a multiple baseline design allows participants to become their own controls and a more causal relation to be derived from introduction of the independent variable – the SMART intervention in this case (Smith, 2012). Participants had differing baseline lengths, and all started the intervention phase (B) after completion of respective baseline. The intervention phase (B) was

for 12 weeks. The first follow-up duration was one week and the second was three months.

Table 1: Enrolment, assessment, and intervention schedule. Subscripts represent weeks in study with the exception of F_1 and F_2. F_1 is one week after the end of training (T_{12}) and F_2 is three months after F_1.

	Activity/Timepoint							
	Enrolment A_{-1}	Baseline A_1	Baseline A_{2-5}	Intervention T_{1-5}	Intervention T_6	Intervention T_{7-12}	Follow-Up F_1	Follow-Up F_2
Enrolment								
Eligibility Screen	•							
Informed Consent	•							
PQ Construction	•							
Assessment								
PQ		•	•	•	•	•	•	•
SDMT		•			•		•	•
RBANS		•			•		•	•
RAI		•		•†	•	•†	•	•
MSQOL-29		•			•		•	•
HADS		•			•		•	•
MFIS		•			•		•	•
Interview								•
Training								
SMART				•	•	•		

Note: PQ – Personal Questionnaire; SDMT – Symbol Digit Modalities Test; RBANS – Repeatable Battery for the Assessment of Neuropsychological Status; RAI – Relational Abilities Index; MSQOL-29 – Multiple Sclerosis Quality of Life scale – 29-Item; HADS – Hospital Anxiety and Depression Scale; MFIS – Modified Fatigue Impact Scale; SMART – Strengthening Mental Abilities with Relational Training. † - RAI was administered bi-weekly.

3.3. Participants

We aimed to recruit nine participants to the study. In single case experimental designs, one demonstration of effect is needed with two replications of this effect (Kratochwill et al., 2010); this can be achieved via three participants (one demonstration and two replications) (Smith, 2012). The Society of Clinical Psychology (DIV12) recommend the replication occurs over three cases (as cited in Smith, 2012), rather than within a single-subject design (Kratochwill et al., 2010). Four or more participants will increase the design strength (Barlow et al., 2009), and it has been recommended to recruit eight to account for attrition (Smith, 2012). The final ninth participant was included to balance the three baseline lengths with three participants in each.

Recruitment took place between July and August 2020. The initial recruitment was via the MS Clinic and then later from the local MS Patient and Public Involvement (PPI) group. All participants met the following *inclusion criteria:* (i) diagnosis of MS; (ii) subjectively reporting cognitive problems; (iii) aged between of 18–78 years old (range curtailed by SDMT validated age range; Smith, 1982); (iv) able to access a computer / laptop with internet connection throughout the study at home and have sufficient computer skills to use the program; (v) residing in the local area; and (vi) able to provide informed consent. Potential participants were not enrolled into the study if they met the following *exclusion criteria:* (i) undertaking other cognitive rehabilitation at the time of the study; and (ii) not able to read and speak English well enough to understand the study material and instructions (which was determined by researcher during consent and information procedures).

3.4. Measures

Participants' cognitive functioning/difficulties were measured using a combination of established psychometrics and subjective idiographic measurements. A feedback interview was completed at follow-up 1. See Table 1 for assessment administration schedule.

3.4.1. Cognitive Functioning

Subjective Reports

Participants were interviewed by the researcher at the Enrolment (A_{-1}) timepoint. At this point, they constructed their own idiographic outcome measure which aimed to track their reported cognitive difficulties over the length of the study. The simplified Phillip's Personal Questionnaire (PQ; Phillips, 1963, 1986) was constructed with each participant as it allows a greater degree of flexibility in the number of statements and a more accessible binary scoring system when

compared to Shapiro's (1961) original PQ. For each item (e.g., "Difficulty completing minutes") participants indicate whether their experience over the past week has been 'Better' or 'Worse' than before. An additional feature was added whereby participants could use a visual slider to indicate the extent to which a difficulty had been better/worse. An error was made in the implementation of the PQ by the accidental inclusion of a middle option ("stayed the same"), rather than forcing a choice of better or worse. After development with the participant, the PQ was administered via an online survey hosting platform. To the author's knowledge the Phillip's PQ has not been used in MS research. Subjective reports are needed due to their discrepancy between objective assessments (Chiaravalloti & DeLuca, 2008; Mantynen et al., 2014; Miller et al., 2013).

Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)

The RBANS (Randolph, 1998) is a relatively short (approximately 25 minutes) neuropsychological assessment of reporting scores for Immediate and Delayed Memory, Language, Attention, and Visuospatial/Constructional indices. The RBANS also provides a Total Score. Each index is composed of at multiple subtests. Two forms, A and B, were used in alternating sequence throughout the study. The RBANS has been validated in an MS population (Davis et al., 2015) and has recently been validated for remote video conferencing delivery (Galusha-Glasscock et al., 2016). The remote delivery test-retest reliability for the Indices ranged from r = .59 to .90 and a mean of .80 (Galusha-Glasscock et al., 2016).

Symbol Digit Modalities Test (SDMT)

The SDMT (Smith, 1982) is a symbol substitution test that examines processing speed and attention. Participants take 90 seconds on the task. Originally designed as a learning and speed test, it now primarily

functions as a processing speed measure - construct validity exploration showed that the SDMT additionally loads onto EF domains (Benedict et al., 2006). Furthermore, the SDMT is the most sensitive predictor of cognitive decline in MS (Amato et al., 2010). Manualised test-retest reliability with healthy participants has been reported at 0.76, with MS participants this has been reported at 0.97 (Benedict et al., 2017; Smith, 1982). Good validity has been reported for processing speed and efficiency and it is reported as the most sensitive test for MS cognitive problems (Benedict et al., 2017).

3.4.2. Process

Relational Abilities Index (RAI)

The RAI (Cassidy et al., 2016) is a 55-item scale measuring derived relational responding skills. These are the skills targeted by the SMART intervention – thus making the RAI a useful process measure to gauge whether the intervention is operating as intended, and whether SMART-targeted skills are associated with outcomes of interest. Each item presents a novel exemplar (similar to those presented in Figure 1, above), increasing in complexity as test progress, resulting in 248 stimuli of three letter nonsense words. There are 29 Same/Opposite exemplars and 26 More/Less exemplars. Higher scores reflect greater relational abilities. The reaction time for each item was also recorded.

3.4.3. Mood, fatigue, and quality of life

Mood, fatigue, and quality of life were measured at A_{-1}, T_6, F_1, and F_2 (see Table 1).

Mood

The Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983) is 14-item measure split into two equal 7-item components: an Anxiety subscale (HADS-A) and a Depression subscale (HADS-D). For people with MS a score of 11 (adjusted from the manual's

recommended score of 8) or above in either domain indicates the possibility of depression or anxiety (Watson et al., 2014). Sensitivity and specificity for Depression are reported at 77% and 81% respectively, and for Anxiety they are reported at 90% and 92% respectively (Watson et al., 2014). The clinical cut-off score of 11 has been validated within an MS population (Marrie et al., 2018; Pais-Ribeiro et al., 2018). Within this population, the HADS demonstrated good test-retest reliability for both the Anxiety scale (ICC = .86) and the Depression scale (ICC = .83).

Fatigue

The Modified Fatigue Impact Scale (MFIS; Fisk et al., 1994) is a 21-item self-report Likert scale that measures the effect of fatigue across cognitive (10-items), psychosocial (2-items), and physical domains (9-items), with higher scores indicative of greater fatigue impact. Additionally, the MFIS calculates a total score output (0-84) which has demonstrated a good test-retest reliability (ICC = .85; Rietberg et al., 2010). The MFIS was designed for MS participants and is one of the components of the MS Quality of Life Inventory. Clinical cut-off scores have recently been revisited, deriving from a large sample, and drawing on supplementary variables such as age, gender, and years of education (Strober et al., 2020).

Quality of Life

The Multiple Sclerosis Quality of Life Scale – 29 Item (MSQOL-29; (Rosato et al., 2016) is a shortened version of the MSQOL-54 (Vickrey et al., 1995). The measure has seven subscales (physical function, bodily pain, emotional well-being, energy, cognitive functioning, health distress, and sexual function) and four single items (health perceptions, social function, overall quality of life, and change in health). The subscales' Cronbach's alphas ranged from .88 to .90 (Rosato et al., 2016).

3.4.4. Feedback Interview

The feedback interview schedule can be found in Appendix E. The interviews were completed by two independent researchers. The semi-structured interview aimed to examine participants' experiences and recommendations for the SMART program, measures used, and design of the study. It additionally explored participants' subjective changes and what these changes were attributed to.

3.5. Intervention

The SMART program used in this study replicates the online SMART program used by Cassidy et al. (2016) in their study of increasing scholastic aptitude with relational training. The SMART program trains participants to respond to the derived relations of 'same/opposite' and 'more/less'. Participants are exposed to 70 levels of relational responding, increasing in difficulty as one completes the course. There are 37 levels of 'same/opposite' relations and 33 levels of 'more/less' relations. Training occurs through audio-visual feedback from the program. Participants complete 45 minutes of this intervention each week. Representative exemplars are depicted in Figure 3.

Each level has a training-phase and a testing-phase (see Figure 3 for a diagrammatic representation of the SMART protocol). In training the participant must consecutively answer 16 exemplars correctly, if answered incorrectly the participant will start the training-phase for that level again. When the participant completes the training-phase they move onto the corresponding testing-phase. Again, the participant must consecutively respond to 16 exemplars correctly to move up to the next level, if answered incorrectly they restart the training-phase for that level. There is a 30-second limit to every answer across both the training and test-phase, if no choice is selected within

the time limit the participant restarts the level. Participants received audio-visual feedback within the training-phase only.

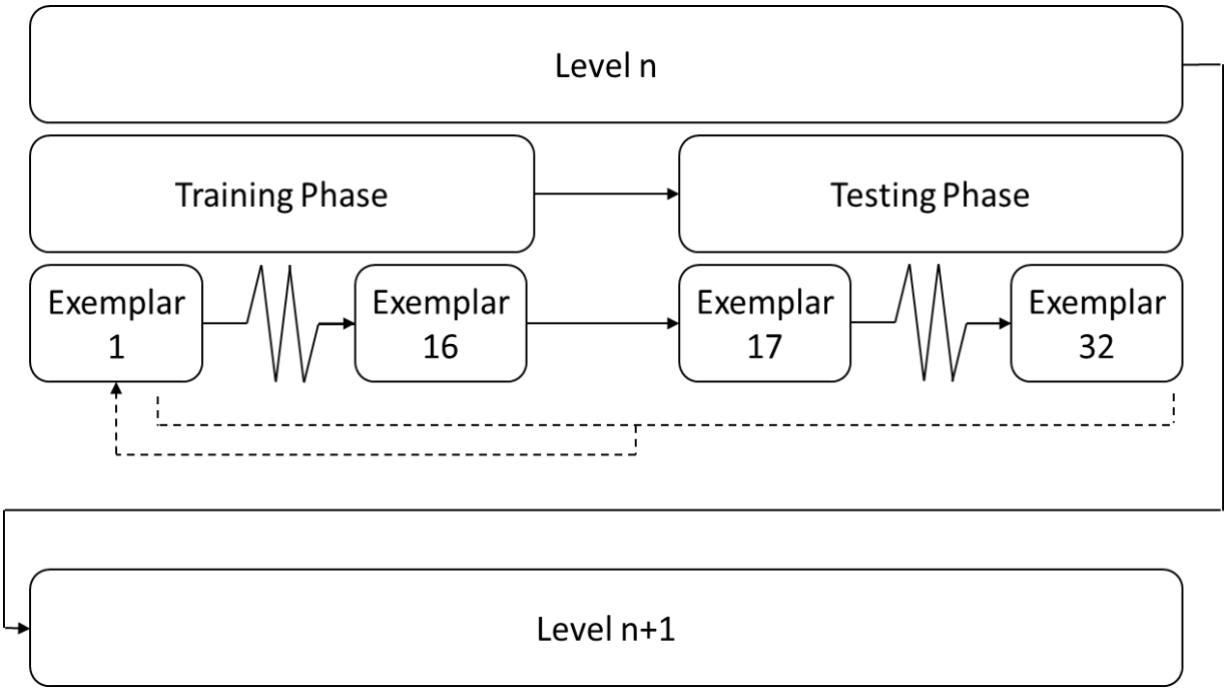

Figure 3: Flow chart representing progression through SMART intervention program and each level's subcomponents.

Note: Zig-zag line represents continuation of exemplars between first and last exemplars. Solid lines represent successful path. Dashed lines represent unsuccessful path – answering incorrectly for exemplars 2 to 32 will start the participant at exemplar 1 of the training-phase.

3.6. Data Analysis

Each participant's weekly PQ outcome data was aggregated and reported as a single score with a range of 0-100 (with higher scores indicating perceived improvement). This data was evaluated using structured visual analysis exploring four features: (i) change in central tendency between phases using the broadened median (BMed; Rosenberger & Gasko, 1983; (ii) change in linear trend between phases using the split-middle method (Kazdin, 1982); (iii) change in variability across phases using trended range (Morley, 2017); and (iv) degree of change between phases using the Conservative Dual Criterion method (CDC; Fisher et al., 2003). Visual analysis techniques were selected

following the recommendations of Morley (2017). Statistical analyses utilised the Tau-*U* statistic to investigate the degree of overlap in the PQ data points and provide an effect estimate of the degree of change between phases (Lee & Cherney, 2018). Tau-*U* can demonstrate good statistical power for smaller data sets (Manolov & Moeyaert, 2017). Vannest et al. (2018) recommend effect sizes are used to analyse findings instead of *p.* Effect sizes are categorised as vary large (>.80), large (.60-.80), medium (.20-.60), and small (<.20) (Vannest & Ninci, 2015). Analysis was completed using the online calculator at www.singlecaseresearch.org (Vannest et al., 2016). Both CDC and Tau-*U* must report differences between phases for data to be deemed significant.

RAI scores, the purported process of change measure, were analysed using raw scores and reaction times. Using the Inverted Efficiency Score (IES; Bruyer & Brysbaert, 2011) the reaction time and accuracy data were conflated into a single metric exploring the speed-accuracy trade-off.

For the RBANS, SDMT, MSQOL-29, HADS, and MFIS reliable and clinical change was assessed using Reliable Change Index (RCI; Jacobson & Truax, 1991) and Clinically Significant Change (CSC; Jacobson & Truax, 1991) criteria respectively. Change was compared for each measure between pre-intervention (A_{-1}), mid-intervention (T_6), and post-intervention (F_1) for each participant. The RCI was set for the 95% confidence interval using a value of 1.96. CSC was calculated using measures' predetermined cut-off scores or, if these were unavailable, by the participant's scores moving either within two standard deviations of the healthy sample mean (Criterion A) (Evans et al., 1998). Normative data was derived from test manuals, where available, and closely related sample studies if no direct MS sample data were available (SDMT: Benedict et al. (2017) and Smith (1982);

RBANS: Randolph (1998); MFIS: Amtmann et al. (2012) and Kos et al. (2003); HADS: Marrie et al. (2018), Pais-Ribeiro et al. (2018), and Zigmond & Snaith (1983); MSQOL-29: Baker et al. (2018), Rosato et al. (2016), and Rosato et al. (2019). The feedback interviews were analysed with Framework Analysis (Ritchie et al., 2013).

4. Results

4.1. Participants

Of the 15 potential participants who expressed interest in the study: two did not have access to a laptop or computer, two did not complete the consent form, one was in the follow-up period of another cognitive rehabilitation study, and one felt that the demands of the study would be too great for them at that time. Nine participants consented to partake in the study. Of the nine participants who consented to take part in the study, eight were included in the analysis. One participant withdrew immediately after the initial assessment timepoint (A_{-1}), citing that the assessment was too taxing on them and that they did not want to continue with the study. This participant did not complete the demographic form and was not reachable to participate in the feedback interview. Participant E withdrew at the mid-intervention timepoint (T_6); their data has been included in the analysis. Participants' demographics and clinical characteristics are shown in Table 2. The included participants were between 36 to 75 years old. The majority (75%) of the participants were women. 75% of the participants displayed the Relapsing Remitting subtype with the remaining two participants displaying the Primary Progressive subtype. Disease duration ranged from nearly six years to just over 19 years. Participants time in education ranged from 12 to 20 years. The majority of participants identified as White British. Participants' employment status varied, with no prevalent categorisation.

Baselines

Participants A, D, and G were allocated to the three-week baseline; Participants B, E, and H to the four-week baseline; and participants C and F to the five-week baseline.

Table 2: Participants' demographics and clinical characteristics.

	Participant Characteristics					Clinical Characteristics	
Participant	Age (years)	Sex	Employment	Ethnicity	Education (years)	Subtype	Disease Duration (years)
A	36	F	Full-time employment within organisation/company	White British	17	Relapsing Remitting	11.59
B	39	F	Part-time employment within organisation/company	White and Asian	17	Relapsing Remitting	9.25
C	48	F	Unemployed	White British	16	Relapsing Remitting	19.09
D	53	F	Self-employed part-time	White British	18	Relapsing Remitting	7.61
E	59	F	Part-time employment within organisation/company	White British	12	Relapsing Remitting	5.83
F	75	M	Retired	White British	12	Primary Progressive	17.68
G	62	M	Retired	White British	18	Primary Progressive	13.34
H	39	F	Unemployed	Other white background	20	Relapsing Remitting	10.77

4.2. Cognitive Functioning

4.2.1. Subjective Reports

Structured visual analysis – PQ scores captured subjective cognitive difficulties (e.g. *Difficulty remembering names/items*) and were scaled such that higher scores indicate improved functioning. Participants E and H showed no changes in their PQ scores throughout the study and have been excluded from the structured visual analysis reporting. Participants B and C both showed an increase in central tendency between baseline and treatment phases in the therapeutic direction (see Figure 4). Participants A and F both showed a contra-therapeutic decrease in central tendency between phases. The central tendency of Participants D and G remained stable. Participants A, C, D, and F all showed therapeutic trend celeration changes between phases. Participant B showed a contra-therapeutic decelerating trend change between phases. Participant G showed a zero-celerating trend in both phases. Participants A, B, D, and E, all showed increased variability of their PQ scores. Participants B and C showed a decrease in the

variability. Participant F showed a stable variability envelope with an overall accelerating trend.

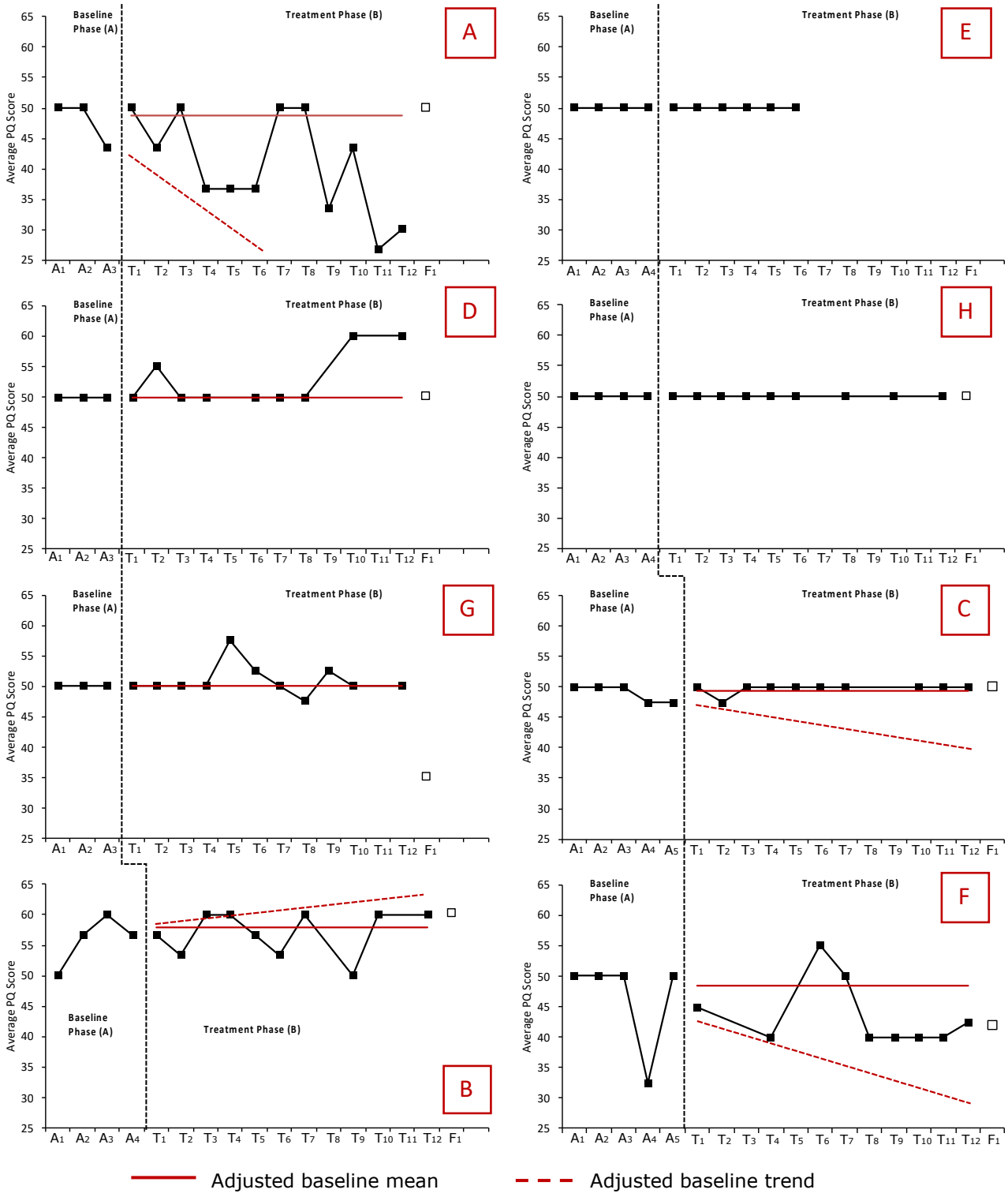

Figure 4: Scatter and line plot of average PQ scores for each participant. Conservative dual criterion analysis shown in red. Therapeutic direction is upwards.

Conservative Dual Criterion – Visual analysis and dual criterion analysis is shown in Figure 4. Results of analysis shown in Table 3. Only Participant C had the required data points above the adjusted baseline

mean and adjusted baseline trend dual criterion. These results indicate that there was a positive change between baseline and treatment phases.

Statistical analysis – There was no significant difference in phase contrasts between baseline and treatment on Tau-*U* for any of the participants nor the combined analysis. See Table 3 for Tau-*U* results.

Table 3: Conservative Dual Criterion and Phase Comparison for PQ results.

	Conservative Dual Criterion			Phase Comparison			
Participant	Intervention Data Points	Required Above	Observed Above	Tau-*U*	*Z*	*p*	CI (90%)
A	12	9	4	-.50	-1.30	.19	-1.00–.13
B	10	8	2	.03	.07	.94	-.56–.61
C	10	8	**9**	.30	.92	.36	-.24–.84
D	9	8	3	.25	.65	.52	-.38–.88
E	6	6	0	.00	.00	1.00	-.64–.64
F	9	8	2	-.33	-1.00	.32	-.88–.22
G	11	9	3	.18	.47	.64	-.46–.82
H	9	8	0	.00	.00	1.00	-.58–.58
Combined				.02	.17	.87	-.19–.23

4.2.2. SDMT

See Table 4 for SDMT scores. All the participants scoring below their respective SDMT clinical cut-off scores at A_1 (C, D, F, and G) showed reliable and clinically significant changes to T_6 which were all maintained to F_1. The remaining participants (A, B, E, and H) all scored above their respective clinical cut-off scores at A_1. Participant H showed a reliable improvement in their score which was maintained to F_1. Participants A and E both showed reliable improvements from A_1 to T_6 and Participant A did not maintain this change (Participant E withdrew at T_6). Participant B's SDMT scores remained stable throughout the study.

Eighty-eight percent achieved a reliable improvement in SDMT score (indicating improved processing speed and efficiency) by intervention-midpoint; this also represented a clinically significant improvement for 100% of participants who were in a clinically impaired range at intake. At the intervention-endpoint 83.33% achieved a reliable improvement and this also represented a clinically significant improvement for 100% of participants who were in a clinically impaired range at intake.

4.2.3. RBANS

See Table 4 for RBANS results.

Immediate Memory – Participants E and F showed improvements with only Participant H having this improvement at F_1. Participant B had an initial clinically significant decrease in score which was not maintained. The remaining participants' scores were stable throughout.

Visuospatial/Constructional – Participant B and G had improvements and Participant G did not maintain this improvement to F_1. Participant C reported an initial clinically significant decrease in scores which was not maintained. Participants A, B, C, and H remained stable throughout.

Language – Participants A, B, D, G, and H showed improvements in this domain. Participant G did not show this improvement at F_1. Participants B and E both showed initial decreases in scores which were not maintained. Participants C and F remained stable throughout.

Table 4: Participants' baseline, mid-intervention, and post-intervention neuropsychological and secondary outcome measure results. Timepoints: A_1 – Baseline week 1, T_6 – Training week 6, and F_1 – Follow-Up 1.

	Participant A			Participant B			Participant C			Participant D		
Measure	A_1	T_6	F_1	A_1	T_6	F_1	A_1	T_6	F_1	A_1	T_6	F_1
SDMT	40	46^{R+}	43	50	48	50	40	46^{R+C+}	50^{R+C+}	32	36^{R+C+}	36^{R+C+}
RBANS												
Immediate Memory	94	85	85	81	69^{R-C-}	87	87	81	94	103	109	112
Visuospatial / Constructional	66	66	62	75	69	102^{R+}	92	53^{R-C-}	105	81	100^{R+}	100^{R+}
Language	92	104^{R+}	96	92	78^{R-}	120^{R+}	103	106	103	117	87^{R-}	94^{R+}
Attention	82	85	97^{R+}	75	85	72	91	85	91	97	100	103
Delayed Memory	77	88	88	48	48	68^{R+}	71	64	81	99	94	105
Total Score	78	81	82	67	62	85^{R+C+}	84	72^{R-}	92	99	96	103
HADS												
Anxiety	8	9	11	8	9	10	9	7	6	4	5	2
Depression	8	9	10	8	8	7	8	6	7	5	5	6
MFIS												
Physical	12	16	15	30	31	28	25	25	32	26	30	20
Cognitive	22	22	22	25	19	19	29	30	34	23	27	24
Psychosocial	3	3	3	8	8	8	5	4	5	5	6	4
Total	37	41	41	63	58	55	59	59	71	54	63	48
MSQOL-29												
Mental Health	60.58	51.08	47.67	20.40	19.93	18.73	31.23	34.83	21.65	48.32	44.78	44.79
Physical Health	51.17	55.67	74.17^{R+}	32.00	29.50	22.00^{R-}	33.67	28.00	30.34	51.17	42.83	46.83

	Participant E			Participant F			Participant G			Participant H		
Measure	A_1	T_6	F_1	A_1	T_6	F_1	A_1	T_6	F_1	A_1	T_6	F_1
SDMT	38	46^{R+}	-	22	29^{R+C+}	32^{R+C+}	33	44^{R+C+}	39^{R+C+}	56	66^{R+}	62^{R+}
RBANS												
Immediate Memory	85	109^{R+}	-	78	97^{R+}	87	120	129	126	120	123	132^{R+}
Visuospatial / Constructional	66	66	-	64	75	72	100	112^{R+}	96	121	109	109
Language	99	84^{R-}	-	96	90	105	92	134^{R+}	111	104	112	116^{R+}
Attention	88	106^{R+}	-	91	100	100	106	109	106	82	97^{R+}	109^{R+}
Delayed Memory	94	101	-	68	7	68	110	121	121	105	109	125^{R+}
Total Score	82	90^{R+}	-	74	83^{R+}	82^{R+}	107	134^{R+}	118^{R+}	108	114	125^{R+}
HADS												
Anxiety	11	7	-	7	9	6	1	1	0	6	7	5
Depression	12	9	-	5	8	6	4	3	5	8	9	9
MFIS												
Physical	20	20	-	22	26	23	31	28	33	31	10^{R+}	10^{R+}
Cognitive	23	21	-	24	23	23	15	14	15	15	20	21
Psychosocial	6	5	-	3	5	4	6	5	6	6	1^{R+}	1^{R+}
Total	49	46	-	49	54	50	52	47	54	52	31^{R+C+}	32^{R+}
MSQOL-29												
Mental Health	54.62	50.03	-	65.13	65.93	49.57	63.50	61.8	55.12	72.17	53.87^{R-}	55.73^{R-}
Physical Health	38.67	47.17	-	53.67	52.50	44.33^{R-}	43.50	41.00	36.00	71.34	73.84	66.33

Note: SDMT – Symbol Digit Modalities Test; RBANS – Repeatable Battery of the Assessment of Neurological Status; HADS – Hospital Anxiety and Depression Scale; MFIS – Modified Fatigue Impact Scale; MSQOL-29 – Multiple Sclerosis Quality of Life – 29-Item; $^{R+}$ – Therapeutic Reliable Change; $^{R-}$: Contra-therapeutic Reliable Change; $^{C+}$: Therapeutic CSC; $^{C-}$: Contra-therapeutic CSC; -: No data.

Attention – Participants A, B, D, E, and H showed improvements in the Attention domain. Participant E did not show this improvement at F_1. Participants D, and H both showed initial decreases in scores. Participants C and F remained stable throughout the study.

Delayed Memory – Participants B and H had improved scores at F_1. The remaining participants remained stable.

Total Score – Participants B, E, F, G, and H showed improvements in their Total Score. Participant B's improvements were also clinically significant. Participant C showed an initial decrease in Total Score which was not maintained. Participants A and D remained stable.

4.3. Relational Responding

Inverted Efficiency Scores, with lower scores indicative of higher efficiency, are shown in Figure 5. Most participants showed a sharp increase in their efficiency between A1 and T2 as their percentage correct increased. After this point, percentage correct scores remained reasonably stable with participants' average response time decreasing – increasing their efficiency. Overall, all participants except B showed a decelerating trend in their Inverted Efficiency Scores.

4.4. Mood, fatigue, and quality of life measures

All participants' mood, fatigue, and quality of life results are shown in Table 4. All participants' HADS scores remained stable throughout the study. Only Participant H showed any changes in their MFIS scores across the study; RCI showed improvements in *Physical*, *Psychosocial,* and *Total Score* with the *Total Score* change also being clinically significant. No deteriorations in fatigue were observed over the course of the study. RCI showed Participant A had a reliable improvement in the *Physical Health Composite* of the MSQOL-29. Participants B and F showed reliable decreases in this composite. Participant H also showed reliable contra-therapeutic changes in the *Mental Health Composite.* The remaining participants' (C, D, E, and G) MSQOL-29 scores remained stable throughout the study.

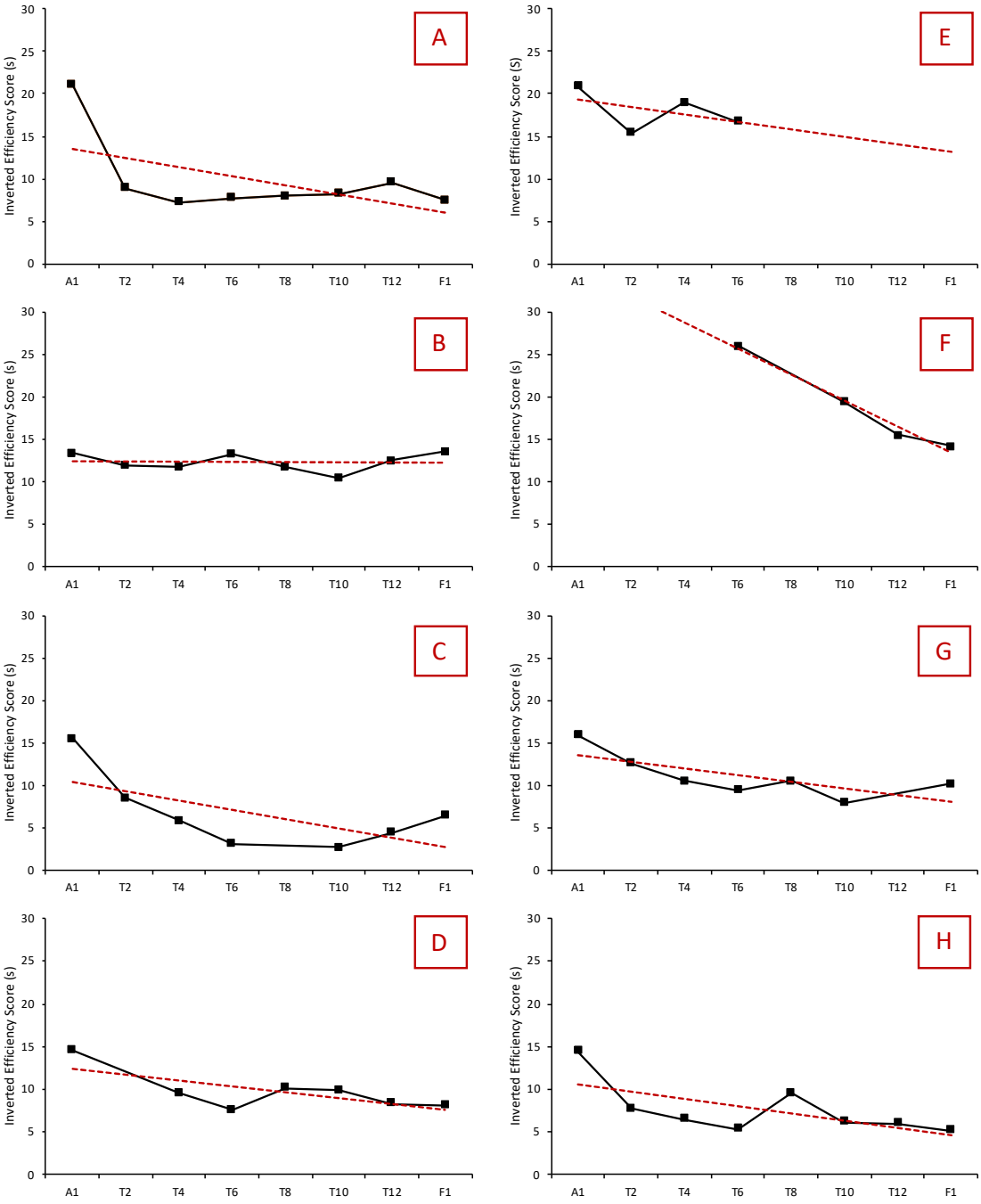

Figure 5: Graphical representation of RAI inverted efficiency scores.

4.5. Feedback Interviews

All participants who began training completed the feedback interview. Participant I, who withdrew from the study after the initial screening assessment, was lost to follow-up. Results of the feedback interview are presented in a summarised form in Table 5.

Overall, participants reported a positive experience of using the SMART program finding it enjoyable (Participants A, B, F, and H) but also challenging (Participants A, B, and H). Two participants reported that they found the program was easy to use/self-explanatory (A and G) but Participant E did not feel this about SMART as they were unsure if they were completing it correctly. Additionally, Participant D reported that they found the purpose of the training difficult to conceptualise. Regarding changes to be made to the program, the majority of participants (A, B, C, D, and F) stated that they would make no changes. However, there were some recommendations: Participant E suggested that there should be more guidance in how to use the program, Participant G suggested there should be a timekeeping feature, and Participant H recommended either an increase in the number of levels in the training or to improve the program's technical rerun capabilities.

All participants, except Participant A, explicitly stated that they either enjoyed or preferred the "face-to-face" (RBANS and SDMT) neuropsychological measures. The online measures (RAI, MSQOL-29, HADS, MFIS, PQ) were reported to be repetitive (Participant A and C). Participant C found the "face-to-face" testing to be stressful but also challenging and enjoyable. Participant E had a negative experience of the online measures that left them feeling "stupid". Regarding changes to be made to the measures utilised in the study, three participants (A, F, and G) stated that they would have preferred feedback within the assessments and/or immediately after them. Participants C and D both spoke of increasing the variety of measures as they reported that they had completed some of the selected measures numerous times before their enrolment in this present study. Participant H suggested the integration of a personalised questionnaire tracking subjective difficulties. When asked about changes to the design of the study, three of the participants (B, C, and E) suggested in-person testing. Three

participants (D, G, and H) recommended increasing the length of the intervention (more weeks in training), whilst two participants (A and H) stated increasing the amount of training per week would be beneficial. Participant D also suggested an intensive training block at the start of the intervention which then stepped down in intensity at a later point. Participant E felt more guidance and clarity was needed regarding training and study procedures. Participant F reported that they would have liked to have a support group/collective to attend.

Participants' subjective changes (not specifically related to the intervention) over the duration of the study were mixed. With four participants stating a beneficial change (Participants B, D, F, and G) and within these, Participants B, F, and G attributing this to the training. Subjective changes attributed to the intervention included increased awareness (Participant B), improved concentration (Participant F), and remaining cognitively stable (Participant G). Regarding the latter, Participant G stated remaining stable was a positive outcome due to the progressive nature of their disease course and in consideration of a physical decline over the study duration (which they attributed to their disease course). Participant D reported improvements in their memory ("sharper") and other cognitive improvements such as being "[more] on the ball" and being "quicker at working things out", which they were unsure where to attribute and suggested an increased awareness. Five participants (A, E, F, G, and H) reported negative changes over the study duration. These included increased anxiety, fatigue, and physical decline. All, with the exception of Participant E, attributed these changes to extra-study factors such as the pandemic (Participants A, E, and F) and changes to their home environment (Participants A and H). Participant E specifically stated that the commitment to the study, in addition with other extra-study factors, had increased their anxiety.

Table 5: Results from feedback interview.

	SMART Items		Design Items			Participant Items	
	SMART Experience	SMART Changes	Measures / Tests	Measures / Tests Changes	Design Changes	Subjective Changes	Change Attributed To
A	Enjoyable, challenging, self-explanatory	None	Repetitive,	Feedback	Alerted to RAI week. Increase duration	Increased stress	Pandemic, home environment
B	Enjoyable, challenging, interesting	None	Enjoyable and accessible. Preferred tests with the researcher	None	In person testing	Increased awareness	Involvement in study
C	Fine, professional	None	Stressful, challenging, enjoyable, repetitive	Increase variation of surveys	In person testing	None	n/a
D	Positive, hard to conceptualise	None	Questionnaires – Repetitive, boring Tests – Enjoyed	More variation, range, and interest	Increase length, intensive block, increase follow-up	Improvement – memory ”sharper”, “on the ball”, “quicker at working things out”	Unknown. Suggested increased awareness
E	Difficulty finding time, unsure if doing correctly	Increased guidance	Liked with researcher, “felt stupid” with online tests	None	In person testing, increased guidance and clarity	Increased anxiety	Training commitments, caring responsibilities, pandemic
F	Good being proactive, enjoyed, looked forward to	None	Enjoyed ”personalised” experience, face-to-face tests “excellent”	Feedback	Collective/group experience/support	Improvement – focus and concentration. Increased fatigue	Training/testing. Fatigue - pandemic
G	Flexible, easy to use, straightforward,	Login / time spent tracker	RAI too long, typos. Face-to-face enjoyable, good variety	Reduce RAI length. Feedback.	Increase timescale	Cognitive remained stable (positive outcome). Physical decline.	Cognitive – training Physical – expected disease course
H	Enjoyed, challenging	Increase number of levels, improve rerun capabilities	Enjoyed face-to-face, interesting	Introduce subjective personal questionnaire	Increase duration and timescale	Fluctuating word finding, increased fatigue	Home environment, childcare

5. Discussion

This study aimed to explore the novel application of the SMART program as an intervention option for those reporting cognitive difficulties in MS. It focused on both subjective and objective assessments of cognitive functioning and also secondary outcomes including mood, fatigue, and quality of life, in line with recommendations for cognitive rehabilitation studies (Goverover et al., 2018; Mitolo et al., 2015). Additionally, the study aimed to explore the relation between reported outcomes and the proposed process of change – relational responding skills. Finally, this study explored the acceptability of the intervention in line with complex intervention development guidance (MRC, 2008).

Participants' subjective PQ measures showed no positive therapeutic changes over the duration of the study. Whilst visual analysis techniques indicated that Participant C did exhibit a positive change between phases, Tau-*U* calculations did not support this conclusion (Tau-*U* = .30, 90% CI [-.24 – .84], z = .92, p = .36). The error in the inclusion of a middle value in the PQ scoring may have produced results significantly different to that if only a binary option had been presented. Yet this accidental inclusion may also have validity within this population. Participant G, diagnosed with a progressive form of MS, reported that cognitive stability, and lack of decline, as a positive outcome. It should be noted that stability was not declared a positive outcome of this study and is not being reported as such. The rationale for having explored stability as a positive outcome is further supported by recent SDMT performance trajectory analysis (Healy et al., 2020). They report that participants who score (at baseline) within the impaired range deteriorate over time, middling scores remain stable, and superior performers improve. Additional subjective changes were captured in the feedback interview. Independent researchers, who the

participants had not met before, conducted the feedback interviews in an attempt to mitigate demand characteristics (Nichols & Maner, 2008). Three of the participants (D, F, and G) that reported a positive cognitive change also showed increasing efficiency in their relational responding skills. However, Participants A, C, E, and H also showed increasing efficiency that did not concur with a reported subjective improvement. Of interest, Participant B was the only participant that did not show increasing relational responding efficiency but did report a positive change in the form of increased awareness, which, through meta-cognitive strategies, can induce therapeutic change (Birnboim, 1995). This discrepancy, or insensitivity between objective and subjective reports of cognitive functioning in MS is well known (Chiaravalloti & DeLuca, 2008). For instance, Mantynen et al. (2014) reported no changes in objective assessments but improvements in participants' perceived deficits. In the opposed directionality, Campbell et al. (2016) reported superior SDMT results in their intervention group compared to control but no differences in subjective reports. Additionally, self-reported functioning has shown as greater association with emotional distress (r = .65) than with objective assessments (r = .18) further complicating the outcomes (Miller et al., 2013).

SDMT performance changes were, overall, positive with 87.5% achieving significant improvements; these results hold particular importance as the SDMT has been reported as the most sensitive measure of cognitive decline in MS (Van Schependom et al., 2014). All participants that scored below their respective clinical cut-off scores (C, D, F, and G) showed reliable and clinically significant improvements that were maintained to follow-up. As stated earlier, Healey et al's. (2020) trajectory analysis would predict worsening performance for those scoring below the clinical threshold. Of the participants who scored above their threshold (A, B, and H) only Participant B did not

show reliable improvements, who was also the only participant not to show improvements in relational skills, further supporting its fundamental role in cognitive skills. It should be noted that this study utilised a more conservative criterion for significant change (RCI = 5) compared with three or four points reported elsewhere (Benedict et al., 2018; Benedict et al., 2014). Whilst this study did utilise this more stringent criterion for the SDMT, practice effects must also be considered in the interpretation of results. A significant practice effect has been reported for the SDMT with a MS sample. Roar et al. (2016) reported a 1.2-point increase in SDMT scores at a six-month retest interval and an additional .4-point increase for each subsequent administration. Pereira et al. (2015) additionally reported a significant practice effect for the SDMT over a short retest interval (150 minutes) in a non-MS sample. However, they also reported that this effect can be nullified by the introduction of alternate forms, such as those presented in Hinton-Bayre & Geffen (2005). Practice effects of the SDMT are further complicated by baseline performance. In their SDMT trajectory models, Healey et al. (2020) reported that those with higher-than-average baseline scores improved in annual administrations whilst those with lower scores worsened. These findings suggest that practice effects are less likely to benefit individuals with impaired performance at baseline. Given this, the improvements demonstrated by study participants C, D, F, and G are noteworthy: suggestive of change over-and-above expectations from retesting.

The present study's general/non-specific (regarding cognitive domains) intervention performed well on processing speed measurements, even when compared to specific processing speed interventions such as Hancock et al. (2015), where they achieved a reliable change in 53% of their active training group on an objective processing speed measure, and Chiaravalloti et al. (2018), where they

achieved clinically significant change in 25% of the treatment group with the Weschler Adult Intelligence Scale-III Coding Subtest (Weschler, 1997).

For the RBANS, by the intervention-midpoint reliable improvements were achieved in 37.50% of participants in Total Score and Language domain and 25.00% in the Immediate Memory and Attention domains. An eighth deteriorated in Immediate Memory and Total Score and 37.50% deteriorated in the Language domain across the same timescale. By the intervention-endpoint, reliable improvements were achieved by 57.14% in Total Score, 42.86% in Language, 28.57% in Visuospatial/Constructional, Attention, and Delayed Memory domains, and 14.29% in Immediate Memory. No reliable deteriorations were achieved by the intervention-endpoint. Reliable changes should be interpreted with caution to due to the multiplicity of testing and the increased likelihood of Type I errors. Across the entire study, Visuospatial/Constructional showed the greatest variation (six positive and three negative) and this may be due to the remote delivery of the visual material to participants as their information technology could not be standardised. Participants B and C both had the highest number of negative changes (three each). As mentioned previously, Participant B also showed no changes in their relational skills. Participant C's results may be explained due to non-ideal testing conditions at mid-intervention timepoint. Whilst the RBANS has been validated in its use in detecting cognitive decline in MS (Davis et al., 2015), it may not be the most sensitive general test available (Aupperle et al., 2002).

Similar improvements have been observed in field of stroke and traumatic brain injury rehabilitation (Cicerone et al., 2019). Specific computerised working memory interventions have also shown improvements in objective measures akin to the SDMT (Åkerlund et al., 2013; Lundqvist et al., 2010). Furthermore, more generalised/non-

specific interventions have shown improvements in attention, executive functioning, and memory (Fernández et al., 2012; Lin et al., 2014). Additionally, the interventions used in these above studies are also the same as those which have been implemented in MS (See section 7.5). Such findings suggest an overlap, in terms of a theoretical process of change and outcomes, between more MS specific studies and those exploring more general cognitive rehabilitation. And whilst there is an overlap in the increased use of computerised interventions targeting specific skills (such as the one implemented presently) in both fields, Cicerone et al's., (2019) review highlights the importance and efficacy of adjunct metacognitive and emotional components in rehabilitation interventions. The present study did not utilise such components and it would be prudent for future studies to consider their integration.

Whilst improving relational efficiencies were observed in all but Participant B, no discernible pattern with either objective or subjective measures, as a whole, were noted. All participants who reported no improvement at the feedback interview (A, C, E, and H) showed increasing efficiencies and Participant B reported a subjective improvement. Regarding SDMT performance, all relational skill improvers except Participant A achieved increased SDMT scores whilst the relational skills non-improver (B) did not. RBANS performance paints a similar picture as Participant B improved in a range of domains and Total Score. Additionally, Participant C was a relational skills improver but also the only participant not to improve on at least one domain of the RBANS. As such, no clear logical relationship between relational skills, as measured by inverted efficiency of the Relational Abilities Index, and objective and subjective assessments of cognitive functioning can be established.

Mood, fatigue, and quality of life remained fairly stable over the course of the study. Mood has been shown to have an instrumental effect on cognitive performance in MS (Arnett, 2005; Arnett et al., 1999; Feinstein, 2006) and as it remained stable, we can attribute reported cognitive changes to the intervention with greater confidence. Whilst improved quality of life is ultimately what rehabilitation interventions aim for, large studies investigating quality of life and cognitive rehabilitation have produced mixed results (Lincoln et al., 2020). Though some cognitive rehabilitation studies have reported increased mood following intervention (Amato et al., 2014; Messinis et al., 2020; Rosti-Otajarvi et al., 2013), we must also consider the current context of a global pandemic and how this would influence ratings of mood, fatigue, and quality of life. For instance, mood and fatigue has been reported to worsen as a result of the restrictions employed (Terry et al., 2020).

The intervention had a low attrition rate with 87.5% of participants reaching the follow-up 1 timepoint. The participant who did withdraw (E), felt the commitment to the intervention too much given her personal circumstances. Overall, the intervention appeared to be accepted well with minimal recommendations of change. Regarding the measurements used, many issues were as a result of the pandemic restrictions in place over the course of the study. Of note, participants recommended increasing both the overall duration of the intervention and the intensity of the training. This increase would bring the current study's comparatively brief intervention (45-minutes per week) more in line with other cognitive rehabilitation interventions in MS that regularly prescribe 30–60-minute sessions for 5 days a week (Blair et al., 2021; Bonzano et al., 2020; Charvet et al., 2017; Chiaravalloti et al., 2018; Chiaravalloti et al., 2021; Covey et al., 2018; De Giglio et al., 2016; Fuchs et al., 2019; Pedulla et al., 2016).

5.1. Limitations

Findings from this study are limited due to the design being built around the PQ as the primary outcome measure. This design aimed to utilise a multiple baseline design which would provide greater confidence in attributing cognitive change causality to the introduction of the training (Morley et al., 2017). However, a phase contrast was not observed and therefore it cannot be determined if there were "true" stable baselines and stable intervention phases, or if these results originate from measurement error. These issues potentially limit the present study to a simple pre-post design. The SDMT and RBANS results may therefore not be part of a controlled design and should be interpreted with caution. Participant adherence to the prescribed allocation was not measured and this may have limited analysis of the relationship between training, process, and outcomes. Whilst participants acted as their own controls within this design, there was no control condition to which intervention effects could be compared, consequently limiting the confidence of reporting an effect elicited by the intervention itself. Finally, issues in the measurement of relational skills weaken a more definitive investigation into the role of these skills in mediating change. As such, the present study cannot state with confidence whether observed changes are attributable to improving relational skills or being enrolled and participating in a cognitive rehabilitation intervention.

5.2. Future Research

The present study provides the initial foundational evidence for the acceptability and potential effects of the SMART intervention. Future research should proceed with the development of this intervention in line with MRC (2008) guidance. A larger study will first need to examine any further changes that need to be made to the intervention prior to a feasibility trial which would then be followed by a larger pilot RCT.

MS specific objective measurement may support findings; however, retaining subjective reports of functioning is still recommended.

5.3. Conclusion

The SMART intervention has shown promising early results at a low dose relative to other cognitive rehabilitation interventions. Furthermore, participants reported an overall positive experience and made recommendations to increase both the intensity and duration of the intervention – providing preliminary support for the intervention's continued development with this population. Mixed results were reported for SMART's effects on general cognitive functioning, but strong evidence was found for its effect on processing speed as measured by the SDMT. Finally, the study provides inconclusive evidence supporting the hypothesis that relational skills mediate cognitive performance in a rehabilitation intervention.

6. References

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Section IV: Extended Paper

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7. Extended Introduction

The additional sections presented in this section to aim to familiarise the reader with MS as whole, from its pathophysiology, to the complex sequalae of this disease profile, and its prevalence across the globe. There is also a particular focus on the processes of neurological change and the theories that may account for recovery and repair in the face of damage.

A systematic literature review has been completed to orientate the reader to the rapidly expanding field of cognitive rehabilitation in MS. It primarily focuses on the quality of evidence supplied by these novel approaches and provides a brief account of recommendations and future considerations.

Finally, the relationship between the behaviourist tradition and intelligent behaviours are examined. Rationales are established postulating that intelligent behaviours can be understood as operant behaviour and consequently, in the appropriate context, be trained.

7.1. Global Prevalence of Multiple Sclerosis

MS prevalence across the world paints a complex picture influenced by global region, regional income, gender, age, and even latitude differences. The most recent Atlas of MS (MSIF, 2020) reports that 2.8 million people are currently living with MS across the world; this gives a prevalence rate of approximately 1 in every 3,000 people globally. In 2013, the total number was reported at 2.3 million (MSIF, 2013). The increase in global prevalence rates may be explained by the improved detection and diagnosis of MS (Schwenkenbecher et al., 2019), developments of treatments and support (Kingwell et al., 2019), greater number of countries reporting data and improved data collection methods, and the overall 9% increase in global population between 2013 to 2020.

Differing prevalence rates, as a whole, appear to map more accurately over World Bank income levels (World Bank, 2019) in comparison to World Health Organisation regions (WHO; 2020); however this may be due to the combination of North and South America into the Americas region for the latter system. Europe and the Americas report the highest prevalence rates, though these rates may again mirror the reasons behind global increase. Changes between 2013 to 2020 for WHO regions are shown in Table 6. It should be noted that these data below are an altered data set as only countries/regions that reported for both years are reported.

Table 6: Global and WHO regional prevalence rate per 100,000 and change from 2013 to 2020. Data adapted from MSIF (2020).

Region	2013	2019	Percentage Change
Global	29	44	51.72
Europe	108	143	32.41
Americas	63	118	87.31
East Mediterranean	24	33	37.50
South East Asia	5	9	80.00
Africa	6	9	50.00
West Pacific	4	5	25.00

Prevalence rates also appear to be influenced by latitude and this does not appear to be a confounding effect of more wealthy countries being in the northern hemisphere (Simpson et al., 2019; Tao et al., 2016). In Australia, the rates of MS are nearly twice as high in its most southern state (furthest from the equator), Tasmania, compared to the most northern, Queensland, with rates of 139 and 75 per 100,000 respectively (MS Research Australia, 2017).

Females are twice as likely to be diagnosed with MS than males with a global ratio of 69% and 31% respectively (MSIF, 2020). This skew appears to be greatest within Western Pacific and Southeast Asian regions where the ratio climbs to three to one. However, this picture is further complicated as areas report drastically difference rates at the country level of analysis in comparison to the region. For example, the East Mediterranean ratio is reported as two to one, female to male. When focusing on individual states the ratio increases dramatically to four to one in Egypt, Sudan, Iran, and Palestine (MSIF, 2020). The reasons behind such a degree of differences between males and females, both globally and state specific, may be due to numerous reasons such as genetics (Russi et al., 2018), hormonal differences (Voskuhl et al., 2018), and socio-economic and environmental variables (MSIF, 2020). Furthermore, inequalities and potential barriers to healthcare may also be involved in varying rates (Socias et al., 2016).

The MS International Federation (2020) report the average age of a person being diagnosed with MS as 32 years old. This age appears stable across the WHO Regions (ranging from 30 to 33), though when focusing on the country level reporting the range again varies greatly from 20 to 50 years old. The average age is significantly lower than other neurodegenerative disorders, such as stroke or Alzheimer's disease, where the average age of onset is approximately 65 years or higher (Alzheimer's Disease International, 2021; Stroke Association, 2017). MSIF (2020) highlight the impact of such a neurodegenerative disease can have at this age, where many are typically establishing themselves in their professions, finding partners, and potentially starting a family. Furthermore, whilst typically viewed as a working age adult disease, there are approximately 30,000 people under the age of 18 currently living with MS globally, and this figure is likely to be a considerable underestimation of the true figure (MSIF, 2020). For

instance, there has been a 330% increase in cases reported for this population since 2013, which is likely due to increased prevalence studies, detection, and that that MS symptomology in this population is oft mistaken for other disease profiles, rather than an uptake in disease probability (see Alroughani et al., 2015; Marrie et al., 2018).

Differing rates in MS subtype are difficult to report across the globe due to the relatively low number of countries reporting this level of data; for instance, Western Pacific regions only report this data for approximately 5% of their MS population (MSIF, 2020). Using what data are available, approximately 85% are diagnosed with Relapse Remitting MS, 12% with Primary Progressive, and with the remaining 3% reporting an unknown subtype (MSIF, 2020). The International Advisory Committee on Clinical Trials in MS state the need to include data such as 'activity' and 'progression' to aid in the understanding of disease rates, variation, and to guide interventions and support (Lublin et al., 2014). The lack of reported data is an additional concern given the views that MS may in fact be numerous divergent diseases categories under a single umbrella diagnosis (Joy & Johnston, 2001).

7.2. Biology of Multiple Sclerosis

7.2.1. Signal Transmission

The Central Nervous System is a complex network of numerous cellular types which support the maintenance of a healthy and functional environment for neuronal cells. Neurons can be viewed as dependant on this network in managing their metabolism, immune response, propagation, locality, synaptic transmission, and axonal transmission. Regarding the latter, the fast, efficient, and successful signal transmission is dependent on the support from Oligodendrocytes. These highly specialised cells have a 'hub-and-spoke' structure; the hub being their main mass housing the nucleus and other key cellular structures and the spokes, or 'processes', being extensions that wrap

around numerous proximal axons, providing a myelin sheath (Prineas & Connell, 1978; Raine, 1997). This structuring differs greatly from the Peripheral Nervous System (PNS), where each myelin sheath is a single Schwann cell.

The myelin sheath provides needed insulation to neuronal axons, maintains healthy homeostasis, and allows for saltatory signal conduction. Saltatory conduction (from the Latin word for 'jump') is the process in which an action potential, or wave of cellular polarisation/depolarisation, is transmitted down a neuronal axon in a jumping fashion, rather than a continuous transmission (Joy & Johnston, 2001). Saltatory conduction can be likened to a digital, versus an analogue, radio frequency transmission or perhaps fibre optic versus copper wiring. It enables a signal that is less vulnerable to degeneration and one that can travel a greater distance; furthermore, due to the cellular mechanics of excitable cells and voltage-gated ion channels, this system has the added benefit of increasing transmission speed. The myelin sheath is not a continuous covering and has regularly interspersed gaps, exposed axonal cellular membranes, named a Node of Ranvier. These nodes have a far greater expression of Sodium channel proteins, a key component in excitable cells depolarisation. The internodal space (covered by the sheath) has a markedly lower expression of these proteins and has a more evenly distributed expression of Potassium channel proteins – the counterpart to the aforementioned channel. The structural relationship between these two channels is paramount to saltatory conduction; if they were arranged in another fashion this type of conduction would not be feasible as the action potential 'jumps' from one Node of Ranvier to the next. Removal of this sheath prevents the formation of these nodes, consequently reducing transmission speed, efficiency, may even halt successful signal conduction, and could lead to axonal transection and cellular death (Joy & Johnston, 2001; Trapp et al., 2016).

The cells that provide this sheath, Oligodendrocytes, are one of the most vulnerable cells within the Central Nervous System (Bradl & Lassmann, 2010). Their vulnerability is not only due to their physiology and metabolism but also their complex pathway of proliferation, migration, and differentiation (Bradl & Lassmann, 2010)

7.2.2. MS Pathology and Subtypes

Multiple Sclerosis is literally translated, from Latin, to mean 'Many Scars' – named after the characteristic lesions observed in the white matter (areas with a high density of neuronal axons) throughout the brain and spinal cord; though these lesions have also been reported in grey matter of the brain (Compston & Coles, 2008). These scars, or lesions, comprise of numerous dead neurons resulting from their protective myelin sheath having been denuded. This outcome is believed to be mediated by autoimmune processes, thought the exact classification of MS as an autoimmune disorder is debated (Rodriguez, 2009; Wootla et al., 2012).

The pathology of MS is complex, and no agreed process has been decided (see (Lassmann, 2018; Lassmann et al., 2007; Lassmann et al., 2012 for detailed reviews of the pathology of MS). The current understanding suggests that autoreactive lymphocytes (such as T-Cells) cross the blood brain barrier and initiate an inflammatory response (Huang et al., 2017; Vandevyver et al., 1995). Questions remain unanswered regarding how this autoreactive process is initiated and what risk factors are in play. Numerous genes and a strong role of environmental factors such as Ultraviolet B exposure (or perhaps more accurately Vitamin D levels), Epstein-Barr virus exposure, smoking, and obesity are believed to be involved (Ascherio, 2013; Dobson & Giovannoni, 2019; Ramagopalan et al., 2010). Migration studies show that the environment may take a greater casual role in the risk of

developing MS; however, the underlying influence of genetics should not be overlooked (Kurtzke, 2013). Dobson & Giovannoni (2019) report Molecular Mimicry to be a leading theory in explaining MS pathology (Lang et al., 2002). In Molecular Mimicry, foreign peptides, presented on smoked tobacco or a virus for instance, may mimic, at least in part, that of a self-antigen. T-Cell receptors will be activated by this foreign antigen, subsequently mounting an inflammatory response against it; however, these antigens are functionally homogenous with self-antigens, such as those presented on Central Nervous System myelin sheaths (Joy & Johnston, 2001). Within the Central Nervous System, the inflammatory response, and its resulting sequalae, can result in gliotic scarring, demyelination, and axonal loss (Huang et al., 2017; Trapp & Nave, 2008). Oligodendrocytes are particular vulnerable to the cytokines and antibodies released in the inflammatory response with their loss of functioning and support perhaps mediating neuronal death, in addition to neuronal vulnerability to this same process (Ferguson et al., 1997; Traugott et al., 1983; van der Valk & De Groot, 2000). Furthermore, these autoreactive T-Cells may be antigen specific to myelin basic protein and myelin associated glycoproteins, marking oligodendrocytes the target of the inflammatory response (Joy & Johnston, 2001).

Damage to the myelin sheath from the inflammatory process (Figure 6, B) results in a slowed signal transmission (Joy & Johnston, 2001). This slowing, however, does not equate to a clinical deficit in people with MS (Halliday & McDonald, 1977; Hume & Waxman, 1988; McDonald, 1977). Denuding can result in a signal transfer failure, not successfully transmitting the length of the axon, which will result in a clinical deficit (Joy & Johnston, 2001). This transmission failure may be a result of the loss of Nodes of Ranvier and the, now exposed, Potassium channels preventing signal propagation (Ritchie, 1982; Waxman, 1982). Signal failure may also occur due to axonal

transection and cellular death (Figure 6, C) as an outcome of the denuding effects or by inflammatory cascade (Joy & Johnston, 2001).

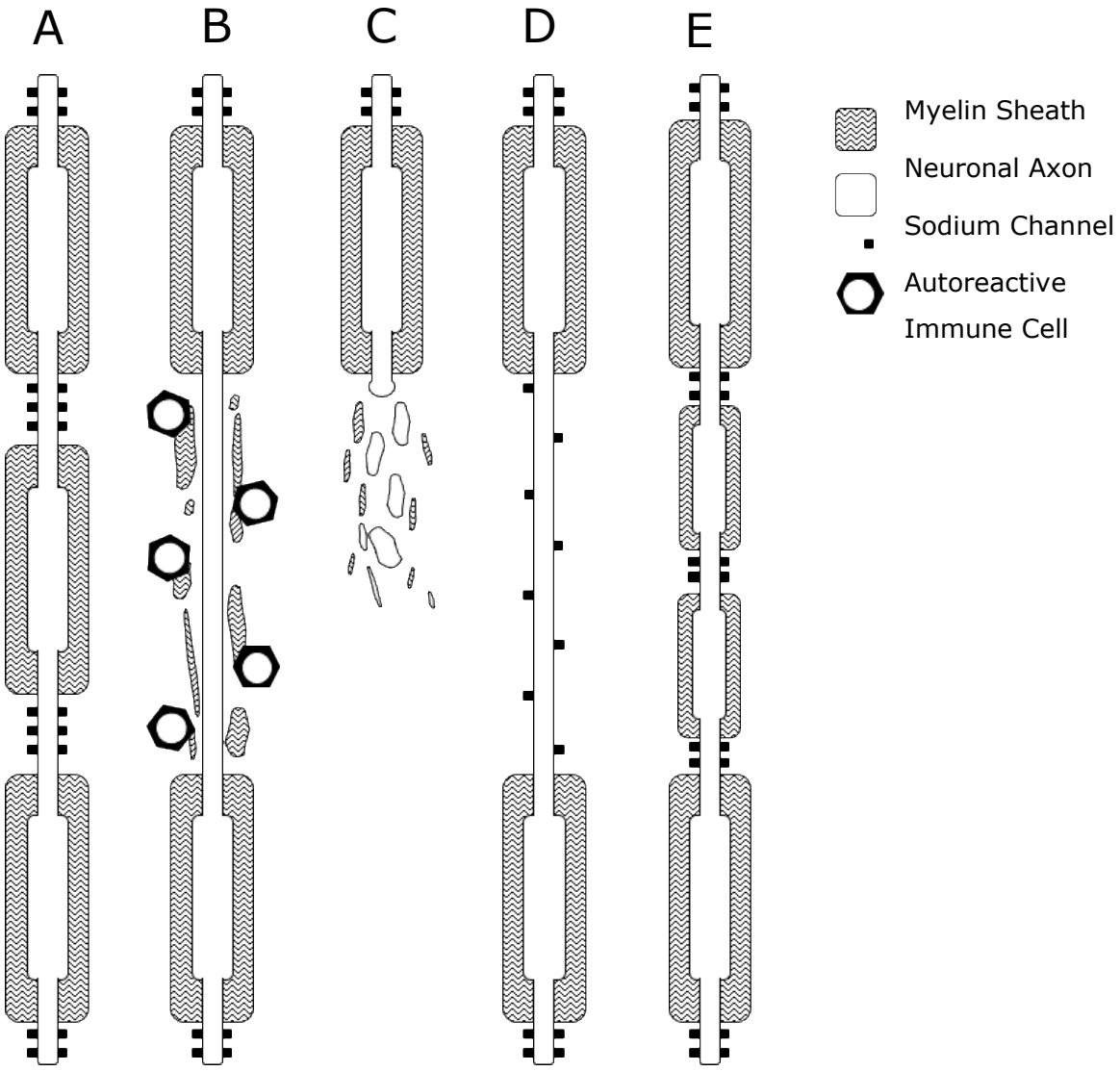

Figure 6: Graphical illustration of cellular structures of a healthy neuronal axon (A), inflammatory mediated denuding (B), axonal transection (C), molecular plasticity and Sodium channel redistribution (D), and neuronal remyelination (E). Adapted from Trapp et al. (1999).

Axons can recover from the damage of these events, and functionality can be restored, as remissions are observed in MS. This remission could be facilitated by molecular plasticity and the remyelination process (Joy & Johnston, 2001). Post denuding, neurons may increase the expression of Sodium channel proteins across the length of the axon (Figure 6, D), effectively amplifying the signal resulting in

successful transmission (Black et al., 1987; Dugandzija-Novakovic et al., 1995; England et al., 1990; Foster et al., 1980; Moll et al., 1991).

The loss of the insulating myelin sheath, resulting from oligodendrocyte cellular death, is not always a permanent or irreversible outcome. In the early stages of MS disease progression, oligodendrocyte precursor cells, that are located within the Central Nervous System, can differentiate into healthy cells and provide myelin sheaths to exposed proximal axons (Prineas et al., 1989; Raine et al., 1981). This early stage of remyelination (Figure 6, E) may be facilitated by growth factors introduced to the local extracellular space by macrophages and the inflammatory process (Diemel et al., 1998; Kotter et al., 2001). However, the remyelination process does not replicate the pre-insult sheath. The remyelinated sheaths have a reduced thickness, in relation to the axonal diameter, and a shorted distance between Nodes of Ranvier (Franklin & Ffrench-Constant, 2008; Ludwin & Maitland, 1984; Prineas, Barnard, Revesz, et al., 1993). The efficiency of this remyelination process decreases in the later, progressive, stages of the disease (Goldschmidt et al., 2009). This decrease is further compounded by age (Rando, 2006; Shields et al., 1999) and by the growing inefficiency of clearing post-inflammatory response cellular debris from the extracellular space (Kotter et al., 2001). In MS, mature lesions (post inflammatory response) still show a decreasing population of oligodendrocytes (Wolswijk, 2000) and that demyelination occurs at a higher rate in previously remyelinated areas (Prineas, Barnard, Kwon, et al., 1993) – continuing the damage post-inflammation. These complex interactions are observed in the differing MS subtypes, with attacks and relapses, the transformation into progressive phenotypes, and relative recovery.

Early stages of the disease are characterised by lesions and resulting demyelination (Karussis, 2014) with axonal loss seen in the later progressive disease types (Trapp et al., 1998). Later stages do not express the archetypal active lesions observed in Relapse Remitting MS but instead inactive mature lesions, with a periphery of activated immune cells (Dobson & Giovannoni, 2019; Prineas et al., 2001). Whilst certain distinct MS subtypes are reported (see Table 7 for subtype characteristics and Figure 7 for subtype disability profile), Dobson and Giovannoni (2019) argue that the hallmarks of each type, for instance remyelination or active plaques, should be viewed on more of a continuum. This continuum accounts for the progression of MS disease course, commonly from Relapse Remitting to the more progressive subtypes (Dobson & Giovannoni, 2019).

Table 7: Summary of MS Subtypes and disease course. Adapted from Joy & Johnston (2001) and Goldenberg (2012).

Type	Disease Course
RRMS – Relapsing Remitting Multiple Sclerosis	Most common type, accounts for approximate 85% of cases. Characterized by discrete attacks that evolve over days to weeks followed by some decree of recovery over weeks to months. In between attacks, the patient has no worsening neurological function.
PPMS – Primary Progressive Multiple Sclerosis	Characterized by steady functional decline from the onset of the disease. No relapses ever.
PRMS – Progressive Relapsing Multiple Sclerosis	Characterized by steady functional decline from onset of the disease with later superimposed acute attacks. PRMS and PPMS cannot be distinguished during early stages, until the relapses occur.
SPMS – Secondary Progressive Multiple Sclerosis	Characterized by initial relapses, followed by gradual neurological deterioration not associated with acute attacks.

7.2.1. Is MS an Autoimmune Disease?

Whilst the current prevailing understanding is that MS is an autoimmune disease, Wootla et al. (2012) argue that is does not meet their six-part revised autoimmune criteria (see Rodriguez, 2009): (i) an exact antigen must be present in all cases of the disease, and no precise antigen has been identified (Wootla et al., 2012); (ii) administering the auto-antibody and/or the auto-reactive T-Cells does not induce the disease profile in animal models consistently (Hao et al., 1994; Saeki et al., 1992); (iii) furthermore, a specific antigen will also not induce lesions; (iv) in MS, isolated autoantibodies or

autoreactive T-Cells drawn from the lesion, or surrounding serum, were at a comparable frequency to that of healthy controls (Wootla et al., 2012); (v) whilst there is a correlation between autoreactive T-Cells and increased disease activity in relapse versus progressive cases, which would imply a relationship, baseline autoreactive T-Cell frequencies in healthy samples are high enough to render these findings inconclusive (Wootla et al., 2012); (vi) lastly, a greater probability of being associated with other autoimmune disorders, and their antibodies, would be expected in an autoimmune disorder, such as seen in Neuromyelitis Optica (Pittock et al., 2008; Wingerchuk, 2006). In addition, whilst there have been associations observed between MS and other autoimmune disorders such as Diabetes Mellitus (Warren & Warren, 1981) and Myasthenia Gravis (Lo & Feasby, 1983), these findings have not been observed in larger population/cohort findings (Wootla et al., 2012; Wynn et al., 1990).

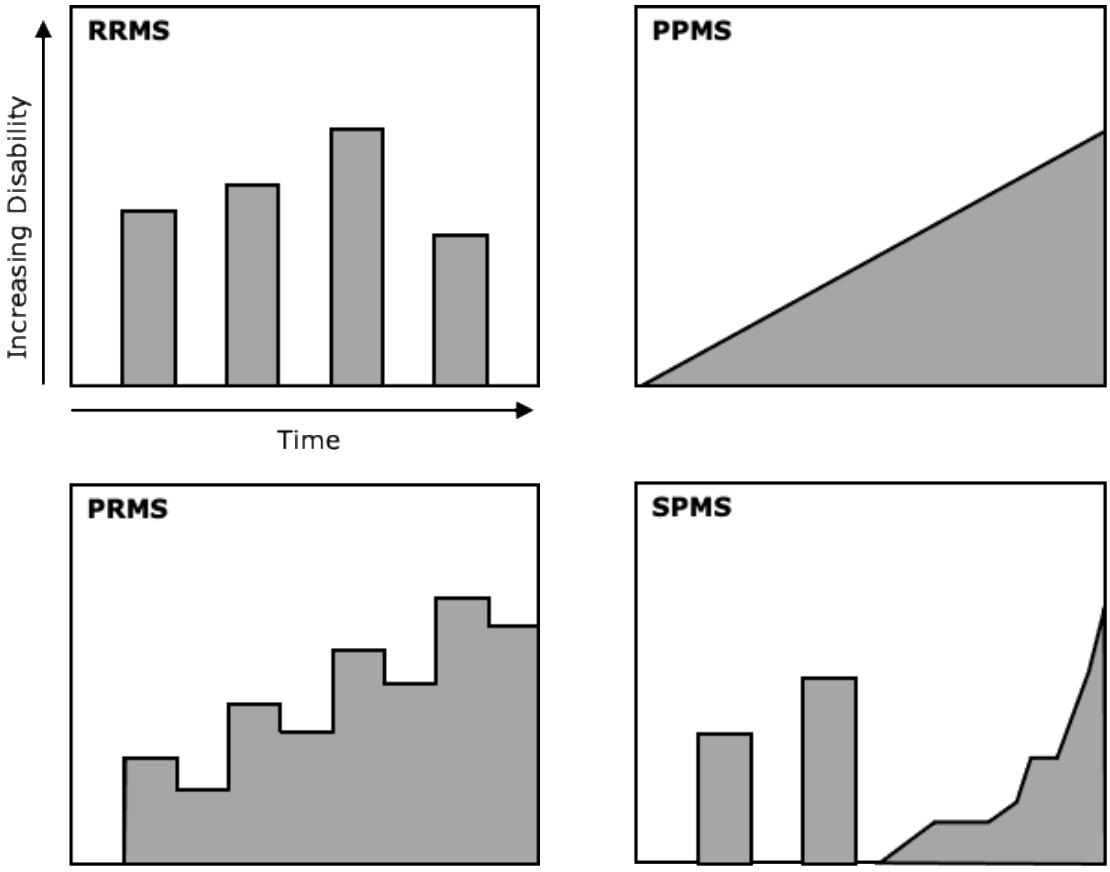

Figure 7: Graphical illustration of MS disease courses over time and changing levels of disability. RRMS – Relapse Remitting MS; PPMS – Primary Progressive MS; PRMS –Progressive Relapsing MS; SPMS – Secondary Progressive MS. Adapted from Lublin & Reingold (1996).

7.3. MS Cognitive Functioning and Sequalae

7.3.1 Lesions and Functioning

The impact of focal lesions and their casual role in MS symptomatology has been thoroughly explored (Paul, 2016; Rocca et al., 2015). Focal white matter lesions have been correlated with performance changes on neuropsychological measures. For instance, focal lesions in the frontal lobe are associated with impaired performance on executive functioning measures (Foong et al., 1997), and cortical lesions with impaired processing speed (Rossi et al., 2012). These cross-sectional correlational studies are further supported by longitudinal examinations (Hohol et al., 1997; Sperling et al., 2001). The role of focal lesions in MS symptomology is challenged by the findings of Benedict et al. (2004), who posit that diffuse grey matter atrophy is a more robust predictor of cognitive decline in MS.

The clarity of association between lesions and functional outcomes is further complicated by the 'clinical-radiologic paradox' (Krieger et al., 2016; Krieger & Sumowski, 2018). This paradox encapsulates the observed discrepancies between lesions and functional outcomes. Lesions occur far more frequently than any measurable or observable impairment or decline. Krieger and colleagues explain how this discrepancy can occur with their topographical model of MS. In essence, the brain can be viewed as a swimming pool, with the water as the functional reserve (see section 7.4.) and focal lesions as protrusions, or stalagmites, from the base of the pool. Some lesions are of an amplitude that they protrude above the water line, signifying a clinical deficit. However, many are below the water line. Through the normal aging process of brain atrophy, which maybe further facilitated by diffuse damage, the water line (read functional reserve) gradually drops, exposing a greater number of lesions. This model can help describe how the transition from relapse orientated MS disease courses to the more progressive subtypes. Krieger and colleagues state that

imaging should be used in conjunction with routine neuropsychological testing and observable functional outcomes to assist in diagnosis and treatment planning.

7.3.2. Affected Cognitive Domains

MS can affect a broad range of cognitive domains such as long-term memory (Brassington & Marsh, 1998; DeLuca et al., 1994; Rao et al., 1993), working memory (Diamond et al., 1997; Grafman et al., 1991; Litvan et al., 1988), executive functioning (Denney et al., 2005; Foong et al., 1997; Lazeron et al., 2004), attention (Beatty & Monson, 1996; Litvan et al., 1988), and processing speed (DeLuca et al., 2004). Visuo-spatial memory and processing speed impairments are the most frequently observed with a rate of 54.30% and 51.90% respectively (Benedict et al., 2006). More recent developments have shown the interaction of domain impairments on outcomes. For instance, impairments in initial learning have been shown to be instrumental in long term memory problems (DeLuca et al., 1994; DeLuca et al., 1998; Thornton et al., 2002). Chiaravalloti & DeLuca (2008) report that when accounting for this initial learning, with more repetitions an MS sample achieved equitable results to healthy controls in measurements of memory (DeLuca et al., 1994; DeLuca et al., 1998). These findings challenge the previously held view that MS specific retrieval issues mediated this issue (Caine et al., 1986; Rao, 1986; Rao et al., 1989). Recent research into the potential stages of cognitive impairment have indicated that domain impairments may be sequential rather than disparate (Wojcik et al., 2021). Their longitudinal study reported that processing speed was the most likely domain to be impaired first and executive functioning last.

7.3.3. Additional MS Sequalae

MS symptomology is not only limited to proximal cognitive impairments and decline but also related outcomes and variables such as mood, fatigue, quality of life, employment, and pain.

Approximately 80% of people with MS report significant levels of fatigue (Krupp et al., 2007) with a further 28% citing it as the primary factor in them reducing their work hours (Smith & Arnett, 2005) and it being attributed the causal role in becoming unemployed (Edgley et al., 1991; Jackson et al., 1991). Difficulties in vocational activities, ultimately ending in either reduced work hours and/or prematurely leaving work is a common occurrence for people with MS. Up to 50% of people with MS leave their vocation early, with the probability increasing in line with disease duration (Gregory et al., 1993; Grønning et al., 1990; Hakim et al., 2000; Hammond et al., 1996; Morales-Gonzales et al., 2004; Rozin et al., 1975). In their multi-national analysis of work-related factors in MS, Uccelli et al. (2009) report MS symptoms and the physical work environment as factoring into a person's decision to leave work.

Quality of life in people with MS has been reported to be significantly lower when compared to non-MS samples (McCabe & McKern, 2002; Yalachkov et al., 2019). In a recent systematic review of quality of life in MS, Gil-Gonzalez et al. (2020) report numerous MS specific factors that can negatively impact a person's quality of life. Relating to the disease directly, functional impairment (Rezapour et al., 2017), disease duration (Brola et al., 2017; Brola et al., 2016), progressive type (Cichy et al., 2016; Gross & Watson, 2017), and progression onset (Zhang et al., 2019) are all associated with reduced quality of life outcomes. Gil-Gonzalez et al. (2020) report additional variables including but not limited to fatigue (Ciampi et al., 2018), motor issues (Cioncoloni et al., 2014; Williams et al., 2014), bladder and bowel problems (Cioncoloni et al., 2014), sexual dysfunction (Schairer et al.,

2014), and sleeping (Tabrizi & Radfar, 2015) to also have a negative effect on quality of life. MS symptomology can even impact activities of daily living. Einarsson et al. (2006) report that 30% of their participants required assistance in completing personal activities of daily living, such as washing and eating, whilst 60% needed assistance in instrumental activities, such as communication and money management. In addition to the above, 50% of people with MS experience significant pain (Indaco et al., 1994; Kassirer & Osterberg, 1987; Moulin et al., 1988; Stenager et al., 1995) which increases over time, as evidenced in a five-year follow study (Stenager et al., 1995)

The probability of experiencing depression in MS over the lifetime is 50%, five to ten-fold greater than the general population (Patten & Metz, 1997; Sadovnick et al., 1996). The processes and cause of such a higher rate have been examined in detail (Arnett et al., 2008). Numerous studies report that depressive symptoms may be a direct result of the demyelination process itself and have also differentiated lesion locality as being instrumental, with temporal regions having the strongest association with these symptoms (Bakshi et al., 2000; Berg et al., 2000; Fassbender et al., 1998; Feinstein, 2004; Pujol et al., 2000; Pujol et al., 1997; Reischies et al., 1988; Zorzon et al., 2001). In light of these findings, and the other related sequalae of MS, Arnett et al. (2008) propose a model of depression in MS. In essence, many of the primary sequalae listed above (pain, fatigue, reduced quality of life) will all contribute to depressive symptomology. Additionally, the secondary effects that these outcome share may compound the issue further. This can include reduced independence, greater strain on relationships, coming to terms with a progressive disease, not being able to engage in vocation, and potential financial strain.

7.4. Protection or Recovery - Reserve, Plasticity, and Flexibility

7.4.1. Brain and Cognitive Reserve

Barulli & Stern (2013) report 'Reserve' is a concept regularly used to account for an individual's discrepancies between cognitive and/or functional deficits and brain pathology (Satz et al., 2011; Stern, 2002, 2009). In other words, Reserve accounts for variations between individual's cognitive and functional performance with those of similar brain pathology – a protective/compensatory system. Reserve is further divided into Brain Reserve, the degree of pathological brain damage and physical characteristics of the brain (e.g., brain size and the number of neurons and synapses) (Satz et al., 2011), and Cognitive Reserve, the current neuronal activity and how this is shaped by lifespan experiences (Barulli & Stern, 2013; Stern, 2002). Whilst these theories were initially built around Alzheimer's Disease and the normal ageing process, there is a growing evidence base of the role of Cognitive and Brain Reserve in MS (Ghaffar et al., 2012; Martins Da Silva et al., 2015; Modica et al., 2016; Rocca et al., 2019; Sumowski et al., 2009; Sumowski & Leavitt, 2013; Sumowski et al., 2014; Sumowski et al., 2013; Sumowski et al., 2010).

Brain reserve, in essence, is a simple threshold model, where clinical deficits are observed once an individual drops below a certain level (Barulli & Stern, 2013; Satz et al., 2011). In MS, the reduction in Brain Reserve will be a result of the aforementioned neuronal transection and demyelination. Whilst Sumowski et al. (2013) report that brain size (measured as Maximal Lifetime Brain Growth) protects against components of cognitive decline in MS (chiefly cognitive inefficiencies), within the confides of the Brain Reserve model, brain size is genetically mediated and pre-insult interventions would not be feasible (Bartley et al., 1997). Consequently, it has been proposed that Brain Reserve be *maintained* with a "Brain Healthy" lifestyle, such as sleep, physical activity, healthy diet, and medication adherence (Brandstadter et al., 2019; Sumowski & Leavitt, 2013). Brain Reserve, as a concept, retains its utility in risk prediction and identifying individuals who may need a

higher intensity of cognitive rehabilitation interventions at an earlier stage; however, it is limited in its pre-morbid understanding of a patient.

Contrasting with the above, Cognitive Reserve is a more flexible construct which is mediated by experience and related cognitive efficiencies (Barulli & Stern, 2013; Stern, 2002). Individuals with similar Brain Reserve can have differing levels of Cognitive Reserve due to their potentially divergent experiences (Stern, 2002). The measurement of Cognitive Reserve remains elusive and problematic, if at all feasible, as it is constructed from, and not limited to, proxies such as socioeconomic status, number and nature of leisure activities, crystallised intelligence, literacy level, and years of education (Stern, 2002). Regarding the measurement of Cognitive Reserve, there have been interesting developments in applying a latent variable model and decomposing variance of a measure of episodic memory (Reed et al., 2010). Jones et al. (2011) discuss that, whilst latent variable models are useful in the attempt to operationalise Cognitive Reserve in comparison to pure proxy measurement, Cognitive Reserve operationalisation is still limited by *in vivo* measurements of brain pathology. Stern (2006) proposed two systems within the Cognitive Reserve model, Neural Reserve and Neural Compensation. Higher Neural Reserve comprises of an individual's improved neural efficiency (defined as requiring less activation to achieve the same results), increased capacity (larger maximum activation threshold to account for increase in task difficulty), and greater flexibility in network selection to achieve task (Barulli & Stern, 2013). The second component, Compensation, is defined as the ability to employ secondary networks to complete a task after pathology has damaged the primary task related network. Similar to the findings in Brain Reserve, higher pre-morbid cognitive reserve (as measured by proxy), were associated with improved cognitive rehabilitation outcomes (L.

Castelli et al., 2020). Lövdén et al. (2010) attempt to unify the Brain and Cognitive Reserve theories under a single conceptual framework of brain plasticity.

7.4.2. Plasticity

The term plasticity has changed greatly since the time of its original conception in the late 19th century (for a comprehensive review see Berlucchi & Buchtel, 2009) and it is mostly commonly understood as the brain's, or neuron's, capacity for change (Lövdén et al., 2010). The term, as we know it now, was formed from works such as the changing of neuronal paths in the formation of habits (James, 1890), the identification of synapses (known as articulations at the time) as a potential location of this plasticity (Tanzi, 1893), the correlation of neuronal and synaptic plasticity (Lugaro, 1909), and the formation of new connections being a result of this plasticity (Ramón y Cajal, 1894). In the early 20th century the term became muddled and synonymous with the reaction to damage and not the more holistic process of learning (Berlucchi & Buchtel, 2009). Not until the mid-20th century did the term regain some of its previous meaning after the seminal work of Hebb (1949) and Konorski (1948). The term remains obfuscated and poorly operationalised to this day (Berlucchi & Buchtel, 2009; Lövdén et al., 2010; Raz, 2007). Lövdén et al. (2010) set out to operationalise the term in its holistic form and demonstrate how this applies to cognitive rehabilitation.

Plasticity can be defined by its capacity for reactive change; the secondary response to a primary change, such as injury. Plasticity is not revealed by the damage but rather the degree of restorative and compensatory strategies observed (Lövdén et al., 2010). Plasticity also relates to the capacity of reactive change in a range of functioning – flexibility. Within Lövdén et al's. (2010) framework, flexibility is understood as the ability to optimise brain performance within the limits of the brain's current structural organismic constraints – the

functional supply. Demands that are placed on the system, such as cognitive tasks, are met using two distinctive systems, flexibility and plasticity. Flexibility reaction demands can be met using the existing functional supply (current representations and processes; see Mercado (2008) for a thorough examination of cognitive representations) and plasticity reaction demands are met through altering the functional supply, and subsequent flexibility, by acquiring new knowledge and processes. In other words, some demands can be met using existing knowledge and processes, whilst others require structural changes to incorporate new knowledge and processes.

Making these distinctions has practical implications within Lövdén et al's. (2010) plasticity framework when considering the proposal of a supply-demand mismatch model (see Figure 8). They postulate that demands placed on the system, within the current limits of the functional supply, can be met flexibly via current representations and processes. This plastic 'resting' stage, or 'Dynamic Equilibrium', meets current demands and is not a manifestation of plasticity. However, in periods of prolonged 'mismatch', by the introduction of a task being at the limit of the current range, such as learning a new language for instance (Figure 8, A), flexibility reactions cannot meet the demand and an impetus for change is established. Likewise, with a decrease in the functional supply, perhaps as a result of injury (Figure 8, B), a prolonged mismatch between environmental demand and optimised functionality is established. Plasticity reactions are required to alter the functional supply, via acquisition of new knowledge or processes. Increasing the functional supply, as a manifestation of plasticity, allows for the outcome of the demands to be met flexibly and restore the dynamic equilibrium. Additionally, introducing a task that the system can easily respond to within the existing flexibility, for instance teaching basic English vocabulary to a proficient English speaker, will not results in a mismatch and consequently no structural changes

(Lovden et al., 2010). Likewise, a task that above the current limit of an individual's capacity, for instance recalling 10,000 digits of Pi, will not result in structural changes as the induvial may give up or utilise an inappropriate strategy (Lovden et al., 2010).

An important distinction is that plastic changes are not initiated by changes of supply or demand, but rather a mismatch between these constructs (Lovden et al., 2010). As such, prolonged decreases in environmental demand will result in a positive supply-demand mismatch (a functional supply above and beyond what is needed) and, analogous to a homeostatic system, the functional supply will be reduced as a manifestation of plasticity. This phenomenon has been observed in animal studies where subjects are placed in an impoverished environment where structural changes are reported (Beaulieu & Colonnier, 1989; Diamond et al., 1975) and even in animal models of MS (Prosperini & Di Filippo, 2019). This homeostatic process has also been observed in a motor activity training task resulting in grey-matter changes (Draganski et al., 2004). Young adults were tasked with learning to juggle for a three-month period and their grey matter was observed, via neuroimaging, before the task, immediately after training period cessation, and again at a three-month follow up period. Draganski et al. (2004) reported grey matter had increased from pre- to post-training and that this reduced at the three-month follow-up period. This study gives evidence for the homeostatic nature of plasticity as the grey matter density rose and fell in line with prolonged mismatch to the system.

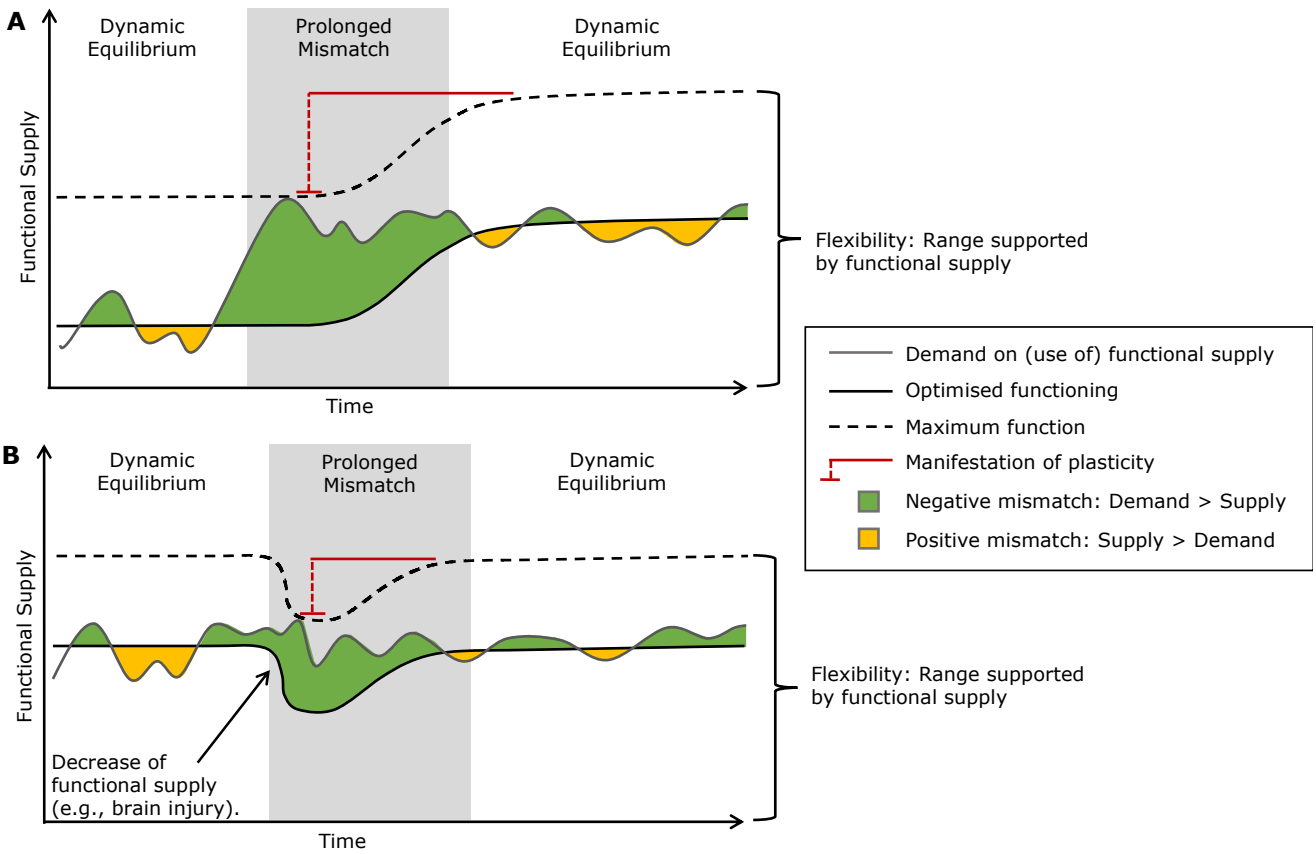

Figure 8: Graphical schematic of the supply-demand mismatch between functional supply and environmental demand, establishing impetus to change. A) Primary increase in demands placed on system (from the environment) increases negative mismatch between demand and supply. B) Primary decrease in functional supply (e.g., from injury), with a relatively stable functional demand, increases mismatch. Adapted from Lövdén et al. (2010).

Lövdén et al. (2010) describe plasticity as a 'sluggish' process. Plastic, or structural changes, must overcome an innate inertia. The brain's relative inertia to structural changes may be neuroprotective; constant and rapid changes in an immediate response to demands would destabilise the system, prevent habit formation, and requires an enormous energy investment to undertake (Lövdén et al., 2010; Siegel & Albers, 1994). Consequently, the proposed mismatch must be to a degree of magnitude and duration for the system to trade stability for plasticity whilst investing vast resources (Bäckman & Dixon, 1992; Lövdén et al., 2010; Piaget & Kesselring, 1983). Finally, within the framework, Lövdén et al. (2010) discriminate knowledge plasticity and process plasticity. Knowledge and process are analogous to the

constructs of Fluid and Crystallised Intelligence respectively (Horn & Cattell, 1966; Lövdén et al., 2010). Studies of normal ageing report that Fluid Intelligence (process) is more closely associated with decline (Lövdén & Lindenberger, 2005) and that age related decreases in crystallised intelligence (knowledge) can be viewed as a consequence of this ageing process, not the cause (Ghisletta & Lindenberger, 2003).

7.4.3. Cognitive Rehabilitation Recommendations

Lövdén et al. (2010) additionally provides a set of recommendations for cognitive rehabilitation based off of their framework. Cognitive rehabilitation should target one central cognitive process with multiple varying practice tasks, as to reduce knowledge acquisition being used to meet the mismatch. A single process, rather than a task with multiple, should increase the magnitude and duration of the mismatch within the confides of limited time and effort. The task needs to be within the upper limits of the functional supply but also at the highest difficulty, if maximum effort is applied (Lindenberger & Lövdén, 2006; Riediger et al., 2006). Training is required to adapt to participants of differing functional supply and scale its difficulty in line with participants' progression, maintaining the mismatch and impetus for change. Finally, the central cognitive process should be generalisable onto a range of ecologically valid behaviours. Of note, regarding the measurement of the supply-demand mismatch, Lövdén et al. (2010) propose time and accuracy (efficiency) recordings as an appropriate means of measuring this construct.

7.5. Cognitive Rehabilitation in MS – State of the Field

The most recent systematic literature review of cognitive rehabilitation in MS was published in 2018 and included papers from January 2007 to March 2016 (Goverover et al., 2018). Their work is a continuation of a previous review of MS specific cognitive rehabilitation from 2003 to 2008 (Cicerone et al., 2011) and from 1993 to 2006 (O'Brien et al.,

2008). A full review is needed at this point as there is now a five-year gap since the most recent and given the accelerating trend of research in this area of late. To meet this need, a systematic review of the literature was completed by the author using the same search procedures, databases, and inclusion/exclusion criteria described in Goverover et al's. (2018) most recent review. Given the nesting of this current review within the context of this portfolio as a whole, certain components such as meta-analysis, quality appraisals, and publication biases could not feasibly be included. The following review's purpose is to portray the current state of the field since the last review, with a focus on study classification following the American Academy of Neurology guidance (Gronseth et al., 2011) and practice standard, guidelines, and options reccomendations (see Cicerone et al., 2011).

A literature search was completed using the following databases: PubMed, PsycINFO, MEDLINE, and CINAHL. The following search terms were used: *multiple sclerosis* AND *cognitive rehabilitation* OR *cognitive remediation* AND *attention, awareness, cognition, cognitive, communication, executive, executive function, language, learning, memory, perception, problem solving, reasoning, remediation, training, processing speed, working memory* (all with OR). The initial search between April 2016 to May 2021 yielded 215 papers of which 27 were duplicates. From the remaining 188 papers, 35 were included in the review. Reasons for exclusion were being a review article (62), non-intervention study (57), no cognitive target (14), same sample/secondary analysis (9), book (2), thesis (1), paediatric sample (1), protocol (1), not empirical (1), not in English (1), MS sample < 50% (1), animal model (1), no access (1), and abstract only (1).

Summary of key study characteristics including domain, participant characteristics, cognitive impairment, classification, treatment and duration, measures, and results are shown in Table 8. The review will

primarily focus on Class I-III studies with the exception of Class IV studies utilising an intervention used in another included study.

When comparing the results between the reviews, their respective search timescales need to be considered. The first, O'Brien et al. (2008), included studies from 1993 to 2007. This review was followed by Goverover et al. (2018), which covered 2007 to 2016. The present review covers a five year gap, compared to nine before, and 14 in the first. Seven Class I studies were identified. Ten Class 1 studies were identified in the previous two reviews. There were also seven Class II studies, compared with 14 over the previous two reviews. Finally, there were 17 Class III studies identified, compared with 27 reported previously. Whilst there are fewer studies overall, when averaging over their respective timeframes, there is a clear increase in both studies undertaken and quality. Between 1993 to 2007 there were on average 2.43 cognitive rehabilitation studies completed per annum, compared with a rate of 7.40 between 2016 to 2021. Goverover et al. (2018), reports an increase in study quality in their review, citing the higher number of Class I studies identified. However, when taken in consideration of the entire field of research, quality appears proportionally the same. Between 1993 to 2016, 17.86% were Class I, 25.00% were Class II, 48.21% were Class III, with the remaining being Class IV. Between 2016 to 2021, 20.00% were Class I, 20.00% were Class II, 48.57% were Class II, and the remainder Class IV. These findings show that, whilst there has been a three-fold increase in rate of publications in this field, quality, when viewed proportionately, has remained stable.

Table 8: Results from the literature review subdivided into cognitive domains.

Domain / Study	Participant characteristics	Cognitive Impairment	Classification	Treatment and Duration	Measures	Results
Attention						
Blair et al. (2021)	30 participants, 15 experimental, 15 control. RR=17, SP=12, PP=1	<1.5 SD on 2 of PASAT, SDMT, DKEFS Colour Word	III	**Cogmed Working Memory Training** 5 weeks, 5 sessions a week, 30–45-minute sessions.	NP, Mood, Fatigue, QoL, Subjective	Mixed
New Learning and Memory						
Brissart et al. (2020)	101 participants. 52 experimental, 49 placebo. PR=22%.	≥2 cognitive functions of NP measures	I	**ProCog-SEP** 6 months, 13 2-hour sessions.	NP, QoL	Mixed
Chiaravalloti et al. (2020)	28 participants, 15 experimental, 13 control. SP=16, PP=10, PR=1	>1.5 SD OT-SRT	I	**modified Story Memory Technique** 5 weeks, 2 sessions a week, 45–60-minute sessions.	NP, QoL, mood	Treatment > Control
Chiaravalloti et al. (2021)	20 participants, 9 experimental, 11 control. RR=13, PP=2, UK=2, SP=2, PR=1.	>1.5 SD OT-SRT	II	**Strategy-based Training to Enhance Memory** 4 weeks, 2 sessions a week, 30–45-minute sessions.	NP, ADL, mood, subjective	Treatment =
Krch et al. (2019)	20 participants, 10 experimental, 10 placebo. RR=100%	<2 perfect recall on two consecutive trials by trial 7 on OT-SRT	I	**modified Story Memory Technique** 10 sessions	NP, QoL, mood	Treatment > Placebo
Lincoln et al. (2020)	449 participants, 245 experimental, 204 control RR=291, SP=112, PP=46	>27 MSNQ >1 SD BRB-N	I	**CRAMMS** 10 weeks, 1.5 hours per session.	NP, QoL, fatigue, mood, subjective	Treatment = Control

Domain / Study	Participant characteristics	Cognitive Impairment	Classification	Treatment and Duration	Measures	Results
Mousavi et al. (2020)	60 participants, 20 experimental, 20 placebo, 20 control. RR=49, SP=11	>2 SD BRB-N	II	**Compensatory strategies** 8 weeks, 1 hour a week	NP	Treatment = Control / Placebo
Shahpouri et al. (2019)	59 participants, 28 experimental, 28 control. RR=39, SP=11, PP=6	Mild to moderate impairment – Everyday Memory Questionnaire	III	**Therapist CR** 10 sessions, 2-hour sessions.	NP, QoL, mood	Treatment > Control
Processing speed and working memory						
Bonzano et al. (2020)	18 participants. RR=12, SP=12	>1.5 SD BRB-N	IV	**COGNI-TRAcK** 8 weeks, 5 sessions per week, 30-minute sessions.	NP, neuroimaging	Post > Pre
Bove et al. (2019)	21 participants. RR=15, PP=4, SP=2	Subjective	IV	**Project:EVO** 4 weeks, 5 sessions a week, 25-minute session.	NP, mood, functional	Post > Pre
Chiaravalloti et al. (2018)	21 participants, 12 experimental, 9 control. RR=100%	<1.5 SD SDMT	I	**Speed of Processing Training** 5 weeks, 2 sessions a week, 30–45-minute sessions.	NP, ADL	Treatment > Control
Covey et al. (2018)	24 participants, 12 MS, 12 HC. RR=11, PP=1	Not stated	III	**N-back** 4 weeks, 5 sessions a week, 25–30-minute sessions.	NP, mood, neuroimaging	Post > Pre
Fuchs et al. (2019)	54 participants. RR=35, SP=12, PP=4	Not stated	IV	**BrainHQ** 12 weeks, 5 sessions a week, 45–60-minute sessions.	NP, mood, neuroimaging, fatigue, subjective	Post > Pre

Domain / Study	Participant characteristics	Cognitive Impairment	Classification	Treatment and Duration	Measures	Results
Pedullà et al. (2016)	28 participants. 14 experimental, 14 control.	>1.5 SD BRB-N	III	**COGNI-TRAcK** 8 weeks, 5 sessions a week, 30-minute sessions.	NP	Mixed
Executive functions						
Sharifi et al. (2019)	20 participants. 10 experimental, 10 control. MS type not reported.	≤20 WCST	III	**Captain's Log** 12 weeks, 2 sessions per week, 50-minute sessions.	NP	Treatment > Control
General / Nonspecific						
Arian et al. (2020)	43 participants, 22 experimental, 21 control. MS type not reported.	Not stated	III	**RehaCom** 10 sessions, 60-minute sessions.	NP	Treatment > Control
Arsoy et al. (2018)	81 participants, 21 benign MS (10 experimental), 22 non-benign MS (RR=14, SP=8), 38 HC.	Not stated	III	**Norosoft** 5 sessions a week, 50-minute sessions	NP, Mood, ambulatory	Mixed
Barbarulo et al. (2018)	63 participants, 32 experimental, 31 control. PP=54, RR=9	Impairment in 1 of: BRB-N, FAB, RCPM, Forward/Backward verbal span, Spatial span, Stroop, PVF	II	Experimental – **ERICA** + Neuromotor 24 weeks, 30 minutes CR and 30 minutes neuromotor Control - Neuromotor 24 weeks, 30 minutes neuromotor	NP, ambulatory, mood	Treatment > Control

Domain / Study	Participant characteristics	Cognitive Impairment	Classification	Treatment and Duration	Measures	Results
Campbell et al. (2016)	38 participants, 19 experimental, 19 control. RR=27, SP=11.	<5th percentile on 1 of BICAMS	II	**RehaCom** 6 weeks, 3 sessions a week, 45-minute session.	NP, QoL, mood, functional, subjective	Mixed
Charvet et al. (2017)	135 participants, 74 experimental, 61 control. PP=89, SP=35, PP=7	<1 SD SDMT	I	**Adaptive Cognitive Remediation** 12 weeks, 5 sessions a week, 60-minute sessions.	NP	Treatment > Control
Chmelařová et al. (2020)	43 participants, 26 experimental, 17 control. MS type not reported.	Not stated	III	**Happy Neuron Brain Jogging** 8 weeks, 4 sessions a week, 30-minute sessions.	NP, mood, subjective	Treatment > Control
Di Giglio et al. (2016)	24 participants, 12 experimental, 12 control. MS type not reported.	One of: <10th percentile SDMT or PASAT, < 3 Stroop	III	**Dr Kawashima's Brain Training** 8 weeks, 5 sessions a week, 30-minute sessions	NP, neuroimaging	Treatment > Control
De Luca et al. (2019)	40 participants, 20 experimental (CCR), 20 control (CR). RR=100%	>18 MoCA	II	**ERICA CCR** 8 weeks, 3 sessions a week, 45-minute sessions	NP, QoL, mood	CCR > CR
Impellizzeri et al. (2020)	30 participants, 15 experimental (NMT), 15 control (CR). RR=15, SP=8, PP=7	Not stated	I	Experimental - **Neurologic Music Therapy** 8 weeks, NMT 3 sessions a week, CR 3 sessions a week. Control – **CR** 8 weeks, CR 6 sessions a week	NP, QoL, motivation, mood.	Mixed
Kober et al. (2019)	14 participants. RR=13, SP=1	Not stated	IV	**Neurofeedback** 3-4 weeks, 10 sessions, 21-minute sessions	NP	Mixed

Domain / Study	Participant characteristics	Cognitive Impairment	Classification	Treatment and Duration	Measures	Results
Lamargue et al. (2020)	56 participants, 35 MS (18 specific CR, 17 non-specific CR), 21 HC. RR=29, SP=4, PP=2	3 scores < 1 SD on selected NP (see paper)	III	Specific – **REACTIV** 4 months, 3 sessions a week, 45-minute sessions	NP, QoL, ADL, neuroimaging	Specific > Non-Specific
Maggio et al. (2020)	60 participants, 30 experimental (sVRT), 30 control (CCR). MS type not reported.	>18 MoCA	III	**semi-immersive Virtual Reality Training** 8 weks, 3 sessions a week, 60-minute session	NP, mood, ambulatory	sVRT > CCR
Mani et al. (2018)	34 participants, 17 experimental, 17 control. RR=100%	>70 ACE	III	**Group CR** 4 weeks, 1 session a week, 2 hour a session	NP	Treatment > Control
Messinis et al. (2017)	58 participants, 32 experimental, 26 control. RR=100%	> 1.5 SD CNSVS	III	**RehaCom** 10 weeks, 2 sessions a week, 60-minute session	NP, mood, fatigue	Treatment > Control
Messinis et al. (2020)	36 participants, 19 experimental, 17 control. SP=100%	> 1.5 SD CNSVS	II	**RehaCom** 8 weeks, 3 sessions a week, 45-minute session	NP, mood, fatigue, QoL, subjective	Treatment > Control
Rahmani et al. (2020)	36 participants, 12 experimental, 12 control, 12 placebo. RR=100%	10-20 MMSE	III	**Pars Cog Rehab Package** 21 weeks, 60 minute a week	NP	Treatment > Control / Placebo
Reilly & Hynes (2018)	12 participants RR=5, UK=4, PP=3	>22 MSNQ	IV	**COB-MS** 2 individual sessions, 6 group sessions. 60-minute session	Daily life occupation, subjective, NP	Post > Pre

Domain / Study	Participant characteristics	Cognitive Impairment	Classification	Treatment and Duration	Measures	Results
Rilo et al. (2016)	42 participants, 21 experimental, 21 control. RR=32, SP=9, PP=1	Not stated	III	**REHACOP** 13 weeks, 3 sessions a week, 60-minute session	NP, IQ, mood, fatigue	Treatment > Control
Stuifbergen et al. (2018)	183 participants, 93 experimental, 90 control. RR=125, SP=24, UK=17, PP=8, BS=6, PR=2	≥10 PDQ	III	Experimental - **MAPSS-MS** Control – **Braingames** Group – 8 weeks, 2 hour a week, computer – 8 weeks, 3 sessions a week, 45-minute session.	NP, IADL	Treatment = Control AND Both post > pre
Vilou et al. (2020)	47 participants, 23 experimental, 24 control. RR=100%	>1.5 SD BICAMS	III	**Brain HQ** 6 weeks, 2 sessions a week, 40-minute session	NP	Treatment > Control

Notes: **Participant Characteristics:** RR – Relapse Remitting, PP – Primary Progressive, SP – Secondary Progressive, PR – Progressive Relapsing, BS – Benign Sensory, UK – Unknown, HC – Healthy Control.
Cognitive Impairment: PASAT – Paced Auditory Serial Addition Test, SDMT – Symbol Digit Modalities Test, DKEFS – Delis-Kaplan Executive Function System, OT-SRT – Open-Trial Selective Reminding Test, MSNQ – MS Neuropsychological Screening Questionnaire, BRB-N – Brief Repeatable Battery of Neuropsychological Tests, WCST – Wisconsin Card Sorting Test, FAB – Frontal Assessment Battery, RCPM – Raven's Coloured Progressive Matrices, PVF – Phonemic Verbal Fluency, BICAMS – Brief International Cognitive Assessment for MS, MoCA – Montreal Cognitive Assessment, ACE – Addenbooke's Cognitive Examination, CNSVS – Central Nervous System Vital Signs, MMSE – Mini-Mental State Examination, PDQ – Percieved Deficits Questionnaire.
Treatment and Duration: CR – Cognitive Rehabilitation, CCR – Computerised Cognitive Rehabilitation, ProCog-SEP – Programme de remédiation Cognitive chez les personnes atteintes de Sclérose En Plaques, CRAMMS – Cognitive Rehabilitation for Attention and Memory in people with MS, NMT – Neurologic Music Therapy, COGNI-TRAcK – Cognitive Training Kit, ERICA - Esercizi di Riabilitazione Cognitiva, COB-MS - Cognitive Occupation-Based Programme for people with MS, MAPSS-MS – Memory, Attention, and Problem Solving Skills in MS.
Measures: NP – Neuropsychological, QoL – Quality of Life, ADL – Activities of Daily Living, I-ADL – Instrumental Activities of Daily Living, IQ – Intelligence Quotient.

Considering prior recommendations for future studies to more closely follow American Academy of Neurology classification of evidence guidelines (Goverover et al., 2018), the above findings indicate that this is still an area that needs further development. A number of studies did not reach Class I due to two common methodological and/or reporting errors – concealed allocation and defining the primary outcome. Four of the Class II studies failed to clearly define their primary outcome (Barbarulo et al., 2018; De Luca et al., 2019; Ernst et al., 2016; Mousavi et al., 2020); additionally, Chiaravalloti et al., (2021) reported a different primary outcome in their abstract than in the main body of their text. The remaining two Class II studies did not conceal their group allocation (Campbell et al., 2016; Messinis et al., 2020).

7.5.1. Attention

Only one study was found to target the attention domain specifically (Blair et al., 2021) which was a Class III study due to a high drop-out rate (26%) and no concealed allocation. The study utilised the Cogmed Working Memory Training program (Shinaver et al., 2014), which was not found to be superior to the control group, though a within group improvement on one of the three primary outcome measures (Delis-Kaplan Executive Function System Colour-Word Interference Test. DKEFS-cw; Delis et al., 2001) was observed in the experimental group. The Cogmed intervention is of relatively high intensity with 25 sessions of 30–45-minute in length engaged with the intervention, in addition to an assigned 'qualified coach' who provides feedback, motivation, and structure (Blair et al., 2021). Sessions train both verbal and spatial working memory tasks. For instance, verbal tasks may include remembering letters or numbers, and spatial may include remembering where an object was on a 16 square grid (Blair et al., 2021). This intervention has not been used previously and does not reach the same recommendations based on evidence as other

Attention interventions have achieved previously (Amato et al., 2014; Cerasa et al., 2013).

7.5.2. New Learning and Memory

A total of seven studies examined rehabilitation of New Learning and Memory specifically. The modified Story Memory Technique (Chiaravalloti et al., 2015) has already reached Practice Standard recommendations based off of a previously reported well designed Class I study (Chiaravalloti et al., 2013). This recommendation is further supported by two additional Class I studies, with positive results, using this intervention (Chiaravalloti et al., 2020; Krch et al., 2019). Additionally, these findings also provide preliminary evidence in the adaption of the modified Story Memory Technique to be used in another language than English (Spanish) and that this intervention has a moderate-large effect size on quality of life measures (Krch et al., 2019). The modified Story Memory Technique aims to develop imagery and context skills. Training is split into three distinct phases: (i) participants create visual aids to help remember a presented story; (ii) participants are presented a list of words and tasked with embedding these words in a story which they then visualise; and (iii) applying these techniques to real world contexts (Chiaravalloti et al., 2020).

Two additional Class I studies were reported but either had mixed (Brissart et al., 2020), or control equivalent outcomes (Lincoln et al., 2020). A Class II study exploring the effects of compensatory memory strategies found that this intervention was not superior to either control or placebo (Mousavi et al., 2020). The final Class II study, Chiaravalloti et al. (2020), was an intervention based off previous studies of self-generation and spaced learning tasks. As stated previously, this study was downgraded to Class II as a result of primary outcome reporting discrepancies; however, their STEM-Strategy Based Learning intervention was not superior than the control condition. One Class III

study (Shahpouri et al., 2019) was reported for this domain. Their intervention was one of the few non-computerised in the review. It comprised of 10 sessions with a therapist, each 2 hours long, focusing on reinforcement, consolidation, and compensation strategies. Their results showed superior outcomes for the experimental group.

These findings provide further support for the recommendation of modified Story Memory Technique as a Practice Standard in New Learning and Memory rehabilitation in MS.

7.5.3. Processing Speed and Working Memory

Six studies were identified that focused primarily on Processing Speed and/or Working Memory. The Speed of Processing Training intervention was evidenced in a Class I study (Chiaravalloti et al., 2018) that reported positive outcomes in both processing speed and activities of daily living. This study's generalisability onto the wider MS population is limited via its inclusion criteria of Relapse Remitting MS subtype exclusively and relatively small sample size. The Speed of Processing Training intervention is a computerised offering consisting of three types of tasks: simple speed of processing; divided attention; and selective attention (Chiaravalloti et al., 2018). Task types are presented sequentially with progression to the next dependant on a 75% accuracy and predetermined task relative reaction time. The first task, simple speed of processing, is a stimulus discrimination test with task variation in deriving stimulus presence/absence, identification, and same/different judgements (Chiaravalloti et al., 2018). The second task, divided attention, presents a task from the first stage with an additional requirement of locating a peripheral target. The final stage, selective attention, adds the additional component of distracting stimuli to the divided attention task.

There was mixed evidence for the COGNI-TRAcK (Tacchino et al., 2015) intervention, with a Class IV study reporting within group improvements (Bonzano et al., 2020) and a Class III study reporting mixed results (Pedulla et al., 2016). The CONGNI-TRAcK intervention focuses on improving Working Memory which is attempted through the use of N-Back, Dual N-Back, and a visuospatial task (Tacchino et al., 2015). In the N-Back, participants are presented with a series of single digit calculations (e.g. first operation = 1+2, second operation = 2+3). Under the N=0 condition, the correct responses are 3 and 5 respectively. In the N=1 condition, participants delay their response, in this it is meant that the correct responses for the second presented operation is the one (N=1) preceding it, 3 in this case. The task increases in complexity as N increases, requiring the participant to hold previous answers for a greater span of operations. The Dual N-Back presents a single digit with a varying orientation (four possible positions, two orientated to left or right). Similar to above but with the additional requirement of responding to which orientation the presented stimulus was in (left or right), this task increased in complexity as N increases. Finally, the visuospatial task presents participants with a 3x3 grid where a coloured circle will appear in a random sequence. Participants must correctly reproduce the sequence within the grid (Tacchino et al., 2015). Another Class III study, Covey et al. (2018), also utilised the N-Back task. They reported improved outcomes in their MS sample when compared to the healthy controls.

Initial findings from the Speed of Processing Training study are promising, however a larger and more representative sample are needed to develop this interventions evidence base. There were mixed results for interventions that utilised some version(s) of the N-Back training task.

7.5.4. Executive Functioning

Only one study was reported for targeting Executive Functioning (Sharifi et al., 2019). This study was defined as Class III as the authors did not clearly define their primary outcome and due to the design having no concealed allocation. Whilst the study reported promising experimental group performance on the Wisconsin Card Sorting Test (Grant & Berg, 1993), it was hindered by its lack of any secondary outcome measures or ecologically valid assessments of Executive Functioning. They utilised the Captain's Log intervention (https://www.braintrain.com/captains-log-mindpower-builder/) which is reportedly comprised of over 2,000 exercises for 20 different cognitive skills. Sharifi et al. (2019) reported the use of two specific exercises, but they fail to adequately describe the exercises in their paper to report them within this review. The exercises appear to be analogous to the go/no-go paradigm of stimuli discrimination and response inhibition.

7.5.5. General / Non-Specific

The General / Non-Specific domain included the highest number of studies with a total of 20. There were two Class I studies, four Class II, 12 Class III, and 2 Class IV. A large Class I study (Charvet et al., 2017), using the Adaptive Cognitive Remediation (https://www.brainhq.com) intervention, showed superior outcomes in the experimental group. The efficacy of this intervention is still debatable given the small effect size (d = .39) and that the only significant change was reported in a neuropsychological battery composite score and not on any individual domain measure. Additionally, they did not measure any secondary outcomes such as mood, fatigue, or quality of life. Adaptive Cognitive Remediation applies a Bayesian algorithm to alter trial challenge for each participant (Charvet et al., 2017). It reportedly maintains a stable difficulty resulting in participants completing approximately 80% of trials

successfully – maintaining challenge but also reducing frustration from failure. It should be noted that Adaptive Cognitive Remediation is a research specific version of the commercial BrainHQ program that was used by another Class III study (Vilou et al., 2020). Comparison between these two studies is hindered by an unknown difference between the research offering and the commercial product and if they used the same exercises. Vilou et al. (2020) also showed superior results in their experimental group compared to control but at on an individual measure level. Similar to the other study using this intervention, Vilou et al. (2020) also only collected neuropsychological outcomes. This intervention is comprised of 15 exercises that target attention, processing speed, working memory, and executive functioning in both auditory and visual stimuli. The other Class I study in this domain (Impellizzeri et al., 2020) explored the effects of Neurologic Music Therapy (Thaut, 1989) in conjunction with conventional cognitive rehabilitation in their experimental group compared against a conventional cognitive rehabilitation only group. Whilst their outcomes were, overall, mixed, there was an improved outcome for quality of life and motivation in the experimental group.

Two Class II studies (Campbell et al., 2016; Messinis et al., 2020) and two Class III studies (Darestani et al., 2020; Messinis et al., 2017) explored the effects of the RehaCom intervention (https://www.rehacom.co.uk/). Messinis et al. (2020) showed the most promising positive results over a range of neuropsycholgical measures and secondary measures of mood, quality of life, and fatigue. However, this study was limited by its specific inclusion of Secondary Progressive MS participants only. The other Class II study, Campbell et al. (2016), showed less impressive results with improvements only observed on the SDMT, which was not sustained to follow-up. Two Class II studies (Barbarulo et al., 2018; De Luca et al., 2019) reported the use of the ERICA intervention (Inzaghi, 2013). Both studies' quality

of evidence was hampered by the unclear definition of their primary outcomes. De Luca et al. (2019) compared computerised cognitive rehabilitation (ERICA) against conventional cognitive rehabilitation and found the ERICA condition to be superior. As with other studies, they recruited an entirely Relapse Remitting MS subtype sample. Barbaulo et al. (2018) conducted an integrated intervention comparison study with the experimental group combining ERICA and motor therapy and the control group receiving motor only. The experimental group showed superior outcomes. Additionally, the experimental group showed greater motor outcomes even when receiving half the dose as the control group.

Five additional Class III studies, all using different interventions, showed their experimental condition to have superior outcomes compared to their control group (Chmelařová et al., 2020; De Giglio et al., 2016; Mani et al., 2018; Rahmani et al., 2020; Rilo et al., 2018). A further three reported within group improvements with varying interventions (Maggio et al., 2020; Reilly & Hynes, 2018; Stuifbergen et al., 2018). Of note, Larmague et al. (2020) showed specifically adapted cognitive rehabilitation to the individual participant to be superior to a non-tailored approach. Their findings are questioned as there were signifcant differences between condition baseline scores in key metrics.

RehaCom remains the most commonly used cognitive rehabilitation intervention in MS. It was rated as a Practice Guideline in Goverover et al's. (2018) review for General / Non-Specific domains. The present review only identifies one Class II study that supports its implementation. Class I and III studies of Adaptive Cognitive Remediation Therapy are promising. However, the lack of data on secondary outcomes, in addition to only observing composite score improvements, limits the understanding of both intervention's broader

effects and which domain it targets. It could be beneficial for other studies to employ the use of certain theoretically sound mechanics, such as their Bayesian algorithm. The Neurological Music Therapy appears to be a promising adjunct intervention to support quality of life and motivation. Finally, the two studies using ERICA also showed promising results. Larger well designed RCTs would help build the evidence base for this intervention.

7.5.6. Review Summary

Whilst there has been a three-fold increase in the rate of published cognitive rehabilitation studies, the relative ratio of quality remains stable. Common omissions of not concealing group allocation or unclearly defining the primary outcome have reduced the overall quality of studies in this field. There were potential changes in the recommendations based on new evidence. The Working Memory and Processing Speed domain showed a promising intervention in Speed of Processing Training and General / Non-Specific domain with Adaptive Cognitive Remediation / BrainHQ. However, the number, quality, and methodological concerns potentially hinder their application without further development. Previous recommendations are supported by additional evidence, such as the modified Story Memory Technique and the RehaCom.

The number of studies exploring interventions targeting the Attention domain appear to decreased compared with previous reviews. Only one was reported, down from three in the most recent review (Goverover et al., 2018). Attention, as a construct, seems to have been chiefly amalgamated into Processing Speed and Working Memory as numerous studies reported measuring both. Additionally, the only Attention study utilised a Working Memory intervention (Blair et al., 2021). This confusion is exemplified in the measurement of these domains. For instance, the SDMT, RBANS Coding task, and Weschler

adult Intelligence Scale-III (WAIS-III; Wechsler, 1997) Coding subtest are all digit symbol substitution tasks, with near identical protocols. Yet the WAIS-III Coding subtest and the SDMT are both processing speed measures, with the latter being the most commonly used processing speed measure in MS (Benedict et al., 2017), and the RBANS Coding task being one of two tasks that inform the Attention index. Of note, when considering measurement of outcomes is how it relates to the intervention. In particular, memory rehabilitation interventions that utilise compensatory strategies may have ecological use (if employed) but are also difficult to measure with neuropsychological assessments. Sumowski et al. (2018) state that many standardised measurements of memory are designed to prevent or hinder the use of compensatory strategies – potentially cancelling the interventions effect.

Twenty-four out of the 36 studies included collected outcomes on at least one additional secondary outcome such as mood, fatigue, and QoL. Future studies need to develop on the inclusion of such measures. For instance, quality of life is often negatively impacted in MS (Benito-León et al., 2003; Gil-Gonzalez et al., 2020; Hyarat et al., 2019; Yalachkov et al., 2019) along with mood (Mitchell et al., 2005) therefore rehabilitation studies should examine the effect their intervention has on these outcomes. Furthermore, such outcomes would not only allow for additional analysis into mood's mediating effect in cognitive performance in MS (Arnett, 2005; Arnett et al., 1999; Feinstein, 2006) but also the exploration of the possible iatrogenic impact related to the intervention.

The majority of the interventions reported in this study were computerised. The benefits completing interventions at home has been highlighted in the context of this current pandemic (Mantovani et al., 2020; Shaw et al., 2021); the remote nature of these interventions has allowed for the continuation of care. Additionally, these benefits

will extend beyond current circumstance as many people with MS struggle with mobility and attending clinics which may be further impeded by where they live (Mantovani et al., 2020). Further development of remote computerised interventions, of equitable or superior quality to that of face-to-face, need a greater evidence base and ease of implementation to support this use. Additionally, as shown in Section 7.1., MS prevalence rates are increasing globally, yet this research is primarily western based. The remote nature of the interventions may facilitate uptake and use in other regions, but we must also consider access to the required instruments. Interventions should also be designed in a way allowing for feasible translations into other languages.

Many cognitive domains are impacted in MS and a recent longitudinal analysis, using Event-Based Modelling (EBM; Fonteijn et al., 2012), of the cognitive domain impairment progression in MS, as measured by neuropsychological tests, report a particular sequence of impairments (Wojcik et al., 2021). The most probable sequence of impairment on tests is as follows: (i) SDMT; (ii) Brief Visuospatial Memory Test–Revised (Benedict et al., 1996) / California Verbal Learning Test, 2nd Edition (Delis, 2000); (iii) Paced Auditory Serial Addition Test (Fischer et al., 1999); (iv) DKEFS Card Sorting Test total correct sorts; and (v) DKEFS Card Sorting Test description score. These results indicate that Processing Speed is the first domain to be impaired in MS disease progression and Executive Functioning the last. Whilst the impacts of Processing Speed interventions would have on this sequence of progression have not yet been explored, it could be suggested to be theoretically sound to target a prevalent upstream impairment. These findings also support the implementation of general / non-specific interventions that can adapt in line with any potential progression and development of an impairment in a novel domain.

7.6. Derived Relational Responding and Intelligence Behaviours

The following section will describe derived relational responding's role in relation to intelligence behaviours, their relation to clinically significant cognitive skills, and its subsequent training. However, the construct of 'Intelligence', as abstracted from Intelligence Quotient (IQ) scores, needs to be operationalised within the parameters of this study.

The behaviourist tradition has a difficult relationship with the concept of an underlying intelligence, or factor 'g' (Spearman, 1904). Skinner (1974) rejected the term which would posit that intelligence is the *cause* of observable behaviour. In contrast, Cassidy et al. (2010) argues that certain cognitive skills underpin the behavioural repertoires observed and measured in IQ assessments. Lohman (2001) report a useful distinction in how intelligence is viewed in psychology from a population-level and essentialist biologist position with the use of Mayr's (1982) biological thinking. In essence, population thinking operates through population-level patterns, variations, and diversity. This position is in contrast with the essentialist biologist, or psychologist, who investigate functional properties and relationships through the experimental manipulation of variables (Cassidy et al., 2015). From a population-level perspective, IQ scores remain relatively stable over life and across population, and this observation leads to the potentially erroneous assumption that intelligence, as abstracted from IQ measures, is an immutable trait (Gardner, 1992). Cassidy et al. (2010) argues that as IQ is a population-level construct that retains its utility in prediction and correlations to related constructs, if *"all other things being equal".* For instance, variables such as education and gender are controlled for, and age is adjusted for in score calculations. The stability of IQ scores is further questioned by the Flynn effect (Flynn, 1998; Flynn, 2007); the steady increase in IQ performance over time at a population-level leading to tests being re-designed to

control for this effect. Cassidy et al. (2010) also states that due to inherent standardisation methods of these assessments, any expected improvements in test performance, as a result of age or practice, are strictly controlled for. From the behaviourist – experimental – perspective the challenge of operationalising intelligence lies in the requirement of being able to reliably manipulate an observable behaviour.

However, what if the condition that *all other things being equal* was manipulated? More recently, there is a growing consensus challenging the concept of intelligence as a trait and is rather influenced by experience and the environment (Nisbett et al., 2012). The stability, and immutability of intelligence, is further challenged by decreases in IQ scores in children who experienced a prolonged absence from schooling (Ceci, 1991; Coleman et al., 1973), the increase in scores following additional schooling (Brinch & Galloway, 2012), and the positive effect of specific educational interventions (Campbell et al., 2001; Campbell et al., 2002; de Acedo Lizarraga et al., 2003; Garber & Begab, 1988; Hernstein et al., 1986). Such findings open discussions around what experiences have an impact on IQ scores, can these behaviours be trained, and does this manipulation alter IQ scores?

Derived Relational Responding (previously summarised in Section 2.3.) has previously been described to underpin a broad range of intelligent behaviours (Cassidy et al., 2015). The evidence supporting the concept that intelligence is a set of hierarchal operant units is growing (Hayes et al., 2021). A correlational study reported a significant relation between temporal relational skills with perceptual organisation and verbal comprehension in the WAIS-III (O'Hora et al., 2008). In addition Dixon et al. (2018) examined the relationship between relational skills and IQ with those diagnosed with an Intellectual Disability. They reported a significant relationship between relational skills and IQ

scores as measured by the Weschler Adult Intelligence Scale-IV (WAIS-IV; Wechsler, 2008)

As stated in Hayes et al. (2021), relating is an operant and can be trained through targeted contingency learning. Numerous studies have now been completed providing supporting evidence that targeted multiple exemplar relational training can improve IQ scores. Cassidy et al. (2011) conducted a training against control group study exploring the effects of relational training. The training group's average IQ scores increased from 105.50 to 132.75 and the control group's scores decreased from 106.50 to 104.50. Additionally, 87.50% of the training group showed an increase of at least one standard deviation. For all showing an increase in scores, these results were maintained at four-year follow-up and remained significantly higher than their baseline scores (Roche et al., 2013). Cassidy et al. (2016) performed two experiments using relational training, one with a sample age ranging from 10 to 12 year and the second with a sample age ranging from 15 to 17 years. In their first experiment, all of the 15 participants' IQ scores increased by at least one standard deviation. The second experiment with the older sample only showed significant increases in verbal and numerical reasoning.

Intelligence, as measured by IQ tests, has previously been described as one of the key factors in Cognitive Reserve and is involved in mediating the effectiveness of cognitive rehabilitation in MS (Castelli et al., 2020). IQ scores have been shown to have a strong relationship with neuropsychological measures. Those with above average IQ scores outperformed those with average IQ on every neuropsychological measure used, and regression models reported IQ predicts neuropsychological performance (Diaz-Asper et al., 2004). These findings are further supported in a study exploring this relationship with children (Foley et al., 2009). Even within the MS

cognitive rehabilitation field, IQ subtests (specifically the WAIS-III Coding subtest), have been used as the primary outcome measure in a Class I study (Chiaravalloti et al., 2018). Colbert et al. (2018) report in their paper of the potentially beneficially impact such training could have on important environmental outcomes as higher IQ scores have are shown to the be the strongest predictor of job performance (Hunter, 2017; Hunter & Schmidt, 1996; Ree & Earles, 1992), income (Lynn & Vanhanen, 2005; Neisser et al., 1996; Zagorsky, 2007), and happiness (Ali et al., 2013).

Following the rationale that relational responding has been evidenced to increase IQ scores and that IQ scores are closely related to neuropsychological measures and its mediating role in cognitive rehabilitation outcomes, there is a logical step to explore the relationship between relational training and neuropsychological measures.

7.7. Summary and Aims

7.7.1. Summary

MS is a highly prevalent disease with evidence of increasing rates across the world. The disease has a complex and not yet fully understood pathophysiology that, in short, causes widespread damage to the Central Nervous System, disrupting or even terminating cellular transmission. Proximal effects are reported through the measurement of cognitive functioning with impairments observed over multiple domains. This neuronal damage is not purely limited to cognitive performance but can additionally impact on mood, fatigue, quality of life, and experience of pain. These experiences may lead to secondary impacts such as having to leave work prematurely or increased strain in relationships.

Theories of how protective factors relate to mitigating damage to the brain and how it can recover have been discussed. A model of neuronal plasticity is presented that has a particular purpose of being applied in cognitive rehabilitation with its accompanying recommendations.

A literature review of cognitive rehabilitation has shown that is an expanding field, but the quality of the evidence remains mixed and has not improved, in relative terms, as stated elsewhere. Common omissions are made reducing the classification of the evidence provided. There are promising developments in this field and authors are urged, as they have been before, to measure secondary outcomes in addition to their focus on neuropsychological measures. The rise of computerised interventions feels of particular use given the current context of a global pandemic and further supporting people with MS to access potentially beneficial interventions.

Finally, the evidence of intelligent behaviours as operant behaviours that can be trained has been presented. In addition, how these behaviours may relate to clinically relevant cognitive domains has been shown.

7.7.2. Aims

- Explored differences in objective assessment of cognitive functioning across the study for each participant. Subtest level comparisons were also explored where available.
- Explored differences in secondary outcome measures for each participant across the study. Subcategories were explored where available.
- Investigated the presence of any phase contrast on repeated subjective measurements of cognitive functioning. Phases defined as baseline (A) and intervention (B).

- Explored changes in trend, variability, and median values of subjective reports of cognitive functioning across phases.
- Investigated the potential role of relational responding by logically comparing observed changes in this measure against outcomes. This relationship was explored statistically where appropriate.
- Assessed if study materials, intervention, and procedure were deemed acceptable, practical, and feasible according to participants' feedback. Completion rates of measures were examined to support this.
- Explored any differences between completers and non-completers.

8. Extended Methods

8.1. Ethics

Ethical approval was granted by the Health Research Authority and the East Midlands – Nottingham 2 Research Ethics Committee on the 14th of April 2020; copies of the ethics approval letters are provided in Appendix B. Nottingham University Hospitals NHS Trust completed their assessment of their capacity and capability to deliver the study and provided approval on the 7th of August 2020.

Two amendments were made to the study following approval and both were non-substantial and not requiring a study-wide review. In the first amendment, the general neuropsychological battery was changed from the Cogstate Brief Battery (https://www.cogstate.com/), as funding could not be secured to access this resource. The RBANS was employed in its stead. The second amendment consisted of adding in previously missing information regarding demographic data collection procedures into the study protocol. Additionally, in the second amendment, the sample size was increased from eight to nine participants. The rationale

for this increase was to balance the number of participants in each of the three baseline lengths.

8.2. Epistemological Position

Relational Frame Theory operates within the philosophy of science of Functional Contextualism; its goals of analysis are to predict and influence psychological events (Biglan & Hayes, 1996; Fox, 2006b). Functional Contextualism has a root metaphor of 'act-in-context', a current event is informed by historical context, and a pragmatic truth criterion whereby non-functional ideas are rejected no matter how well they 'mirror' reality (Biglan & Hayes, 1996; Fox, 2006a). SCEDs, whereby an independent variable is modulated to investigate causal relation on a dependant variable, lends itself to the epistemological position of Functional Contextualism through the prediction and influence of these events (Smith, 2012).

8.3. Recruitment Procedure

The study recruited from the Nottingham University Hospital NHS Trust's MS clinic and from the local MS PPI group.

For MS clinic recruitment: the initial approach was made from a member of the patient's usual care team, and information about the study will be provided at this point (see Appendix C for the Participant Information Sheet). Contact details for members of the research team were provided in the study information packs. Staff from the usual care team directed interested potential participants to these contact details.

For MS Patient and Public Involvement group: the research group has a database of the MS Patient and Public Involvement group who are routinely informed about ongoing studies through their newsletters. Interested parties were able to contact the researchers to find out more about the study.

We explained to each potential participant that entry into the study is entirely voluntary and that their treatment and care will not be affected by their decision. We explained that they can withdraw at any time, but attempts will be made to avoid this occurrence. In the event of their withdrawal we explained that their data collected so far cannot be erased and would seek consent to use the data in the final analyses where appropriate.

8.4. Study Procedure

An illustration of the participants' journey through the study can be found in Figure 9*,* the measures to be used and the timepoint that they are to be administered can be found in Table 2 (Section 3.2.).

Screening (S): once recruited and having provided consent (see Appendix D for consent form), participants completed screening (S). The SDMT is the objective screening measure. During screening participants created their own idiographic Personal Questionnaire. The participant's details were then anonymised and provided with a subject number to use on their survey responses and provided with login details for the SMART program.

Baseline Length: See Journal Paper (Section 3.2.)

Assessment (A_1): all participants completed the Relational Abilities Index, RBANS, MFIS, HADS, and the MSQOL-29 at first assessment time-point (A_1), which is also the baseline measurement. The results from the screening timepoint were incorporated into the A_1 data when reporting the results.

Assessment (A_2–A_3): all participants completed PQ at weeks A_2 and A_3. Baseline A started the SMART training after A_3.

Assessment (A_4): participants in baselines B and C completed the PQ. Baseline B started the SMART training after A_4.

Assessment (A_5): only participants in baseline C completed the PQ. Baseline C started the SMART training after A_5.

Training (T_1–T_{12}): after the completion of their respective assessment phase (A_1-A_5), participants began the 12-week training phase (T_1-T_{12}). Every other week, the participants were required to complete the Relational Abilities Index. The participant completed the PQ weekly. Participants were asked to complete 45 minutes of SMART training per week. The participant was asked complete this schedule for the full 12 weeks (T_1-T_{12}). At T_6 participants completed the same measures as described in A_1. Participants were asked if they would like to receive an optional weekly call to check in issues surrounding the training.

*Follow-Up 1 (F_1)**:*** in the week immediately after the end of training (T_{12}) the participants completed the Relational Abilities Index, SDMT, RBANS, HADS, MFIS, and the MSQOL-29. The participant completed all measures, except the SDMT and RBANS on Qualtrics. The *Feedback Interview* was conducted after this assessment at the participants earliest convenience. These interviews were completed by an independent researcher who had not previously been involved with the project.

Follow-Up 2 (F_2): *t*hree months from the end of the training (T_{12}) the participants will follow the same procedure as *Follow-Up 2* (F_2) with the exception of the *Feedback Interview.*

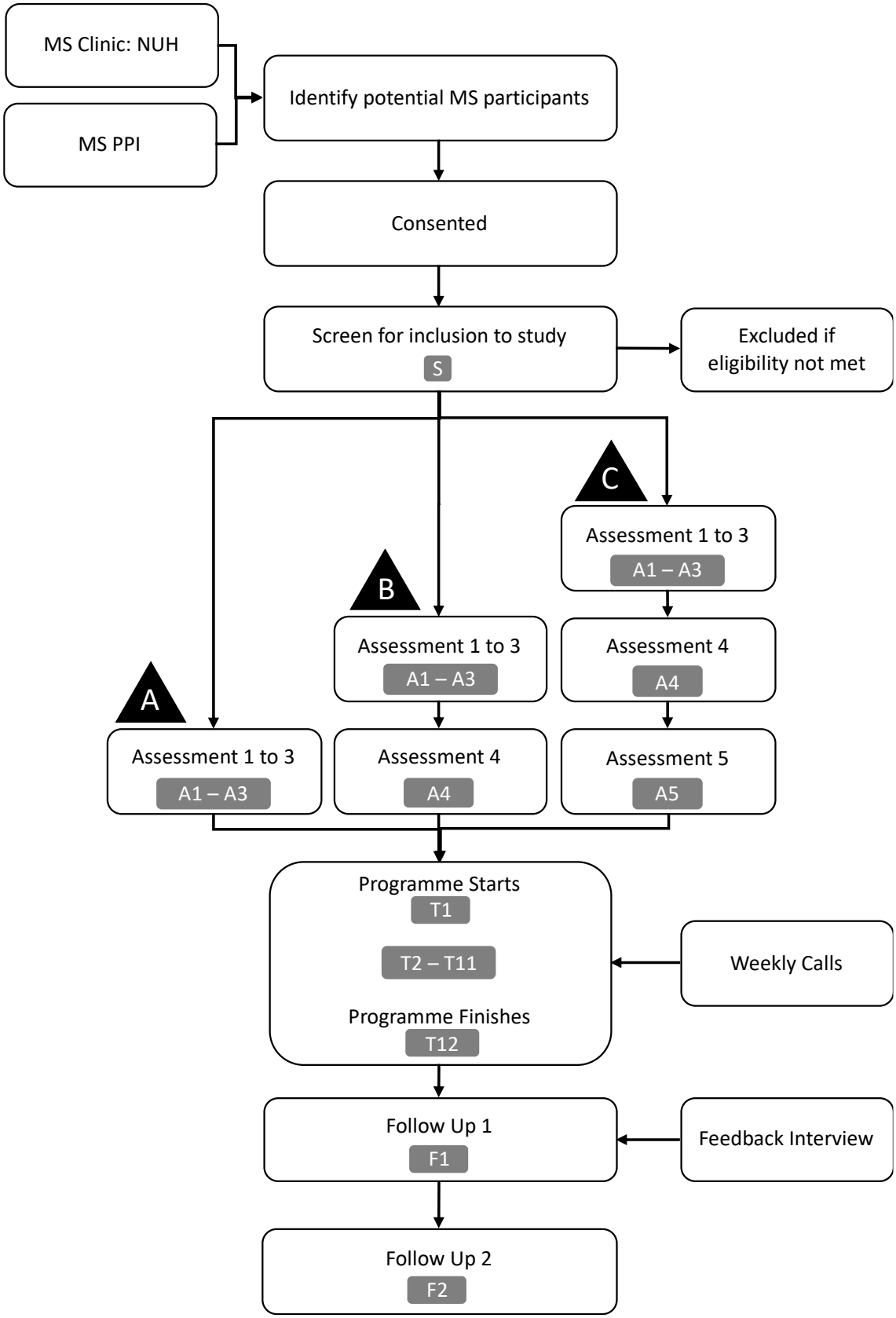

Figure 9: Flow chart representing Participants' journey through the study and baseline differences.

8.5. Selection of Measures

Quality of Life, Mood, and Fatigue measures were chosen drawing from the recommendations presented by the National MS Society (https://www.nationalmssociety.org/). The SDMT was included as it is commonly used in MS literature for processing speed in the prevalent MS specific test batteries (Benedict et al., 2017). Additionally, SDMT results would allow for more accessible comparisons of effects and changes. Furthermore, the SDMT has been cited as a "sentinel" measure of cognitive decline in MS, a sensitive screening measure that exhibits superior performance, compared to other assessments, at predicting the outcome of an entire battery (Van Schependom et al., 2014).

Two measures used in the study, the Relational Abilities Index and the RBANS, are not included in the National MS Society's recommended measures. The Relational Abilities Index, merited inclusion as it is the measure of the proposed process of change, relational skills. Additionally, regarding its acceptability by participants, the Relational Abilities Index is analogous to the training tasks themselves. The RBANS was selected partly due to its namesake, repeatability, which is a study specific requirement given the nature of this design. There is a limited selection of repeatable neuropsychological assessments, which would also measure multiple domains. A possible solution was to create a battery of composite measures; however, this approach was impeded by the additional restrictions enforced by the current pandemic context, resulting in the need for remote online delivery, and the researcher's abilities, or lack thereof, in coding. Consequently, a measure(s) which could be delivered remotely, be repeated, and investigate multiple domains was needed. As stated earlier (Section 8.1.) the Cogstate Battery was initially identified as it met these requirements and could provide a MS specific test battery consisting of: Detection Test (Psychomotor Function), Identification Test

(Attention), One Card Learning Test (Visual Learning), One Back Test (Working Memory), Two Back Test (Working Memory), International Shopping List Test (Verbal Learning), Groton Maze Learning Test (Executive Function) (Cogstate, 2021). There is a degree of precedent in the use of the RBANS as a general neuropsychological assessment in MS (Aupperle et al., 2002; Beatty, 2004; Bollaert et al., 2017; Davis et al., 2015) and the RBANS has recently been validated for remote video conferencing delivery (Galusha-Glasscock et al., 2016). Furthermore, the remote delivery validation study reported test-retest correlations, with counterbalanced forms (A and B) across two conditions (face-to-face and video conference), for the Indices ranging from r = .59 to .90 and a mean of .80. A key component in testing batteries in MS is being mindful of the cognitive fatigue that measurement and testing can have and many of the recommended measures are included, at least in part, as a result of their brevity. The RBANS meets this criterion as it has a relatively short administration time, ranging from around 20 to 30 minutes (Randolph et al., 1998).

8.6. Testing Procedures

All testing and data collection, with the exception of the feedback interview, was completed online either via surveys constructed and delivered through the Qualtrics platform (https://www.qualtrics.com/uk/) or completed with the researcher via Microsoft Teams (MS Teams). Demographics, PQs, Relational Abilities Index, HADS, MSQOL-29, and the MFIS were all delivered via the Qualtrics platform. Participants were emailed their personalised survey links (as each was constructed individually to accommodate their PQ) at the end of the work week. They were asked to complete the survey by the beginning of the next week. The RBANS and the SDMT were both completed via MS Teams. Standardisation of participant's audio-visual technology was not feasible in this study. However, participants were asked to complete the MS Teams appointments in a quiet room

with minimal distractions using a screen of sufficient size as to not influence visual based task performance. The researcher provided a consistent testing environment and ensured that there was sufficient lighting for the participants. Additionally, to address the issue of internet connectivity issues affecting audio quality, occasional minor breaks were needed as to not skew participants' responses as a results of audio signal degradation. A SDMT form, and RBANS *Figure Copy* and *Recall* sheets, and RBANS *Coding* sheets were posted to the participants in time for their MS Teams assessment. Participants were provided with a return envelope to send the completed forms back to the researcher.

8.7. Data Extraction and Analysis

Details of visual analysis techniques have been outlined previously in section 3.6. of the Research Paper. The following section will provide additional details of the data extraction for the measures used, any calculations performed, and further analysis techniques.

8.7.1. Demographics

Data relating to participants' age, gender, ethnicity, level of education, employment, MS diagnostic subgroup, and time since diagnosis will be recorded. These factors may affect treatment, cognitive functioning, and test performance, and should be explored at an individual level (Benedict & Zivadinov, 2011; Lewis et al., 2009; Ruano et al., 2017). This data was collected at the A_1 timepoint via Qualtrics.

8.7.2. Reliable Change Calculations

Reliable Change calculations were used with all measures used in the study with the exception of the Relational Abilities Index. Changes on an individual level are to be calculated using the Reliable Change Index (RCI; Jacobson & Truax, 1991). The Reliable Change Index is

calculated using the Standard Error of Measurement (SEM) and the Standard Error of the Difference (S_{DIFF}):

$$SEM = s\sqrt{1 - r}$$
$$S_{DIFF} = \sqrt{2(SEM^2)}$$
$$RCI = 1.96(S_{DIFF})$$

8.7.3. SDMT

The SDMT was administered and scored following the procedure guidance reported in the manual (Smith, 1982). Participants were posted a blank SDMT testing form which they were instructed to open once the assessment began. Participants were familiarised with the test's procedures and the sample items were completed together. Participants were then given 90 seconds to complete as many items as possible. Once complete, participants were asked to place the SDMT form inside the provided return envelope. The oral version was also completed following manualised procedures. The participant spoke their responses aloud to the researcher, over MS Teams, who then wrote them down.

SDMT scores are reported as a raw score with no further calculations. Results are compared with heathy control scores categorised by age, gender, years of education, and SDMT administration type (oral or written). A participant's raw score can be compared to their categories' normative data, which is used to decide how far, or close, a participant's score is from the mean. For the SDMT, a participant's raw score being 1.5 Standard Deviations below the normative mean would be indicative of a clinical case (Benedict et al., 2017; Smith, 1982).

8.7.4. RBANS

Where possible, the RBANS standard procedures were followed as reported in the manual (Randolph, 1998). Adaptations were needed to

accommodate the delivery of the RBANS via MS Teams and remote validation protocols were followed (Galusha-Glasscock et al., 2016). *List Learning, Story Memory, Semantic Fluence, Digit Span, List Recall, List Recognition,* and *Story Recall* needed no adaptations as they are all delivered verbally. *Figure Copy, Picture Naming, Coding*, and *Line Orientation* could not be completed in line with the manual procedures due to the remote delivery. The researcher's web camera was placed and angled in an attempt to emulate the manualised requirements of viewing the graphical stimulus. Participants received a photocopy version of the RBANS *Coding, Figure Copy*, and *Figure Recall* forms for them to complete at the appropriate time. Participants were asked to place their *Figure Copy* form in the return envelope immediately following completion as to not influence the later recall task. There is no procedure for completing the RBANS *Coding* as a verbal test. The researcher followed and adapted version of the SDMT Oral administration procedure when completing an Oral version of the RBANS *Coding* as they are analogous tests regarding their structure and delivery.

Participants completed Form A at timepoints A_1 and F_1 and completed Form B at timepoint T_6.

Subtest raw scores were aggregated and used to calculate index scores via age and gender indexed norms as described in the RBANS manual. Reporting RBANS subtest raw scores as an additional metric, rather than collapsing into the index scores, preserves sensitivity of the data and allow for a more meaningful and individualised comparative between timepoints. No adaptations were made to the RBANS raw score calculations.

For the Reliable Change Index calculations, the RBANS manual provided the data required for the Index level comparisons. However,

the manual does not report subtest level norms and test-retest reliability values. No study reporting MS RBANS subtest repeated testing values could be found. Studies reporting RBANS subtest repeated values, had samples such as a small (N = 28) "cognitively intact" group from a memory clinic (Dong et al., 2013), a large (N = 445) elderly sample (Duff et al., 2005), and a large (N = 315) Turkish version validation study (Safaz et al., 2016). No individual study appeared a suitable fit to take values from for the Reliable Change Index calculations. Using Meta-Essential Correlations calculations (Suurmond et al., 2017) the above studies' data were pooled and a random effects model applied to output a single *r*-value for each subtest (Appendix F). The second component of the Reliable Change Index calculations, the standard deviation of the subtest score, was taken from an evaluation of the RBANS in a MS population (Davis et al., 2015). The results of these calculations are reported in Table 9.

Table 9: RBANS Subtests' statistics derived from meta-analysis and the RCI calculated from these data.

Subtest	*SD*	*r*	*SE*	RCI	RCI Rounded
List Learning	5.62	.69	4.43	8.67	9
Story	4.04	.74	2.91	5.71	6
Figure Copy	1.89	.52	1.85	3.63	4
Line Orientation	2.97	.72	2.22	4.36	5
Picture Naming	.54	.64	.46	.90	1
Semantic Fluency	4.81	.64	4.08	8.00	8
Digit Span	2.61	.68	2.09	4.09	5
Coding	13.39	.87	6.83	13.38	14
List Recall	2.90	.65	1.75	3.43	4
List Recognition	1.66	.53	1.61	3.15	4
Story Recall	2.75	.62	2.40	4.70	5
Figure Recall	4.58	.68	3.66	7.18	8

Note: *SD* – Standard Deviation; *r* – test-retest reliability; *SE* – standard error; RCI – Reliable Change index.

8.7.5. Relational Abilities Index and Inverted Efficiency Score

The Relational Abilities Index is a 55-item measure of derived relational responding skills. The measure presents two categories of relations to the participant: 'Same/Opposite' and 'More/Less'. There are 29 and 26 exemplars for each category respectively. The entire selection of the one category is presented before alternating to the second category at item number 30. Within each category, the exemplars increase in complexity, requiring greater relational skills to complete. For example, a typical first item will appear as following:

NUQ is the same as **VEK**
*Is **NUQ** the opposite to **VEK**?*

As the participant progresses through the measure the items increase in relations, to a maximum of three. An example is shown below:

NUK is opposite to **ZEQ**
ZEQ is opposite to **BIL**
BIL is the same as **BEL**
*Is **NUK** opposite to **BEL**?*

These nonsense words are constructed following a simple procedure. The words are arranged as constant, vowel, constant. The words cannot be a 'real' word and cannot be repeated. Each exemplar, regardless of its complexity, is scored as one point for a correct answer. An additional metric of time taken to respond to each item was included by the researcher. Participants are given a maximum time of 30 seconds to respond to an item, after which the next exemplar will be presented, and the participant will score 0 for the first item.

The equation for the Inverted Efficiency Score (Townsend & Ashby, 1978, 1983) is shown below:

$$IES = \frac{TIME}{1 - ERROR}$$

To calculate the Inverted Efficiency Score, the total Relational Abilities Index response time was averaged to provide a score scaled more in line with item specific efficiencies. Error was calculated by subtracting participants' Relational Abilities Index score from the maximum score (55) and dividing the output by 55. For example, if a participant scored 40 items correctly and took a total of 600 seconds to complete the Relational Abilities Index, their Inverted Efficiency Score would be calculated as:

$$IES = \frac{600/55}{1 - (55 - 40/55)} = 15.00$$

Lower Inverted Efficiency Score denotes greater efficiency in response.

8.7.6 RBANS Predictor Calculations

RBANS predictor difference scores were calculated following the regression formulas presented in Duff et al. (2004) and Duff et al. (2005). Values for each subtest and index score are used in addition to age, gender, education, gender, and time between assessments. *List Learning* is presented below as an example of the equations and not all equations will be presented to save the reader a potentially tedious volume of information. See Duff et al. (2004) and Duff et al. (2005) for the formulas used. The formula outputs a *Z*-score with values above 1.64 being of significant difference.

$$List\ Learning\ = \frac{Observed\ Difference - Predicted\ Difference}{3.74}$$

$$Observed\ Difference = Time\ 1\ Data - Time\ 2\ Data$$

$$Predicted\ Difference = Time\ 2 - Predicted\ Data$$

$$Predicted\ Data = 19.432 + .555(Time\ 1) + 1.177(Education) - .162(Age)$$

8.7.7. Correlations

Pearson correlations were performed for SDMT raw scores, Relational Abilities Index raw scores, Inverted Efficiency Score, all RBANS Indices and Subtests, Age, Education, and disease duration. Correlations were completed using SPSS 26.0 (IBM Corp, Released 2019).

8.7.8. Completers and non-completers

A small sample size limits the use of inferential statistics to use in investigating the difference of a participant's score, or other variables, when comparing with others. The differences between completers and non-completers will be conducted by averaging completers' data from the initial timepoint, A_1, and using the calculated standard deviation to investigate if a non-completer's A_1 timepoint data was significantly different. In these calculations, the threshold of a significant difference is set as one standard deviation from the completers' mean score.

9. Extended Results

9.1. Individual Participant Results

The following section will report additional data collected from observations during the undertaking of the test battery at each timepoint, a more in-depth visual analysis of each participant's Personal Questionnaire data, RBANS subtest scores, and greater detail of Relational Abilities Index and Inverted Efficiency Score scores. SDMT scores are reported in full in Section 4.2.2. of the Research Paper. The participant specific clinical threshold scores, adjusting for age, years of education, and administration of either the written or oral version of the assessment for the SDMT are presented below in Table 10. Additionally, MFIS cut-off scores are also presented in Table 10. Participants who are within the same scoring category are grouped together.

Table 10: Participant specific cut-off scores and standard deviations for SDMT and MFIS.

	SDMT - Standard Deviations from Mean								
Participants	-2.5	-2.0	-1.5	-1.0	-.5	.0	.5	1.0	MFIS
A, B, H	26	32	37	43	49	54	60	65	27
C, D	31	35	40	44	48	52	57	61	22
E	23	27	31	35	39	43	47	51	33
F†	14	20	25	31	36	42	48	53	39
G	27	31	35	39	43	48	52	56	29

Note: † - Oral version administered. SDMT – Symbol Digit Modalities Test; MFIS – Modified Fatigue Impact Scale

9.1.1. Participant A

Participant A is a 36-year-old White British woman who has completed 17 years of education and holds full-time employment within an organisation/company. She was diagnosed with the relapsing remitting subtype of MS 11.59 years ago. Participant A was felt to have provided rushed answers during the RBANS at the F_1 timepoint when compared to previous testing.

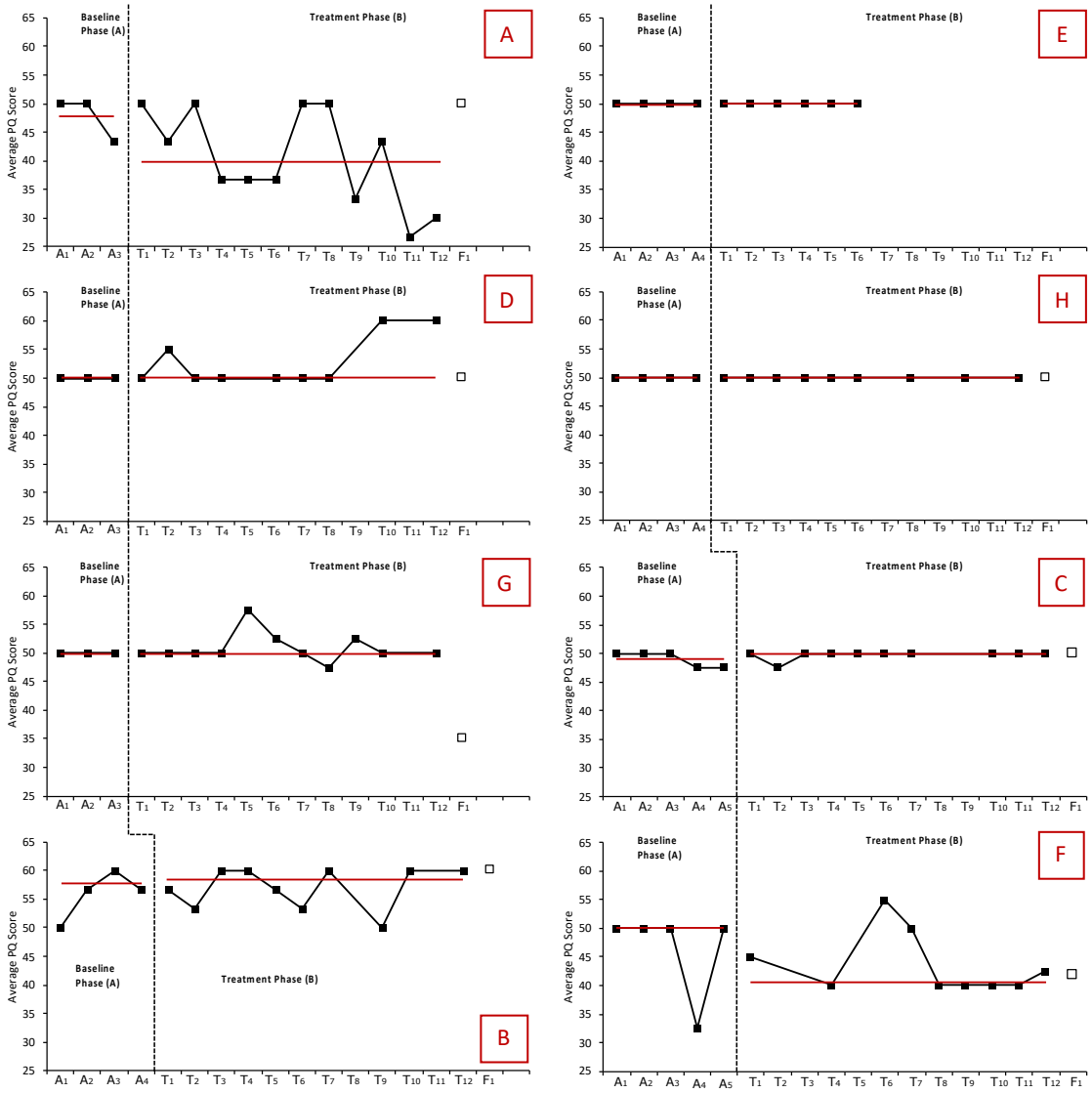

Figure 10: PQ items scores with broadened median calculations (red line).

Personal Questionnaire Structured Visual Analysis – She completed 100% of her Personal Questionnaire measures over the study. There

was a decrease in central tendency between the baseline phase and treatment phase in the contra-therapeutic direction (Figure 10). There was a decelerating contra-therapeutic trend in both phases, the degree of this trend was reduced in the treatment phase, moving towards the therapeutic direction (Figure 11). Variability in PQ scores increased over the duration of the study (Figure 12). There were 12 data points in the treatment phase, and 9 data points were required to be above both the adjusted baseline mean and adjusted baseline trend for positive (improving) change to have occurred between phases (Fisher et al., 2003). Four data points are above the dual criterion indicating that positive change had not occurred between phases (Figure 3, Section 4.2.1.).

RBANS Subtests – Participants' RBANS Subtest data are shown in Table 11. RCI reported an increase in *Picture Naming* from A_1 to T_6 and A_1 to F_1. The remaining subtest scores were stable throughout. Participant A reached maximum scores for *Picture Naming* at T_6 and F_1 and *List Recognition* across all three timepoints. She obtained the maximum possible score for *Picture Naming* at T_6 and F_1 and *List Recognition* across all three timepoints.

SDMT – At the initial timepoint, Participant A's score was greater than -1.0 standard deviations away from the mean. At the T_6 and F_1 timepoints their score was less than -1.0 standard deviation away from the mean.

Process - After the initial improvement in both accuracy and from A_1 to T_2, Participant A's raw score remained largely stable, with minor fluctuations in their response time (see Table 12 for all Relational Abilities Index data). Overall, there was a decelerating trend in Inverted Efficiency Score over the duration of the study (see Figure 5 (Section 4.2.1.) for all participants' Inverted Efficiency Score graphs).

Table 11: RBANS Subtest scores and reliable change results across all timepoints.

	Participant A						Participant B						Participant C						Participant D					
				RCI						RCI						RCI						RCI		
Subtest	A_1	T_6	F_1	A_1-T_6	A_1-F_1	T_6-F_1	A_1	T_6	F_1	A_1-T_6	A_1-F_1	T_6-F_1	A_1	T_6	F_1	A_1-T_6	A_1-F_1	T_6-F_1	A_1	T_6	F_1	A_1-T_6	A_1-F_1	T_6-F_1
List Learning	28	30	33				25	29	28				24	19	26				27	25	26			
Story	20	15	15				15	6	18	▽		▲	16	16	18				19	23	23			
Figure Copy	16	14	15				16	14	19			▲	17	14	18			▲	16	17	19			
Line Orientation	14	15	12				18	16	19				17	7	18	▽		▲	15	18	16			
Picture naming	9	10	10	▲	▲		10	10	10				10	10	10				10	9	10	▽		▲
Semantic Fluency	19	23	20				19	13	30		▲	▲	23	25	23				30	15	19	▽	▽	
Digit Span	11	10	13				8	10	7				10	8	8				12	14	14			
Coding	41	49	52				47	49	47				46	47	53				38	36	38			
List Recall	6	8	6				3	3	5				4	4	5				7	4	6			
List Recognition	20	20	20				17	16	18			▲	17	17	16				20	20	20			
Story Recall	10	9	7				8	4	9			▲	9	7	8				10	12	12			
Figure Recall	9	11	15				6	9	15		▲		8	7	10				11	8	13			
	Participant E						Participant F						Participant G						Participant H					
				RCI						RCI						RCI						RCI		
Subtest	A_1	T_6	F_1	A_1-T_6	A_1-F_1	T_6-F_1	A_1	T_6	F_1	A_1-T_6	A_1-F_1	T_6-F_1	A_1	T_6	F_1	A_1-T_6	A_1-F_1	T_6-F_1	A_1	T_6	F_1	A_1-T_6	A_1-F_1	T_6-F_1
List Learning	19	32	-	▲			15	26	21	▲			36	38	36				35	37	36			
Story	19	20	-				15	16	15				21	22	22				23	22	24			
Figure Copy	12	11	-				7	11	12	▲	▲		16	18	12		▽	▽	20	20	20			
Line Orientation	14	15	-				14	17	15				20	20	20				20	19	19			
Picture naming	9	10	-	▲			9	9	9				10	10	10				10	10	10			
Semantic Fluency	22	14	-	▽			17	14	21				17	35	26	▲	▲	▽	23	27	29			
Digit Span	11	13	-				10	12	11				15	16	16				8	10	11			
Coding	33	43	-				31	33	38				33	38	34				54	61	62			
List Recall	5	8	-				0	4	0	▲	▽		9	10	10				8	9	10			
List Recognition	20	20	-				18	18	17				20	20	20				20	20	20			
Story Recall	7	11	-				5	4	6				12	12	12				11	11	12			
Figure Recall	10	11	-				4	6	8				12	16	16				19	19	20			

RCI – Reliable Change Index; CSC – Clinically Significant Change; Pairwise Comparison - ▲: Positive Reliable Change, ▽: Negative Reliable Change

Table 12: Relational Abilities Index percentage correct and averaged completion time.

	RAI Score (%) and Average Reaction Time (s)							
Participant	A1	T2	T4	T6	T8	T10	T12	F1
A	60.00 (12.60)	78.18 (6.98)	87.27 (6.34)	89.09 (6.90)	85.45 (6.81)	85.45 (7.03)	87.27 (8.33)	90.91 (6.78)
B	58.18 (7.78)	69.09 (8.29)	70.91 (8.37)	70.91 (9.44)	65.45 (7.74)	80.00 (8.38)	78.18 (9.80)	74.55 (10.12)
C	56.36 (8.75)	67.27 (5.69)	65.45 (3.80)	67.27 (2.08)	-	72.73 (1.94)	**66.67 (2.97)**	54.55 (3.50)
D	83.64 (12.22)	-	90.91 (8.65)	83.64 (6.32)	**92.00 (8.10)**	81.82 (8.10)	85.45 (7.11)	89.09 (7.27)
E	60 (12.51)	76.36 (11.76)	61.82(11.71)	56.36 (9.42)	-	-	-	-
F	-	-	-	52.73 (13.73)	-	54.55 (10.62)	**63.89 (9.93)**	70.91 (10.07)
G	94.55 (15.00)	94.55 (11.92)	96.36 (10.09)	94.55 (8.91)	96.36 (10.10)	-	98.18 (7.74)	98.18 (9.99)
H	94.55 (13.61)	98.18 (7.63)	100 (6.48)	100 (5.31)	98.18 (9.35)	100 (6.20)	98.18 (5.86)	100 (5.17)

Note: Bold denotes participant ended the assessment early and did not complete. Percentage scores calculated from completed items.

9.1.2. Participant B

Participant B is a 39-year-old White and Asian woman who has completed 17 years of education and holds part-time employment within an organisation/company. She was diagnosed with the relapsing remitting subtype of MS 9.25 years ago. Participant B reported that they were feeling unwell during the testing at the T_6 timepoint and they did not want to reschedule the appointment to another date. At the F1 timepoint, Participant B reported that they had recently been prescribed a new medication that had disrupted their sleeping patterns and left them feeling drowsy and "drugged up".

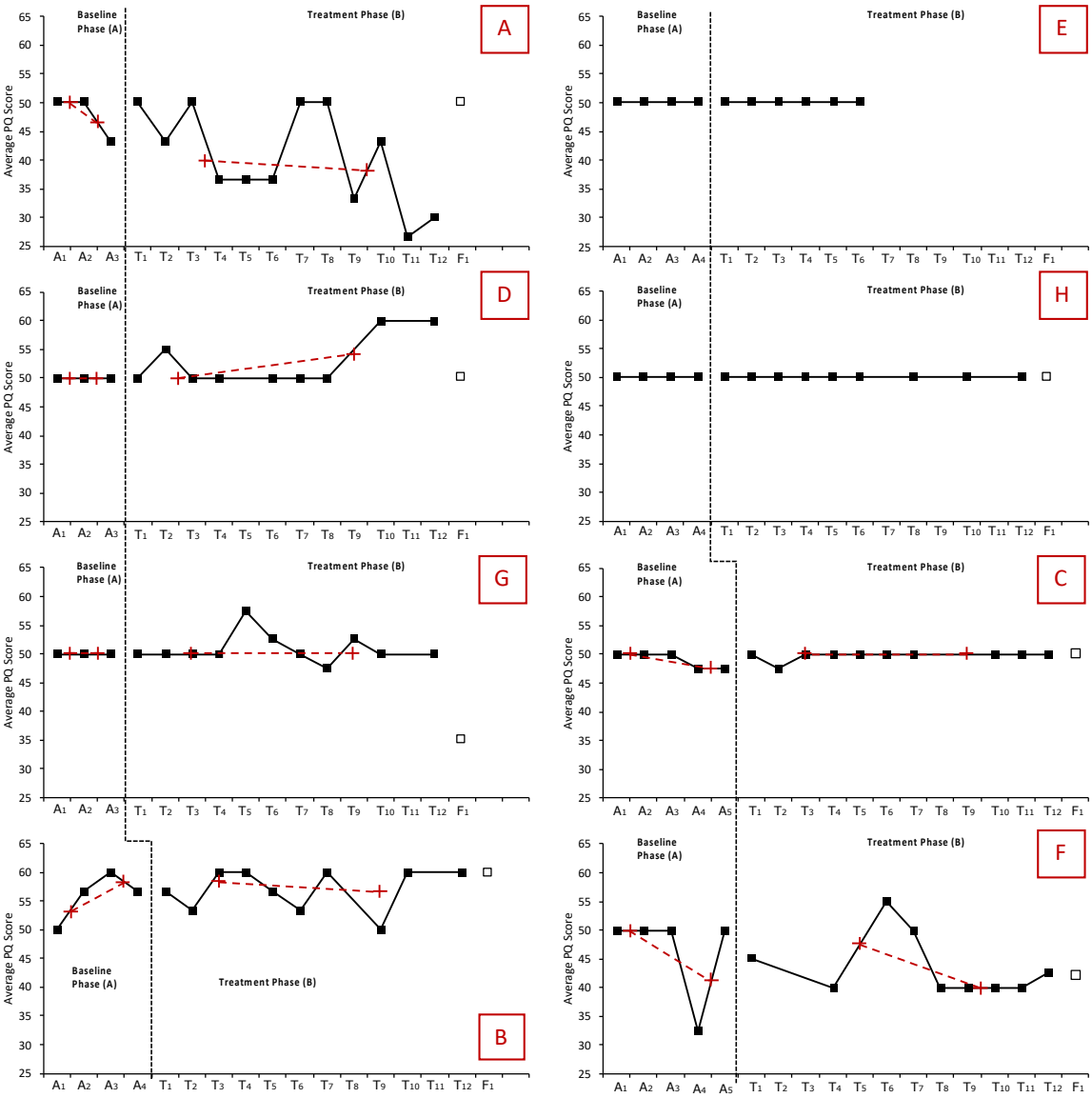

Figure 11: PQ items scores with split middle calculations (red dashed line).

Personal Questionnaire Structured Visual Analysis – She completed 88.25% of her Personal Questionnaire measures over the study. Broadened median calculations showed a slight increase in central tendency between phases in the therapeutic direction. Split-middle trend calculations show an accelerating therapeutic trend in the baseline and a decelerating trend in the treatment phase. Trended ranges showed a slight increase in the variability of scores over the

phases. Zero data points were above dual criterion indicating no positive change had occurred between the phases.

RBANS Subtests – RCI reported a reliable decrease in *Story* from A_1 to T_6 and then an improvement from T_6 to F_1. There were improvements in *Figure Copy, Line Orientation, List Recognition,* and *Story Recall* from T_6 to F_1 and *Figure Recall* from A_1 to F_1. Lastly, there were reliable improvements in *Semantic Fluency* from A_1 to T_6 and from T_6 to F_1. All over subtests remained stable. She obtained the maximum possible score for *Picture Naming* across all three timepoints.

SDMT – At the initial timepoint, Participant B's score was less than .5 standard deviations away from the mean. At the T_6 this fell to less than -1.0 standard deviations and then rose again to less than .5 standard deviations at F_1.

Process - Participant B's raw score showed minor improvements and fluctuating reaction times. There was a zero-celeration trend in Inverted Efficiency Score over the duration of the study.

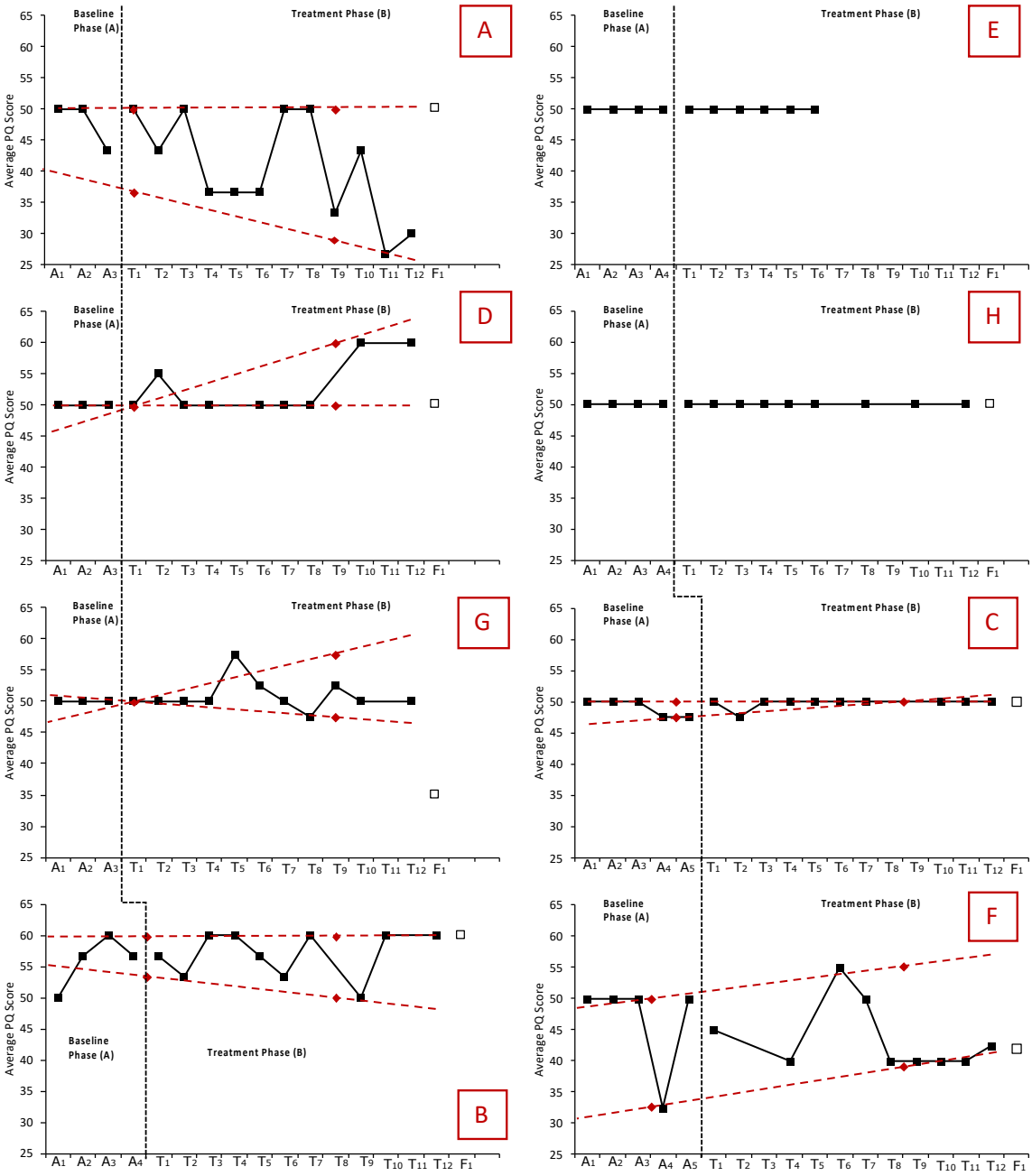

Figure 12: PQ items scores with trended range calculations (red dashed lines).

9.1.3. Participant C

Participant C is a 48-year-old White British woman who has completed 16 years of education and is unemployed. She was diagnosed with the relapsing remitting subtype of MS 19.09 years ago. Participant C

unfortunately experienced a death in the family during their time in the study. The funeral was the day before testing at the T_6 timepoint and they did not wish to reschedule. Additionally, testing conditions were not ideal at this timepoint as there was a high volume of noise in the background due to family members and used a tablet. Lastly, there was a potential audio distraction during the RBANS coding task as a result of an email alert on the researcher's computer.

Personal Questionnaire Structured Visual Analysis – She completed 88.89% of her Personal Questionnaire measures over the study. There was a slight increase in her central tendency between phases, moving in the therapeutic direction. The baseline trend was decelerating and was zero-celerating during treatment. A slight decrease in variability was shown over the phases. Nine data points were above the dual criterion, above the required eight needed. These results indicate that there was a positive change between baseline and treatment phases.

RBANS Subtests – RCI showed a reliable improvement in *Figure Copy* from T_6 to F_1. For *Line Orientation*, there was a significant decrease from A_1 to T_6 followed by a reliable increase from T_6 to F_1. All over subtests remained stable. She obtained the maximum possible score for *Picture Naming* across all three timepoints.

SDMT – At the initial timepoint, Participant C's score was -1.5 standard deviations less than the mean. At the T_6, their score was less than -1.0 standard deviation from the mean and at F_1, their score was less than -.5 standard deviations away from the mean.

Process - Relational Abilities Index scores remained reasonably stable, but reaction time sharply decreased over the duration of the study. Overall, there was a decelerating trend in Inverted Efficiency Score. Participant C exited the Relational Abilities Index assessment early at

timepoint T_{12}; their percentage score was calculated from the items completed rather than the entire Relational Abilities Index.

9.1.4. Participant D

Participant D is a 53-year-old White British woman who has completed 18 years of education and is self-employed part-time. She was diagnosed with the relapsing remitting subtype of MS 7.61 years ago.

Personal Questionnaire Structured Visual Analysis – She completed 81.25% of her Personal Questionnaire measures. There was no change in the central tendency between phases, as calculated by the broadened median. A zero-celeration trend was reported for the baseline phase and an accelerating trend in the treatment phase. Variability increased across the phases. The researcher decided to include the value at T_2, which would have been deleted for the calculation otherwise, due to it being one of the three values that differed from neither contra- nor therapeutic directionality. As there was no variation in baseline scores, the adjusted mean and adjusted trend line are superimposed and have the same value. Three data points are above the dual criterion when eight are needed for change to be positive between phases.

RBANS Subtests – RCI showed a reliable decrease in *Semantic Fluency* from A_1 to T_6 and again from A_1 to F_1. There was also a decrease om *Picture Naming* from A_1 to T_6, followed by an increase from T_6 and F_1. She obtained the maximum possible score for *Picture Naming* at A_1 and F_1, *List Recognition* across all three timepoints, and *Story Recall* at T_6 and F_1.

SDMT – At the initial timepoint, Participant D's score was greater than -2.0 standard deviations away from the mean. At the T_6 and F_1

timepoints their score was less than -2.0 standard deviation away from the mean.

Process - Relational Abilities Index scores remained reasonably stable, and reaction time generally improved over the duration of the study. Overall, there was a decelerating trend in Inverted Efficiency Score. Participant D exited the Relational Abilities Index assessment early at timepoint T_8; there percentage score was calculated from the items completed rather than the entire Relational Abilities Index.

9.1.5. Participant E

Participant E is a 59-year-old White British woman who has completed 12 years of education and holds part-time employment within an organisation/company. She was diagnosed with the relapsing remitting subtype of MS 5.83 years ago. She withdrew after the assessment at T_6 timepoint, there is no F_1 data to report. Participant had continuing issues with technology and successfully connecting to the appointment for the cognitive testing. Additionally, it was felt that they stopped early on tasks within the RBANS.

Personal Questionnaire Structured Visual Analysis – She completed 100% of her Personal Questionnaire measures. Neither structured visual nor statistical analysis were possible for Participant E as she reported the same PQ value for each timepoint in both phases.

RBANS Subtests – RCI showed a significant improvement in *List Learning* and *Picture Naming* from A_1 to T_6 and reliable decrease in *Semantic Fluency* score from A_1 to T_6. All over subtest scores remained stable. She obtained the maximum possible score for *List Recognition* at A_1 and T_6 and *Picture Naming* at T_6.

SDMT – At the initial timepoint, Participant E's score was -1.0 standard deviations less than the mean. At the $T_{6,}$ their score was greater than the mean.

Process - Relational Abilities Index scores steadily worsened across the study but were offset with reductions in reaction time. There was a decelerating trend in Inverted Efficiency Score.

9.1.6. Participant F

Participant F is a 75-year-old White British man who has completed 12 years of education and is retired. He was diagnosed with the primary progressive subtype of MS 14.68 years ago. He reported that he did not have sufficient dexterity in his dominant hand (right) to complete the written version of the SDMT. As such, the oral version of the SDMT and RBANS coding was administered. It should be noted that there is no manualised protocol for administering an oral version of RBANS coding. The researcher adapted the SDMT protocol as they deemed appropriate to enable the participants' best performance.

Personal Questionnaire Structured Visual Analysis – He completed 82.35% of his Personal Questionnaire measures. Broadened median calculations showed a contra-therapeutic decrease in central tendency between phases. Linear trend, assessed with split middle calculations, showed a decelerating trend for both baseline and treatment phases. The trend in the treatment phase moved in the therapeutic direction in comparison to baseline. Variability appears to slightly decrease across the duration of the study with an upward trend. There is a significant outlier in the baseline phase. Zero points where above the dual criterion, indicating no positive change had occurred between phases.

RBANS Subtests – RCI showed a significant improvement in *Figure Copy* from A_1 to T_6 and again to F_1. There were also improvements in

List Learning and List recall from A_1 to T_6 with the latter decreasing from A_1 to F_1. All over subtest scores remained stable.

SDMT – At the initial timepoint, Participant F's score was less than -2.0 standard deviations away from the mean. At the T_6, their score was less then -1.5 standard deviation from the mean and at F_1, their score was less than -1.0 standard deviations away from the mean.

Process - Relational Abilities Index scores steadily worsened across the study but were offset with reductions in reaction time. There was a decelerating trend in Inverted Efficiency Score.

9.1.7. Participant G

Participant G is a 62-year-old White British man who has completed 18 years of education and is retired. He was diagnosed with the primary progressive subtype of MS 13.34 years ago. He reported that he had issues with penmanship but chose to complete the written version of the SDMT. At the T_6 timepoint, his partner entered and exited the room multiple times during the RBANS administration. At the F_1 timepoint, he was not at his usual desk position and completed the RBANS from his sofa due to a progression in issues with his mobility.

Personal Questionnaire Structured Visual Analysis – He completed 93.75% of his Personal Questionnaire measures. No difference was observed in central tendency between phases. Similarly, there were zero-celerating trends for both phases. Variance increased across the phases. Four of the required nine data points were above the dual criteria, indicating there had not been a positive change between phases.

RBANS Subtests – RCI reported significant improvements in *Semantic Fluency* from A_1 to T_6 and A_1 to F_1 and a decrease from T_6 to F_1.

Additionally, there was a decrease in *Figure Copy* score from A_1 to F_1 and T_6 to F_1. All over subtest scores remained stable. He obtained the maximum possible score for *Line Orientation*, Picture Naming, List Recognition, and Story Recall across all three timepoints; and *Digit Span* and *List Recall* at T_6 and F_1.

SDMT – At the initial timepoint, Participant G's score was more than -1.5 standard deviations away from the mean. At the T_6, their score was less then -.5 standard deviation from the mean and at F_1, their score was less -1.0 standard deviations away from the mean.

Process - Relational Abilities Index scores remained stable at near 100% with a gradually decreasing reaction time reported. There was a decelerating trend in Inverted Efficiency Score.

9.1.8. Participant H

Participant H is a 39-year-old other White background woman who has completed 20 years of education and is currently unemployed. She was diagnosed with the relapsing remitting subtype of MS 10.77 years ago. Whilst fluent in English, her first language is German.

Personal Questionnaire Structured Visual Analysis – She completed 82.35% of her Personal Questionnaire measures. Neither structured visual nor statistical analysis were possible for Participant H as she reported the same PQ value for each timepoint in both phases.

RBANS Subtests – Participant H showed no reliable changes in any subtest scores across any of the timepoints. She obtained the maximum possible score for *Line Orientation* at A_1; *Figure Copy*, *Picture Naming*, and *List Recognition* across all three timepoints; and Story, List Recall, *Story Recall*, and *Figure Recall* at F_1.

SDMT – At the initial timepoint, Participant H's score was less than .5 standard deviations greater than the mean. At the T_6, their score was greater than 1.0 standard deviation above the mean and at F_1, their score was greater than .5 standard deviations above the mean.

Process - Relational Abilities Index scores remained stable at near 100% with a gradually decreasing reaction time reported. There was a decelerating trend in Inverted Efficiency Score.

9.2. RBANS Predictor Score Calculations

Difference from predicted RBANS index and subtest scores adjusted for age, time-between administrations, education, gender, ethnicity, and practice effects are shown in Table 13 for the Indices and Table 14 for the Subtests. Difference between observed and predicted represented by *Z*-score.

9.2.1. Index score calculations

Immediate Memory - Participants B and C showed significant decreases in *Immediate Memory* index scores from A_1 to T_6 which was not maintained to F_1. Participant B had a decrease from A_1 to T_6 which was maintained to F_1. Participant E had a significant improvement in *Immediate Memory* from A_1 to T_6; they withdrew from the study after this assessment and maintenance of this improvement could not be measured.

Visuospatial / Constructional – Participant A had a significant decrease in this index score from A_1 to T_6 and from T_6 to F_1. Participant B had a significant decrease from A_1 to T_6 and this was not maintained at F_1. Participant C had a significant decrease from A_1 to T_6 and a significant increase from T_6 to F_1.

Table 13: RBANS Index predictor score calculations results.

	Participant A						Participant B						Participant C						Participant D					
	Pre	Mid	Post	*z*			Pre	Mid	Post	*z*			Pre	Mid	Post	*z*			Pre	Mid	Post	*z*		
Subtest	(A)	(B)	(C)	A-B	A-C	B-C	(A)	(B)	(C)	A-B	A-C	B-C	(A)	(B)	(C)	A-B	A-C	B-C	(A)	(B)	(C)	A-B	A-C	B-C
Immediate Memory	94	85	90	**-2.25**	**-1.80**	-1.29	81	69	87	**-2.86**	-1.23	-.55	87	81	94	**-1.82**	-0.64	-.30	103	109	112	-.03	.24	-.10
Visuospatial / Constructional	66	66	62	-1.50	**-1.82**	**-1.82**	75	69	102	**-1.67**	.97	1.24	92	53	105	**-3.73**	.43	**2.21**	81	100	100	.54	.54	-.33
Language	92	104	96	1.22	.31	-.55	92	78	120	**-1.73**	**3.04**	**4.05**	103	106	103	.66	.32	.11	117	87	94	**-2.50**	**-1.71**	.44
Attention	82	85	97	-.46	.63	.57	75	85	72	.16	-1.34	**-1.92**	91	85	91	-.83	-.36	.33	97	100	103	.46	.62	.56
Delayed Memory	77	88	88	.24	.24	-.44	48	48	68	-1.46	.29	.29	71	64	81	-1.48	.00	.43	99	94	105	-.60	.36	.67
Total Score	78	81	82	-1.63	-1.50	**-1.79**	67	62	85	**-2.92**	.02	.50	84	72	92	**-3.01**	-.45	.71	99	96	103	-1.23	-.33	-.04

	Participant E						Participant F						Participant G						Participant H					
	Pre	Mid	Post	*z*			Pre	Mid	Post	*z*			Pre	Mid	Post	*z*			Pre	Mid	Post	*z*		
Subtest	(A)	(B)	(C)	A-B	A-C	B-C	(A)	(B)	(C)	A-B	A-C	B-C	(A)	(B)	(C)	A-B	A-C	B-C	(A)	(B)	(C)	A-B	A-C	B-C
Immediate Memory	85	109	-	**1.66**	-	-	78	97	87	1.51	.60	-.48	120	129	126	1.11	.84	.32	120	123	132	-.20	.61	.44
Visuospatial / Constructional	66	66	-	-1.05	-	-	64	75	72	-.24	-.48	-.98	100	112	96	.63	-.65	-1.20	121	109	109	-.57	-.57	-.02
Language	99	84	-	-1.55	-	-	96	90	105	-.66	1.05	1.48	92	134	111	**4.64**	**2.02**	-.99	104	112	116	1.27	**1.73**	1.16
Attention	88	106	-	**1.96**	-	-	91	100	100	1.57	1.41	.93	106	109	106	.97	.51	.45	82	97	109	.86	1.33	.36
Delayed Memory	94	101	-	.32	-	-	68	75	68	-.34	-.95	-1.38	110	121	121	1.07	1.07	.39	105	109	125	.34	**1.73**	1.48
Total Score	82	90	-	.19	-	-	74	83	82	.53	.40	-.46	107	134	118	**3.1**3	1.09	-1.51	108	114	125	-.20	1.21	.63

Note: Bold denotes reliable change (z>1.64).

Table 14: RBANS Subtest predictor score calculations results.

	Participant A						Participant B						Participant C						Participant D					
				z						*z*						*z*						*z*		
Subtest	Pre (A)	Mid (B)	Post (C)	A-B	A-C	B-C	Pre (A)	Mid (B)	Post (C)	A-B	A-C	B-C	Pre (A)	Mid (B)	Post (C)	A-B	A-C	B-C	Pre (A)	Mid (B)	Post (C)	A-B	A-C	B-C
List Learning	28	30	33	-1.00	-.76	-.50	25	29	28	-.70	-.96	-1.56	24	19	26	**-2.83**	-.96	-.22	27	25	26	-1.46	-1.19	-.89
Story	20	15	15	**-2.64**	**-9.20**	**-1.77**	15	6	18	**-4.21**	-.76	.82	16	16	18	-1.06	-.48	-.48	19	23	23	.68	.68	-.02
Figure Copy	16	14	15	**-1.84**	**-2.03**	-.59	16	14	19	**-1.84**	1.19	**1.84**	17	14	18	**-2.16**	.26	1.23	16	17	19	-.02	1.19	.87
Line Orientation	14	15	12	**-1.66**	**-6.78**	**-3.17**	18	16	19	**-1.91**	-.59	-.20	17	7	18	**-5.35**	-.53	1.45	15	18	16	.04	-.84	-1.44
Picture naming	9	10	10	1.57	.93	.52	10	10	10	.52	.52	.52	10	10	10	.52	.52	.52	10	9	10	-1.18	.52	1.57
Semantic Fluency	19	23	20	1.15	1.14	-.27	19	13	30	-1.63	**3.09**	**3.97**	23	25	23	1.12	.56	.27	30	15	19	**-2.68**	-1.57	.62
Digit Span	11	10	13	-.92	.97	.95	8	10	7	-.02	**-1.75**	**-2.09**	10	8	8	-1.31	-1.46	-.70	12	14	14	1.53	1.38	1.02
Coding	41	49	52	.29	**4.60**	-.42	47	49	47	-.55	-.92	-1.24	46	47	53	-.45	.65	.50	38	36	38	-1.02	-.66	-.34
List Recall	6	8	6	-.07	**-2.14**	-1.75	3	3	5	-1.54	-.52	-.52	4	4	5	-1.04	-.53	-.53	7	4	6	**-1.84**	-.82	.16
List Recognition	20	20	20	-.66	-.80	-.66	17	16	18	**-2.60**	-.96	-.54	17	17	16	-1.52	**-2.34**	**-2.34**	20	20	20	-.17	-.17	-.17
Story Recall	10	9	7	-.31	**-2.65**	-.96	8	4	9	**-2.09**	.29	1.48	9	7	8	-.96	-.49	.11	10	12	12	1.12	1.12	.52
Figure Recall	9	11	15	-1.30	-.11	-.40	6	9	15	-1.32	.58	.04	8	7	10	**-2.10**	-1.15	-.97	11	8	13	**-2.21**	-.63	-.09

	Participant E						Participant F						Participant G						Participant H					
				z						*z*						*z*						*z*		
Subtest	Pre (A)	Mid (B)	Post (C)	A-B	A-C	B-C	Pre (A)	Mid (B)	Post (C)	A-B	A-C	B-C	Pre (A)	Mid (B)	Post (C)	A-B	A-C	B-C	Pre (A)	Mid (B)	Post (C)	A-B	A-C	B-C
List Learning	19	32	-	**2.49**	-	-	15	26	21	**2.17**	.84	-.80	36	38	36	1.07	.54	.24	35	37	36	-.04	-.31	-.61
Story	19	20	-	.11	-	-	15	16	15	.46	.17	.00	21	22	22	.49	.49	.31	23	22	24	-1.01	-.43	-.26
Figure Copy	12	11	-	**-2.36**	-	-	7	11	12	-.75	-.14	-1.43	16	18	12	.59	**-3.05**	**-3.70**	20	20	20	.51	.51	.51
Line Orientation	14	15	-	-.38	-	-	14	17	15	.73	-.15	-.74	20	20	20	-.08	-.08	-.08	20	19	19	-.99	-.99	-.79
Picture naming	9	10	-	1.57	-	-	9	9	9	-.48	-.48	-.48	10	10	10	.16	.16	.16	10	10	10	.52	.52	.52
Semantic Fluency	22	14	-	-1.46	-	-	17	14	21	-.73	1.22	**1.65**	17	35	26	**4.78**	**2.28**	-.36	23	27	29	**1.67**	**2.23**	**1.64**
Digit Span	11	13	-	1.49	-	-	10	12	11	**1.78**	1.10	.78	15	16	16	**2.10**	**1.95**	**1.86**	8	10	11	-.02	.35	.01
Coding	33	43	-	1.26	-	-	31	33	38	.30	1.22	.90	33	38	34	.45	-.29	-1.08	54	61	62	.54	.72	-.38
List Recall	5	8	-	1.06	-	-	0	4	0	1.22	-.82	**-2.13**	9	10	10	.88	.88	.55	8	9	10	-.11	.40	.07
List Recognition	20	20	-	.00	-	-	18	18	17	-.34	-1.16	-1.16	20	20	20	.09	.09	.09	20	20	20	-.57	-.57	-.57
Story Recall	7	11	-	**1.86**	-	-	5	4	6	-.88	.08	.37	12	12	12	.52	.52	.52	11	11	12	.35	.82	.82
Figure Recall	10	11	-	-.56	-	-	4	6	8	-.68	-.05	-.41	12	16	16	.36	.36	-.37	19	19	20	-.50	-.19	-.19

Note: Bold denotes reliable change (z>1.64).

Language – Participant B showed a decrease in *Language* index scores from T_6 to F_1 and a significant improvement from A_1 to F_1 and again from T_6 to F_1. Participant G also showed a significant improvement from A_1 to T_6 which was maintained to F_1. Participant improved from A_1 to F_1. Participant D showed reliable decreased from A_1 to T_6 and this was maintained to F_1.

Attention – Participant B showed a reliable decrease in scores from T_6 to F_1. Participant E had a reliable increase from A_1 to T_6.

Delayed Memory – Only Participant H showed any changes in Delayed Memory index scores with an improvement from A_1 to F_1.

Total Score – Participants B and C both showed a decrease in total scores from A_1 to T_6 and neither were maintained to F1. Participant A had a decrease from T_6 to F_1. Participant C had an increase from A_1 to T_6.

9.2.2. Subtest score calculations

List Learning – Participants E and F both showed a reliable increase in this index score from A_1 to T_6, Participant F did not maintain this change. Participant C had a reliable decrease from A_1 to T_6 and this decrease was also not maintained.

Story – Participant A showed a reliable decrease in *Story* scores across all three timepoints. Participant C had a reliable decrease from A1 to T6 which was not maintained to F1.

Figure Copy – Participant A's scores decreased from A_1 to F_1 and this was maintained to F_1. Participant E decreased from A_1 to F_1. Participant

B also decreased from A_1 to T_6 but improved from T_6 to F_1. Participant G decreased from A_1 to F_1 and again from T_6 to F_1.

Line Orientation – Participant A decreased across all three timepoints. Participants B and C decreased from A_1 to T_6, but these were not maintained to F_1.

Picture Naming – No significant differences between predicted and observed score were reported for any participants in the *Picture Naming* subtest.

Semantic Fluency – Participant H showed reliable improvements across all three timepoints. Participant G showed reliable changes from A_1 to T_6 and this was maintained to F_1. Participant F increased from T_6 to F_1. Participant D decreased from A_1 to T_6.

Digit Span – Participant G improved across all three timepoints in this subtest. Participant F improved from A_1 to T_6. Participant B decreased from A_1 to F_1 and from T_6 to F_1.

List Recall – Participant A decreased from A_1 to F_1, Participant D from A_1 to T_6, and Participant F from T_6 to F_1.

List Recognition – Participant B decreased from A_1 to T_6 and Participant C from A_1 to F_1 and T_6 to F_1.

Story Recall – Participant E increased from A_1 to T_6. Participant B decreased from A_1 to T_6 and Participant A from A_1 to F_1.

Figure Recall – Participants C and D both decreased from A_1 to T_6.

Table 15: Correlations with RBANS index scores

		Variable	1	2	3	4	5	6	7	8	9	10	11	12
RAI	1.	Raw Score	–	**-.54****	.28	**.68****	**.53***	**.49***	.38	**.71****	**.72****	-.17	**.74****	-.23
	2.	IES		–	**-.52***	-.23	-.27	.01	-.01	-.24	-.31	.42	**-.59****	-.07
	3.	SDMT			–	.29	**.41***	.02	-.25	.19	.28	**-.74****	**.59****	-.23
RBANS Index	4.	Immediate Memory				–	**.74****	.28	**.66****	**.92****	**.96****	.07	**.54****	-.20
	5.	Visuospatial/Constructional					–	.06	.24	**.56****	**.78****	-.12	**.65****	-.08
	6.	Language						–	.10	.29	.33	.03	.22	-.22
	7.	Attention							–	**.69****	**.64****	**.55****	-.02	.03
	8.	Delayed Memory								–	**.92****	.08	**.44***	-.28
	9.	Total									–	.09	**.54****	-.12
Participant	10.	Age										–	**-.65****	.34
	11.	Education											–	-.25
	12.	Disease Duration												–

Note: RAI – Relational Abilities Index; IES – Inverted Efficiency Score; SDMT – Symbol Digit Modalities Test; RBANS – Repeatable Battery for the Assessment of Neuropsychological Status. ** - Correlation significant at the .01 level; * - Correlation significant at the .05 level.

Table 16: Correlations with RBANS Subtest scores

	Variable	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
RAI	1. Raw Score	–	**-.54****	.28	**.71****	**.48****	**.46****	.37	.39	**.44***	.41	.21	**.67****	**.62****	**.61****	**.79****	-.17	**.74****	-.23
	2. IES		–	**-.52***	-.23	-.18	**-.48***	.06	**-.56****	-.40	.05	**-.55****	-.27	-.03	-.35	-.40	.42	**-.59****	-.07
	3. SDMT			–	**.54****	.19	**.67****	.27	**.58****	.38	-.40	**.91****	**.48***	.04	.31	**.66****	**-.74****	**.59****	-.23
RBANS Subtest	4. List Learning				–	**.43***	**.52***	**.61****	**.57****	.33	.40	.40	**.87****	**.52***	**.63****	**.82****	-.34	**.67****	-.28
	5. Story					–	**.47***	**.44***	.06	.39	.39	-.00	**.64****	**.71****	**.86****	**.58****	.04	**.42***	-.26
	6. Figure Copy						–	**.46***	.51	**.49***	-.14	**.61****	.47	.19	**.59****	**.64****	**-.34****	**.82****	-.23
	7. Line Orientation							–	.22	.21	.22	.08	**.44***	.20	**.50***	**.49***	.01	**.44***	-.16
	8. Picture Naming								–	.41	-.07	**.56****	**.55****	.02	.39	**.53****	**-.51***	**.60****	-.12
	9. Semantic Fluency									–	-.05	.29	**.46***	.21	.40	**.58****	-.20	**.45***	.05
	10. Digit Span										–	**-.52***	**.53***	**.58***	**.45***	.18	**.44***	.06	-.19
	11. Coding											–	.28	-.10	.12	**.54****	**-.78****	**.53****	-.04
	12. List Recall												–	**.70****	**.77****	**.80****	-.29	**.62****	-.34
	13. List Recognition													–	**.69****	**.56****	-.07	.34	**-.57****
	14. Story Recall														–	**.63****	-.21	**.65****	-.39
	15. Figure Recall															–	-.40	**.68****	-.33
Participant	16. Age																–	**-.65****	.34
	17. Education																	–	-.25
	18. Disease Duration																		–

Note: RAI – Relational Abilities Index; IES – Inverted Efficiency Score; SDMT – Symbol Digit Modalities Test; RBANS – Repeatable Battery for the Assessment of Neuropsychological Status.
** - Correlation significant at the .01 level; * - Correlation significant at the .05 level.

9.3. Correlations

Results from Pearson correlation calculations between Relational Abilities Index raw score and Inverted Efficiency Score, SDMT raw score, RBANS Indices, and Participant variables are shown in Table 15. Additionally, correlations were completed with the same variables listed with the RBANS Indices being replaced with RBANS Subtest raw scores, which are shown in Table 16. Regarding the celeration of the Inverted Efficiency Score correlations, it should be noted that Inverted Efficiency Score scores are calculated in a way that lower scores denote greater efficiency.

9.3.1. Relational Abilities Index Correlates

Pearson correlation calculations report a significant positive relationship between Relational Abilities Index raw scores and *Immediate Memory*, *Visuospatial/Constructional, Language, Delayed Memory*, and *Total Score* RBANS Indices. There is also a significant positive relationship between Relational Abilities Index raw scores and years of education. Additionally, Relational Abilities Index raw scores had a significant positive relationship with *List Learning*, *Story*, *Figure Copy, Semantic Fluency, List recall, List Recognition, Story Recall*, and *Figure Recall* RBANS Subtests.

The Inverted Efficiency Score correlation calculations report a significant negative relationship with SDMT raw score and years of education. Additionally, Inverted Efficiency Score shad a significant negative relationship with *Figure Copy, Picture Naming*, and *Coding* RBANS Subtests.

9.3.2. Age, Education, and Disease Duration Correlates

Correlation calculations report a significant positive relationship between age and the *Attention* RBANS Index and a significant negative relationship with SDMT raw score. In the RBANS Subtest analysis, age

was significantly negatively correlated with *Figure Copy, Picture Naming*, and *Coding*. There was a significant positive correlation with *Digit Span.*

Years of education was significantly positively correlated with Relational Abilities Index Raw Score, SDMT Raw Score, and the *Immediate Memory, Visuospatial/Constructional, Delayed Memory,* and *Total Score* RBANS Indices. Education was showed a significant negative relationship with Inverted Efficiency Score and age. Years of education showed a significant positive correlation between all of the RBANS Subtests with the exception of *Coding* and *List Recognition.*

Disease duration, in years, showed a significant negative correlation with the *List Recognition* Subtest.

9.4. Completers / Non-Completers

Aggregated completer (n = 7) data from the A_1 timepoint is shown in Table 17. The two non-completers', Participant E and I, data are also shown independently (where available). Participant I's data has not been presented elsewhere in this report; they completed the initial SDMT and RBANS and withdrew at this point. Their RBANS Index scores were not able to be calculated as they did not complete the initial survey that collected their age.

Participant E's data from the A_1 timepoint was significantly different from the completers' data, as defined by a difference greater than one standard deviation from the completers' mean. Their years of education (12.00) and disease duration (5.94) was significantly lower than the completers' (Education = 16.86, SD = 2.48; Disease Duration = 12.88, SD = 5.94). Participant E's HADS-A score (11.00) was significantly higher than the completers (HADS-A = 6.14, SD = 2.79) and their HADS-D score (12.00) was greater than two standard

deviations from the completers' scores (HADS-D = 6.57, SD = 1.81). Finally, Participant E's Inverted Efficiency Score (20.85) was significantly higher than the completers' (Inverted Efficiency Score = 15.79, SD = 2.70). Only Participant I's SDMT score (35.00) can be reported, and this score is within one standard deviation of the completers' scores (SDMT = 39.00, SD = 11.45).

Table 17: Differences between completers and non-completers.

Variable	Completers (n = 7)	Non-Completers	
		Participant E	Participant I
Age	50.78 (14.25)	59.77	
Education	16.86 (2.48)	**12.00***	
Disease Duration	12.88 (4.26)	**5.94***	
SDMT	39.00 (11.45)	38.00	35.00
RAI	41.00 (10.12)	33.00	
IES	15.79 (2.70)	**20.85***	
RBANS			
Immediate Memory	97.57 (17.41)	85.00	
Visuospatial / Constructional	85.57 (20.35)	66.00	
Language	99.43 (9.31)	99.00	
Attention	89.14 (10.45)	88.00	
Delayed Memory	82.57 (22.72)	94.00	
Total Score	88.14 (16.51)	82.00	
HADS			
Anxiety	6.14 (2.79)	**11.00***	
Depression	6.57 (1.81)	**12.00****	
MFIS			
Physical	25.29 (6.78)	20.00	
Cognitive	23.14 (4.22)	23.00	
Psychosocial	4.71 (1.89)	6.00	
Total	51.86 (8.34)	49.00	
MSQOL-29			
Mental Health	51.62 (19.27)	54.62	
Physical Health	48.07 (13.41)	38.67	

Note: ** – Difference greater than 1 SD; ** - Difference greater than 2 SD.*

9.5. Measures completed

An additional component of addressing feasibility questions regarding this study was exploring the completion of measures. Measures that were started, but not finished, were scored a non-completed measure. Results of information regarding measurements are shown in Table 18.

Table 18: Completion rate for all measures used.

Measure	Percent completed
Personal Questionnaire	87.06
SDMT	100
RBANS	100
RAI	83.33
MSQOL-29	100
HADS	100
MFIS	100
Interview	100

10. Extended Discussion

10.1. Impairment and Decline

The present study has used the clinically significant change in relation to cognitive impairment throughout. Whilst this concept retains its value in attempts of generalising findings with the wider field of research, it loses value on the individual level. To phrase this differently, reliable changes, irrespective of clinical change are perhaps more valuable to the participant. Take, for example, Participant H's baseline SDMT score, which was within half a standard deviation from her category's norm. This would not be perceived as an impairment but very well could be a decline in performance over the course of the disease progression. For the purpose of this argument, if we hypothesise that the intervention has returned her to her pre-morbid functioning (half a standard deviation above the norm) she would have to score 25 points lower (over two standard deviations) to be categories as impaired. Routine measurement would help detect decline in those who are not impaired (Sumowski et al., 2018).

10.2. RBANS

10.2.1. Indices

RBANS predictor calculations were used as an alternative method of exploring significant differences between Participants' scores. At the index level of analysis, by intervention-midpoint 12.50% of the participants had improved in Immediate Memory, Visuospatial Constructional, Language, Attention, and Total Score. Twenty-five percent has reliably deteriorated over the same indices and timescale. At the intervention-endpoint, 42.86% had improved in the Language index, and 14.26% in the Attention and Delayed Memory domains. Regarding deteriorations, 14.26% had significant decreases in Immediate Memory, Visuospatial/Constructional, and Language. Improvements in language are in line with theoretical predictions of relational abilities instrumental role in these skills (Cassidy et al.,

2011). The predictor score analysis, when compared to RCI calculations appears more prone to Type II errors, or vice versa with Type I errors, as these calculations reported a total of 21 significant changes compared to the 32 reported by RCI. Additionally, the proportions of improvements to deteriorations were inverted. Of all the RBANS index changes reported by RCI (32), 81.25% were positive and 18.75% were negative. Contrastingly, the predictor calculations reported 42.86% therapeutic changes and 57.14% contra-therapeutic changes. Applying a strict dual criterion of significance reported by both RCI and predictor calculations reduces the number of 'passes' significantly. At intervention-endpoint, Participant B met dual criterion improvement in Language, Participant E in Immediate Memory and Attention, Participant G in Language, and Participant H in Language and Delayed Memory. The relevance of this analysis technique is questionable given the data set that the regression formulas were derived from. Duff et al. (2004) and Duff et al. (2005), drew from an elderly sample with a particular focus on Alzheimer's disease and its progression. Of note in this comparison of analysis techniques is that the predictor calculations did not detect any change in Total Score at the intervention-endpoint whilst it was the most prevalent change, seen in 57.14% of participants, in the RCI calculations.

10.2.2. Subtests

For RCI, at the intervention-midpoint 37.5% improved in Picture Naming, 25.00% in List Learning, and 12.5% in Semantic Fluency and List Recall. Deteriorations were also reported in Semantic Fluency (25.00%), and Story and Line Orientation (12.50%). At the intervention-endpoint. Improvements were reported in Semantic Fluency (28.52%), and Figure Copy, Line Orientation, Semantic Fluency, and List Recall (14.28%). Similar to the findings at the Index Level of analysis, predictor score calculations result in a greater proportion of deteriorations. Accounting for all subtests, RCI reported

improvement in 14.58% of tests and deteriorations in 9.52%. Predictor scores showed improvements in 14.58% and deteriorations in 26.04%. Applying the dual criterion to endpoint comparisons, only Participants B and G achieved this and on the same subtest – Semantic Fluency.

10.2.3 RBANS Discussion

Issues surround the use of the RBANS in an MS population have been discussed previously in the Journal Paper (Section 5.0). This measure is particularly vulnerable to floor and ceiling effects in a selection of the subtests which may have altered the findings. All but one participant (F) scored maximum marks on the Picture Naming subtest. Additionally, RCI calculations set reliable change as one point, which may increase the likelihood of Type 1 errors as this was the smallest increment of change possible in this subtest. As most were already scoring maximum marks on this subtest no improvements could be recorded, only deteriorations. Similarly, maximum scores were regularly achieved on List Recognition, Line Orientation, and Story Recall. Furthermore, some subtests, such as List Recall were vulnerable to floor effects, as seen in Participant F's responses at baseline and at the intervention-endpoint.

It could be argued that the RBANS certainly retains its value in its brevity and measurement of multiple domains; however the aforementioned issues limit the range and sensitivity of the assessment. The present study was limited regarding choice of assessments available that could be delivered effectively remotely. MS specific test batteries such as the Brief International Cognitive Assessment for MS (Benedict et al., 2012) or the Minimal Assessment of Cognitive Function in MS (Benedict et al., 2006) may have been more sensitive to the MS specific cognitive profile and would have allowed for more direct contextualisation of findings with other rehabilitation studies. Additionally, the RBANS does not report certain

key values for the subtests as it does for the Indices, such as a reliability value or sample standard deviations. Calculations were performed drawing on a range of studies as no directly comparable group reported this data (Dong et al., 2013; Duff et al., 2005; Safaz et al., 2016). The use of this data, and its application to setting a reliable change criterion, may have over and/or underestimated the change required. MS participants have been shown to have their own distinct neuropsychological profile on the RBANS and the use of MS norms may increase the accuracy and sensitivity to change (Aupperle et al., 2002; Davis et al., 2015). The issue of sensitivity of the RBANS within the MS sample is exemplified in the comparison between the SDMT and RBANS Coding reliable change criteria. These are near identical tasks yet the literature surrounding the SDMT reports significant change as an increase of three to four points (Benedict et al., 2018; Benedict et al., 2014) and the present study used a stricter criterion of five points. This change criterion is in stark contrast to the 14-point change required in the RBANS Coding subtest which was generated from non-MS specific normative data.

Whilst no direct comparisons can be made regarding RBANS performance with other cognitive rehabilitation studies in MS, associations can be made with the measured domains. In this present study, the improvements were observed in the Total Score, Language, Visuospatial/Constructional, Attention, and Delayed Memory. Similar improvements were reported in other general/non-specific cognitive interventions studies. For instance, Charvet et al's. (2017) class I study using Adaptive Cognitive Remediation only showed improvements in their battery composite score, equitable to the RBANS Total Score (which was the most frequent improver). Additionally, other general interventions (Arsoy et al., 2018; Darestani et al., 2020) displayed improvements in verbal skills, as measured by the Controlled Oral Word Association Test (Sumerall et al., 1997) which is directly

comparable to the Semantic Fluency subtest of the Language Index. Attention increases have also been reported in general cognitive rehabilitation studies (Arsoy et al., 2018; Barbarulo et al., 2018). However, there is a potential bias in the RBANS coding task being near identical to the SDMT. The same test could be viewed as being performed twice, analysed twice, and reported as two different outcomes – introducing a multiplicity of testing bias (Li et al., 2016).

10.3. Correlations

Due to the nature of this analysis discussions are limited to the associations between variables and how these relate to wider research. Causal relationships cannot be inferred.

Relational Abilities Index raw scores showed a strong association with RBANS Immediate Memory, Visuospatial/Constructional, Delayed Memory, and Total Score indices, in addition to years of education. Of note, the only moderate association reported was with the Language domain. This is a domain which, theoretically, should exhibit one of the stronger associations (Cassidy et al., 2011; Hayes et al., 2021). However, the Relational Abilities Index raw scores was the only variable to show any significant association with the Language Index, perhaps supporting the theoretical role of derived relational responding in language skills. This relationship has been reported by O'Hara et al. (2008) who reported a significant relationship between relational skills and verbal comprehension domain scores. Furthermore, Dixon et al. (2018) reported a strong association between Full Scale IQ and relational skills, with IQ itself being related to RBANS Total (r = .78) (Randolph et al., 1998). Relational Abilities Index raw scores also showed strong associations with RBANS List Learning, List Recall, List Recognition, and Figure Recall. Moderate associations were reported with Figure Copy, Line Orientation, and Semantic Fluency. The latter, again, is below predictions in terms of the strength of association

between relational skills and language skills. These findings are in line with a pervious extensive examination of the association of relational responding, as measured by the Relational Abilities Index raw score (Colbert et al., 2017). They reported associations with visuospatial functioning, memory, and verbal abilities.

When factoring in reaction time in the Relational Abilities Index, creating the Inverted Efficiency Score, strong associations were reported with the SDMT and years of education. The Inverted Efficiency Score has moderate associations with Figure Copy and Picture Naming and a strong association with Coding. The SDMT, Coding subtest, and Semantic Fluency were the only timed tasks in the testing battery. The association between Inverted Efficiency Score and Coding and SDMT is questionable through the increased intervention-test correspondence established via the conflating of metrics. Yet again, the lack of a significant association between the Inverted Efficiency Score and Semantic Fluency (a timed verbal association test) goes against expectations. The relationship between the Inverted Efficiency Score and the Figure Copy subtest may be explained by the Speed-Accuracy Trade-off and differing cognitive styles (Bogacz et al., 2010; Jones et al., 2020; Wickelgren, 1977). Applying a potentially overly reductionist explanation of these styles could explain the difference. For instance, one could employ a 'slow and safe' behavioural repertoire to meet the task demands or a 'risky and fast' approach (Bogacz et al., 2010). Take, for instance, the worst Relational Abilities Index (as measured by percentage correct) performer, Participant C, and compare with the best, Participant H. Participant C had an average Relational Abilities Index score of 63.64% whilst Participant H scored 98.64% on average. Their average time per exemplar was 4.11 seconds and 7.45 seconds respectively. Here we can clearly see the potential difference in the Speed-Accuracy Trade-off styles that may account for differences in a seemingly unrelated test – Figure Copy. Their average Figure Copy

times were 43 seconds and 57 seconds respectively. These results also highlight the Inverted Efficiency Score's vulnerability to low reaction times being prioritised over accuracy. In Figure 5 (Section 4.3.) we can see that Participants C and H have similar data and trendlines, with Participant C perhaps showing greater efficiency. Another issue with these calculations lies in the binary 'Yes' and 'No' responses. For Participant C was approaching scores (50%) that could be accounted for by chance and yet showed good efficiency.

Years of education, as expected (Le Carret et al., 2003; Sheridan et al., 2006), showed associations with nearly all of the studied variables. Only Language and Attention Indices, and List Recognition and Coding subtests, did not show a relationship. The breadth of these positive associations on outcomes provides further support for the neuroprotective effects of education on objective assessments in line with the Cognitive Reserve model (Martins Da Silva et al., 2015).

10.4. Process of Change

As reported in the Journal Paper (Section 5. and 5.3) the evidence of relational responding as being the mediator of cognitive change remains inconclusive. Findings are further complicated by the aforementioned issues with the measurement of relational skills through the conflated metrics of Relational Abilities Index raw scores and average exemplar completion time. However, removing the time element to the measurement may not have proven a useful alternate as, with the exception of their initial to second test administration, participants' raw scores remained relatively stable with only the time taken to complete showing changes. Nonetheless, we have to explore the possibility that improving relational skills were not the mediator of cognitive changes.

The difficulty in discerning intervention specific effects on outcomes in MS cognitive rehabilitation is not limited to this present study. For example, in Stuifbergen et al's. (2018) Memory, Attention, and Problem-Solving Skills for people with MS intervention (Stuifbergen et al., 2011; Stuifbergen et al., 2012), the control group also significantly improved in every outcome measure. This control group were allocated 'brain games' (https://multiplesclerosis.com). These findings suggest that even any intensive cognitive intervention may improve outcomes (Melby-Lervåg & Hulme, 2013) or perhaps evidence of the Hawthorne Effect in cognitive rehabilitation (McCambridge et al., 2014). However, it does not appear that any intervention will result in a positive effect, placebo or otherwise. Rahmani et al. (2018) reported no improvements in their placebo (physical intervention) group compared to the cognitive rehabilitation groups. Outside of the most recent, and more comparable, general/non-specific interventions, in their everyday memory intervention Mousavi et al. (2020) reported no differences between their intervention and the placebo group who were allocated body relaxation techniques.

The Speed of Processing Training intervention (Ball et al., 2002; Ball et al., 2007; Chiaravalloti et al., 2018) has several shared mechanics with the SMART intervention and produced results in equitable areas – significant improvements in symbol digit substitutions tests and verbal/language skills. Three demands (stimulus detection, identification, and same/different judgements) are performed in ever more complex tasks. The three level of tasks are single discrimination, divided attention (where the participant must also identify a peripheral target), and selective attention (where there are numerous distractors). This training has participants make simple same/opposite relational decisions of increasing complexity. If one were to remove the concept of derived relational responding from the SMART training, the two interventions would appear similar. For instance, in SMART

participants are required to quickly detect, identify, and discriminate between stimuli. Furthermore, as the training becomes more complex, the exemplars grow in complexity requiring participants to utilise visual scanning skills, detect stimuli over greater distances, and selectively attend to the stimuli amidst a range of distractions. Given the inconclusive findings of relational skills in relation to the outcomes, and the topographical similarities and outcomes with Speed of Processing Training, it could be suggested that the SMART intervention is a processing speed intervention drawing on the same mechanics as Speed of Processing Training.

10.5. Measure Completion

All face-to-face measurements were completed by all participants. Furthermore, all online measurements delivered at the significant study timepoints (baseline, intervention-midpoint, and intervention-endpoint) had a 100% completion rate. The Personal Questionnaire and the Relational Abilities index were delivered more frequently compared with the above. Personal Questionnaires (87.06% completion rate) were sent out every week for the duration of the study and the Relational Abilities Index (83.33% completion rate) was sent out every other week during the intervention phase only. Supported by the results from the feedback and the 100% completion rate, we can conclude that the RBANS, SDMT, MFIS, HADS, and MSQOL-29 were acceptable to participants. The reduction in the response rates for the Personal Questionnaire and Relational Abilities could be understood by the higher number of responses required, increasing the probability of a non-response, or by participants not finding value in the measures or not accepting them. For example, Participant H suggested in their feedback interview (Table 5, Section 4.5.) that the study incorporates a subjective assessment of cognitive difficulties. As this was the intended function of the Personal Questionnaire, their comments

suggest the Personal Questionnaire was not operationalised in a way that had face validity for this participant.

10.7. Environmental Contingencies

As reported earlier, relational responding is a generalised operant (Hayes et al., 2021). Colbert et al. (2018) states bringing this repertoire under strict contextual control, through multiple exemplar training. is useful as it increases the repertoire's effectiveness in a broad range of day-to-day activities (Barnes-Holmes et al., 2001; Barnes-Holmes et al., 2004; Berens & Hayes, 2007; Gómez et al., 2007; Luciano et al., 2007). Yet we must consider the environment that the participants were in during this study. This study took place over the strictest application of lockdown procedures in response to the COVID-19 pandemic. This included a stay-at-home order, workplaces being closed, limited social engagements, and more at-risk individuals having to shield and isolate. Such conditions undoubtedly equate to an impoverished environment, reducing the access to broad range of environmental contingencies. Consequently, we could hypothesise that the relational repertoire may have been limited in its generalisation in a broader range of contexts as access to these contingencies had been removed. Theoretically, the inability to be utilised in a range of contexts may have reduced the behaviour's reinforcement and subsequent far transfer effects to ecologically valid behaviours. The lack of generalisation may also be accounted for the limited selection of relational frames employed by the training. The SMART programme only utilised "Same/Opposite" and "More/Less" frames of coordination. Colbert et al. (2018) propose the inclusion of a greater range of relational frames such as temporal, analogical, and categorical, which have also been shown to have associations with measurement of intelligence (Gore et al., 2010; McHugh et al., 2004; O'Hora et al., 2008). The training of these additional frames may increase the

generalisability of the intervention onto even more ecologically valid behaviours.

10.8. Future research

The present study establishes the preliminary evidence of supporting the development of the SMART intervention for people with MS and initial attempts at modelling processes and outcomes have been established. However, in line with Medical Research Council (2008) guidance on the development of complex interventions, further development of the intervention is required before initial piloting trials are conducted. Findings from this study may help inform a larger feasibility study with a specific focus on adaptations to the intervention and outcome measures. Whilst initially promising results were reported, this was not an evaluation of the effectiveness of SMART intervention for people with MS. Practical issues with outcome measurement have been identified and this study used an "off the shelf" offering of the SMART programme with no adaptations made. More detailed exploration into the delivery and dosage of the intervention are required. There appears to be preliminary support to increase both the length and intensity of the intervention, as identified by the feedback interviews. Furthermore, no iatrogenic effects were reported as defined as reliable deterioration in secondary measurements of quality of life, mood, or fatigue.

Process of change remains elusive and this maybe a result of poor measurement of this process or its irrelevance in mediating change. O'Cathain et al. (2019) state that researchers need to be flexible with the applied theory and be open to other understandings of what may be driving change. To better understand the process of change, a discrimination approach, rather than association approach used in this study, may further understanding in this area. For example, a three-armed RCT could help differentiate treatment effects and process of

change. With the use of validated MS cognitive batteries, and retaining the use of the Relational Abilities Index, along with the secondary outcome measures, effects could be explored across three study conditions. The first condition being the SMART intervention, the second being a "sham" or active control condition, with the third being and an inactive control. The active control condition could complete another topographically similar intervention, such as the Speed of Processing Training, or a Go-No Go paradigm. The Speed of Processing Training may be a more acceptable offering as it has already been piloted in MS (Chiaravalloti et al., 2018). Yet this proposed experiment is similar to the evaluation stage of the MRC framework and consequently may not be appropriate at this early stage.

10.8. Summary and Conclusions

It is important to consider performance decline in relation to a participant's pre-morbid functioning. Many studies in MS cognitive rehabilitation set inclusion criteria as being impaired in at least one neuropsychological measure. However, this cut-off does not take into consideration a potential participant's relative decline and what is meaningful to them. Future studies could include a broader range of cognitive performance profiles and examine the possible protective effects of cognitive rehabilitation.

The relevance of utilising the regression-based formulas in calculating significant change on the RBANS is questionable. The norms from which the formula is derived from is an older adult sample that could exhibit a divergent cognitive profile over time. Whilst it could certainly be viewed as a more rigorous approach in examining change, there were notable differences in the proportion of negative changes when compared to the RCI calculations. On the subtest level of analysis, increase in the Picture Naming task was observed the most frequently. This could be understood as an effect of increased relational skills, as

the test utilises a simple visual and verbal stimulus coordination relation. It may also be done to the RCI being calculated at one point, increasing the probability of Type I errors. Increases in semantic fluency task were observed, in line with theoretical predictions. The appropriateness of using the RBANS is questionable due to the presence of other more widely used, and potentially sensitive, neuropsychological batteries for people with MS. This insensitivity is exemplified by the change needed in the near identical tests of RBANS Coding and the SDMT.

Correlations between relational responding skills and outcomes were mostly in line with prior research in this area. However, the novel conflation of the Relational Abilities Index yielded new associations (with processing speed for instance). This conflation may have forced an association with timed task increasing a convergent bias, as such, findings should be interpreted cautiously. The process of change, as already stated in the Journal Paper, remains elusive. The mediator for observed changes may not have been accurately measured in this present study. Additionally, conceptual similarities between the SMART multiple exemplar training tasks and the Speed of Processing Speed Training have been drawn. These similarities, in both tasks and outcomes, questions the role of relational responding mediating improved cognitive outcomes. However, this is a *coordination* relation, as such Speed of Processing Training improvements may have been mediated by a form on relational skill improvements. Finally, the lack of environmental contingencies in the context of the study may have limited the generalisation and reinforcement of these relational skills onto a broader range of ecologically, and personally meaningful behaviours.

11. Reflection

Ethical Considerations

I have always been interested in the mechanics and processes of how things worked. At a young age there were concerns over my attention to academia as I would spend my time constructing and testing my Meccano creations, rather than attend to the subject matter being taught. My disinterest in academia was exemplified by my erroneous conclusion that being six out of six in remedial mathematics as being cause for celebration. These behaviours persevered and many, seemingly functional, mechanical and electrical objects have fallen prey to my exploratory dissembling. I attribute my selection of Neuroscience as my undergraduate degree to this repertoire, as I wanted to understand how such a complex structure functioned. However, this subject did not satisfy me as I was regularly left with a phrase synonymous with the Trent DClinPsy experience – "so what?". This phrase encapsulates the more pragmatic side of Clinical Psychology. One can describe and explain things, but can you enact meaningful change?

The chance to create and conduct my own experiment could then be viewed as being years in the making. Yet I look back at my thought processes and planning of the project as perhaps more aligning with those child behaviours. In this I mean I do not believe I took full consideration of conducting human experiments but rather viewed it as more variables to manipulate and problems to solve. The realisation of how taxing and potentially harmful such an intervention could be on a participant was brought to my attention after the initial protocol submission. From an ethical position, at that time, I do not feel I fully appreciated the burden and stress that this study could have on an individual as I had not developed a comprehensive understanding of the difficulties experienced by people with MS. To make matters worse,

I attempted to complete the intervention program myself and found it difficult, frustrating, and dull.

So what to do? Numerous strategies were employed to mitigate the burden of the study on participants. Firstly, the protocol and intervention were presented to the MS PPI group to gauge their interest and what initial changes they would make. The study was, overall, met warmly and with interest. PPI members suggested halving the intervention 'dose' from an hour and a half a week to 45-minutes a week. Presenting at this panel was also an important step for me to move away from the distant experimenter to considering the impact on the people in that room. It did however raise another consideration – the want and need for interventions in this area. Many of the PPI group spoke of how this was an important area to develop, with one participant saying cognition was their primary concern. It was at this point that realisation that I was offering a theoretical intervention with no directly comparable evidence base became a concern of mine. I believe this issue still remains one of the greatest ethical considerations of this study. When speaking to potential participants, I found myself trying to downplay expectations to the point of almost endorsing a null effect. On a personal note, I found the name of the intervention somewhat troublesome (SMART: Strengthening Mental Abilities with Relational Training) and this is before considering my dislike of contrived acronyms.

In conclusion, I believe that both on a personal and project level, greater consideration could have been made to the iatrogenic effects of an intensive cognitive rehabilitation project whilst also managing potential participants' expectations. Going forwards, I would aim to build future experiments with participants well-being at the centre of the design.

Considerations on Design

The choices of study design in MS cognitive rehabilitation and how they contrasted with the design utilised in the present study became quickly apparent when completing the review. Only three studies recruited less than 20 participants (Bonzano et al., 2020; Kober et al., 2019; Reilly & Hynes, 2018). Most employed a controlled study with comparative groups. Not one single case experimental design study was identified. In hindsight this does induce a degree of concern that this design was not appropriate, if we were to follow the majority. Yet many of these studies were applying a novel untested intervention to people with MS and many others did not measure mood, fatigue, or quality of life. All important considerations when conducting intervention research but even more so if the intervention has not been tested before. Single case experimental designs are commonplace in the neuropsychological field, which is seen in a quick browse of the Neuropsychological Rehabilitation journal. The questions as to why single case designs are not observed in MS remains.

From the author's perspective, this design was appropriate for meeting its intended goals. The multiple baseline design was to allow for a greater confidence in attributing the initiation of training on changes in weekly subjective measures, providing power to a relatively small N design (Lanovaz & Turgeon, 2020). There were additional benefits in allowing for the repeated measurement of a proposed process of change and the regular assessments would track any iatrogenic effects of the intervention, increasing its safety. No other single case design would have been a conceptual fit. Take for instance, an ABAB reversal design. The immediacy of effect from the training would not be fast enough to induce measurable changes and for these changes to decrease with the training's withdrawal. A simple quasi-experimental pre-post design would not have met the studies objectives of exploring the process of change and would leave the participants with no contact

for 12 weeks, reducing safety. Whilst a larger study with group comparisons has been recommended in the future research, this is only done so in line with the MRC (2008) guidance as the study has completed its proof-of-concept stage. Such a design could potentially help in identifying the role of relational responding.

Returning to the question as to why single case designs are not overserved in MS research I remain at a loss. There could potentially be a rationale regarding the establishment of stable baselines due to the progressive nature of the disease, or perhaps the risk of a participant experiencing a relapse. Yet any progressive decline could be controlled for, and fewer outcome assessment studies are even more vulnerable to the effects of relapse. For example, if a participant was in the midst of a relapse at the baseline assessment and they had recovered at endpoint assessment, one would expect a noticeable improvement in performance (Morrow et al., 2011). A pre-post design experiment could then erroneously attribute the performance improvement the to the participants study condition.

Personal Reflection

Beginning this portfolio with an excerpt from the Litany Against Fear from Frank Herbert's Dune could certainly be viewed as dramatic and I am sure that, throughout the reading of this portfolio, the rationale for its inclusion has been the only question at the forefront of your mind. Its purpose was to encapsulate the most prevalent theme in this research project – my worries and fears in writing (in addition to being from one of my favourite books). This fear of writing has grown over the duration of my time on the course though a turning point occurred after a failed assignment in April 2020. Loosely applying 'two factor theory' (Mowrer, 1956), the writing of assignments, previously a neutral stimulus, was associated with the fearful event of failure. Placing this behaviour in context, we had entered national lockdown

and I was also in the midst of substantial personal circumstance change which severely limited my access to positive reinforcement contingencies. The removal of these positive contingencies and the addition of a novel noxious association with written work established a predominantly negatively reinforced repertoire.

A strong avoidance/avoidance conflict was established. 'I do not want to write this / I do not want to fail the course'. Admittedly, this is quite literally a textbook example to the point it I am concerned it will appear plagiarised from Dawson et al. (2016). Nonetheless, the experience was tangible, with delaying the writing of this portfolio until the fear of failure was becoming an all too real eventuality. Following the guidance of Skinner (1981) 'How to discover what you have to say', writing began in short intervals but unfortunately on reasonably distal topics. These sessions' length and focus were increased almost in line with graded exposure hierarchy. I feel I wasted a great deal of time worrying about what to write and never writing, resulting a panicked rush to the end. Now, reaching the conclusion, I ironically want to carry on or redo vast swathes of the project. A direct quote from Skinner's paper encapsulates the experience I am trying to relay *"Of course I wish I had more to say and that I had said it better, and I wish I could tell you more clearly what I have learned about saying it."* (Skinner, 1981, p. 7).

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Section V: Appendices

Appendix A: Journal Guidelines

Format-Free Submission

Authors may submit their paper in any scholarly format or layout. Manuscripts may be supplied as single or multiple files. These can be Word, rich text format (rtf), open document format (odt), or PDF files. Figures and tables can be placed within the text or submitted as separate documents. Figures should be of sufficient resolution to enable refereeing.

- There are no strict formatting requirements, but all manuscripts must contain the essential elements needed to evaluate a manuscript: abstract, author affiliation, figures, tables, funder information, and references. Further details may be requested upon acceptance.
- References can be in any style or format, so long as a consistent scholarly citation format is applied. Author name(s), journal or book title, article or chapter title, year of publication, volume and issue (where appropriate) and page numbers are essential. All bibliographic entries must contain a corresponding in-text citation. The addition of DOI (Digital Object Identifier) numbers is recommended but not essential.
- The journal reference style will be applied to the paper post-acceptance by Taylor & Francis.
- Spelling can be US or UK English so long as usage is consistent.

Note that, regardless of the file format of the original submission, an editable version of the article must be supplied at the revision stage

Appendix B: Ethical Approval Documentation

Health Research Authority

East Midlands - Nottingham 2 Research Ethics Committee
The Old Chapel
Royal Standard Place
Nottingham
NG1 6FS

Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

14 April 2020

Professor Roshan das Nair
Professor of Clinical Psychology and Neuropsychology
University of Nottingham
C22, Division of Psychiatry & Applied Psychology, Institute of Mental Health
Jubilee Campus
Nottingham
NG7 2TU

Dear Professor das Nair

Study title:	**SMART Rehab: Exploring the effects of Strengthening Mental Abilities with Relational Training on Cognitive Functioning for People with Multiple Sclerosis**
REC reference:	**20/EM/0080**
Protocol number:	**20013**
IRAS project ID:	**270463**

Thank you for your letter of 03 April 2020, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair and Lead Reviewer.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Recommendations

1. Add into your PIS that any audio recordings will be deleted once transcribed
2. Please check the spelling of Programme throughout your PIS.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Confirmation of Capacity and Capability (in England, Northern Ireland and Wales) or NHS management permission (in Scotland) should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for HRA and HCRW Approval (England and Wales)/ NHS permission for research is available in the Integrated Research Application System.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations

Registration of Clinical Trials

It is a condition of the REC favourable opinion that **all clinical trials are registered** on a publicly accessible database. For this purpose, 'clinical trials' are defined as the first four project categories in IRAS project filter question 2. Registration is a legal requirement for clinical trials of investigational medicinal products (CTIMPs), except for phase I trials in healthy volunteers (these must still register as a condition of the REC favourable opinion).

Registration should take place as early as possible and within six weeks of recruiting the first research participant at the latest. Failure to register is a breach of these approval conditions, unless a deferral has been agreed by or on behalf of the Research Ethics Committee (see here for more information on requesting a deferral:
https://www.hra.nhs.uk/planning-and-improving-research/research-planning/research-registration-research-project-identifiers/

As set out in the UK Policy Framework, research sponsors are responsible for making information about research publicly available before it starts e.g. by registering the research project on a publicly accessible register. Further guidance on registration is available at:

https://www.hra.nhs.uk/planning-and-improving-research/research-planning/transparency-responsibilities/

You should notify the REC of the registration details. We will audit these as part of the annual progress reporting process.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

After ethical review: Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study, including early termination of the study
- Final report

The latest guidance on these topics can be found at https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/.

Ethical review of research sites

NHS/HSC sites

The favourable opinion applies to all NHS/HSC sites listed in the application subject to confirmation of Capacity and Capability (in England, Northern Ireland and Wales) or management permission (in Scotland) being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS/HSC sites

I am pleased to confirm that the favourable opinion applies to any non-NHS/HSC sites listed in the application, subject to site management permission being obtained prior to the start of the study at the site.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Contract/Study Agreement template [Study Delegation Log]		21 February 2020
Copies of advertisement materials for research participants [Poster]	1.0	21 February 2020
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Evidence of Insurance]		21 February 2020

Interview schedules or topic guides for participants [Feedback Interview]	1.0	21 February 2020
Interview schedules or topic guides for participants [Feedback Interview]	1.0	21 February 2020
IRAS Application Form [IRAS_Form_21022020]		21 February 2020
IRAS Application Form XML file [IRAS_Form_21022020]		21 February 2020
IRAS Checklist XML [Checklist_03032020]		03 March 2020
IRAS Checklist XML [Checklist_06042020]		06 April 2020
Letter from funder [Clarification on funding]		27 February 2020
Letter from sponsor [Sponsor Letter]		21 February 2020
Non-validated questionnaire [RAI]		
Participant consent form [PCF]	1.0	21 February 2020
Participant information sheet (PIS) [PIS]	2.4	03 April 2020
Referee's report or other scientific critique report [Critique]		21 February 2020
Research protocol or project proposal [Protocol]	1.1	03 April 2020
Summary CV for Chief Investigator (CI) [CI CV]		21 February 2020
Summary CV for student [Stuent RB CV]		27 February 2020
Summary CV for supervisor (student research) [DD CV]		21 February 2020
Summary CV for supervisor (student research) [NM CV]		21 February 2020
Validated questionnaire [HADS]		
Validated questionnaire [MFIS]		
Validated questionnaire [MSQOL]		
Validated questionnaire [PQ]		
Validated questionnaire [SDMT]		

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:
http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Learning

We are pleased to welcome researchers and research staff to our HRA Learning Events and online learning opportunities– see details at:
https://www.hra.nhs.uk/planning-and-improving-research/learning/

IRAS project ID: 270463 Please quote this number on all correspondence

With the Committee's best wishes for the success of this project.

Yours sincerely

PP

Ms Bernadette Roberts
Chair

Email:nottingham2.rec@hra.nhs.uk

Enclosures: "After ethical review – guidance for researchers

Copy to: Ms Angela Shone

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Professor Roshan das Nair
Professor of Clinical Psychology and Neuropsychology
University of Nottingham
C22, Division of Psychiatry & Applied Psychology,
Institute of Mental Health
Jubilee Campus
Nottingham
NG7 2TU

Email: approvals@hra.nhs.uk
HCRW.approvals@wales.nhs.uk

14 April 2020

Dear Professor das Nair

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**SMART Rehab: Exploring the effects of Strengthening Mental Abilities with Relational Training on Cognitive Functioning for People with Multiple Sclerosis**
IRAS project ID:	**270463**
Protocol number:	**20013**
REC reference:	**20/EM/0080**
Sponsor	**University of Nottingham**

I am pleased to confirm that **HRA and Health and Care Research Wales (HCRW) Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

Please now work with participating NHS organisations to confirm capacity and capability, in line with the instructions provided in the "Information to support study set up" section towards the end of this letter.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?
HRA and HCRW Approval does not apply to NHS/HSC organisations within Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report

(including this letter) have been sent to the coordinating centre of each participating nation. The relevant national coordinating function/s will contact you as appropriate.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?
HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

What are my notification responsibilities during the study?

The standard conditions document "*After Ethical Review – guidance for sponsors and investigators*", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

Who should I contact for further information?
Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **270463**. Please quote this on all correspondence.

Yours sincerely,
Kelly Rowe

Approvals Manager

Email: approvals@hra.nhs.uk

Copy to: *Ms Angela Shone*

List of Documents

The final document set assessed and approved by HRA and HCRW Approval is listed below.

Document	*Version*	*Date*
Contract/Study Agreement template [Study Delegation Log]		21 February 2020
Copies of advertisement materials for research participants [Poster]	1.0	21 February 2020
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Evidence of Insurance]		21 February 2020
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Letter from sponsor [Sponsor Letter]		21 February 2020
Non-validated questionnaire [RAI]		
Organisation Information Document [OID]	1.0	21 February 2020
Participant consent form [PCF]	1.0	21 February 2020
Participant information sheet (PIS) [PIS]	2.4	03 April 2020
Referee's report or other scientific critique report [Critique]		21 February 2020
Research protocol or project proposal [Protocol]	1.1	03 April 2020
Response to Request for Further Information [Response to PO]		03 April 2020
Schedule of Events or SoECAT [SoE]	1.0	21 February 2020
Summary CV for Chief Investigator (CI) [CI CV]		21 February 2020
Summary CV for student [Stuent RB CV]		27 February 2020
Summary CV for supervisor (student research) [DD CV]		21 February 2020
Summary CV for supervisor (student research) [NM CV]		21 February 2020
Validated questionnaire [HADS]		
Validated questionnaire [MFIS]		
Validated questionnaire [MSQOL]		
Validated questionnaire [PQ]		
Validated questionnaire [SDMT]		

IRAS project ID	270463

Information to support study set up

The below provides all parties with information to support the arranging and confirming of capacity and capability with participating NHS organisations in England and Wales. This is intended to be an accurate reflection of the study at the time of issue of this letter.

Types of participating NHS organisation	Expectations related to confirmation of capacity and capability	Agreement to be used	Funding arrangements	Oversight expectations	HR Good Practice Resource Pack expectations
Participating NHS organisations will conduct all study activities as per protocol	Research activities should not commence at participating NHS organisations in England or Wales prior to their formal confirmation of capacity and capability to deliver the study	An Organisation Information Document has been submitted and the sponsor is not requesting and does not expect any other site agreement to be used.	Funding has been secured from Health Education England for studentship	A Principal investigator is expected at participating NHS organisations	Where arrangements are not already in place, research staff not employed by the NHS host organisation undertaking any of the research activities listed in the research application would be expected to obtain a Letter of Access based on standard DBS checks and occupational health clearance.

Other information to aid study set-up and delivery

This details any other information that may be helpful to sponsors and participating NHS organisations in England and Wales in study set-up.
The applicant has indicated that they do not intend to apply for inclusion on the NIHR CRN Portfolio.

Appendix C: Participant Information Sheet

Participant Information Sheet

(Final Version 2.4: 11.08.20)

IRAS Project ID: **270463**

Title of Study: **SMART Rehab: Exploring the effects of Strengthening Mental Abilities with Relational Training on Cognitive Functioning for People with Multiple Sclerosis**

Name of Chief Investigator: Roshan das Nair

Local Researcher(s): Rupert Burge

We would like to invite you to take part in our research study. Before you decide we would like you to understand why the research is being done and what it would involve for you. One of our team will go through the information sheet with you and answer any questions you have. Talk to others about the study if you wish. Ask us if there is anything that is not clear.

What is the purpose of the study?

This study aims to explore the effects that a novel computerised programme may have on improving 'cognitive functioning' (such as problem solving, reasoning, and memory). This programme is called SMART which stands for **S**trengthening **M**ental **A**bilities with **R**elational **T**raining. SMART was created by psychologists interested in how we learn and how this learning could be potentially improved. This

programme is accessed online and can be used on your home computer, laptop, or tablet.

A large portion of people with MS report experiencing problems with cognitive functioning. The purpose of this study is to see if SMART can help people who are experiencing these problems. As this is the first time SMART will be used with people with MS another element of study is to explore peoples' experience of using the SMART programme.

The results from this study will may go on to inform the creation of a larger study that will further explore the potential positive effects this programme may have.

Why have I been invited?

You are being invited to take part because you have been diagnosed with MS. We are inviting nine participants like you to take part

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part, you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part, you are still free to withdraw at any time and without giving a reason; this withdrawal would not affect your legal rights. The consent form states that this study is entirely voluntary, that being or not being a part of it will not affect your standard care, and that you are free to withdraw at any time amongst other things. (Please see Consent Form).

What will happen to me if I take part?

Once you have provided your consent to be a part of the study, you will be asked to complete an assessment of your cognitive abilities (such as those listed above), that will be conducted online, and then

to complete questionnaire on the same topic, with the whole session lasting approximately one hour. If any potential cognitive issues are raised, either through the assessment or reported by yourself, you will be included in the next part of the study. If no problem is identified in either you will not proceed further into the study.

There are four distinct phases to your involvement: Assessment, Training, and Follow Up One, and Follow Up Two. Please see below for a detailed description of the events you will be involved. There is an accompanying diagram overleaf that graphically represents your journey through the study. We appreciate that there is a lot of information to take on board so please do feel free to contact the research team via the supplied email address if you have any queries.

- Assessment - There will be an initial three to five-week phase where you will be asked to complete a series of questionnaires and tests, with the majority of the tests in the first week. The first set of testing will last approximately one hour and will be completed online. There will be three assessment length groups (A, B, and C), varying from three (A), four (B), and five (C) weeks. You will be assigned to one of these groups. Throughout the assessment phase you will need to complete a weekly questionnaire which will take approximately five minutes; this questionnaire can be completed online from home. A researcher will also call you weekly to see how you are getting on with the questionnaire you are completing at home; these calls will last for approximately 10 minutes and will be audio recorded.

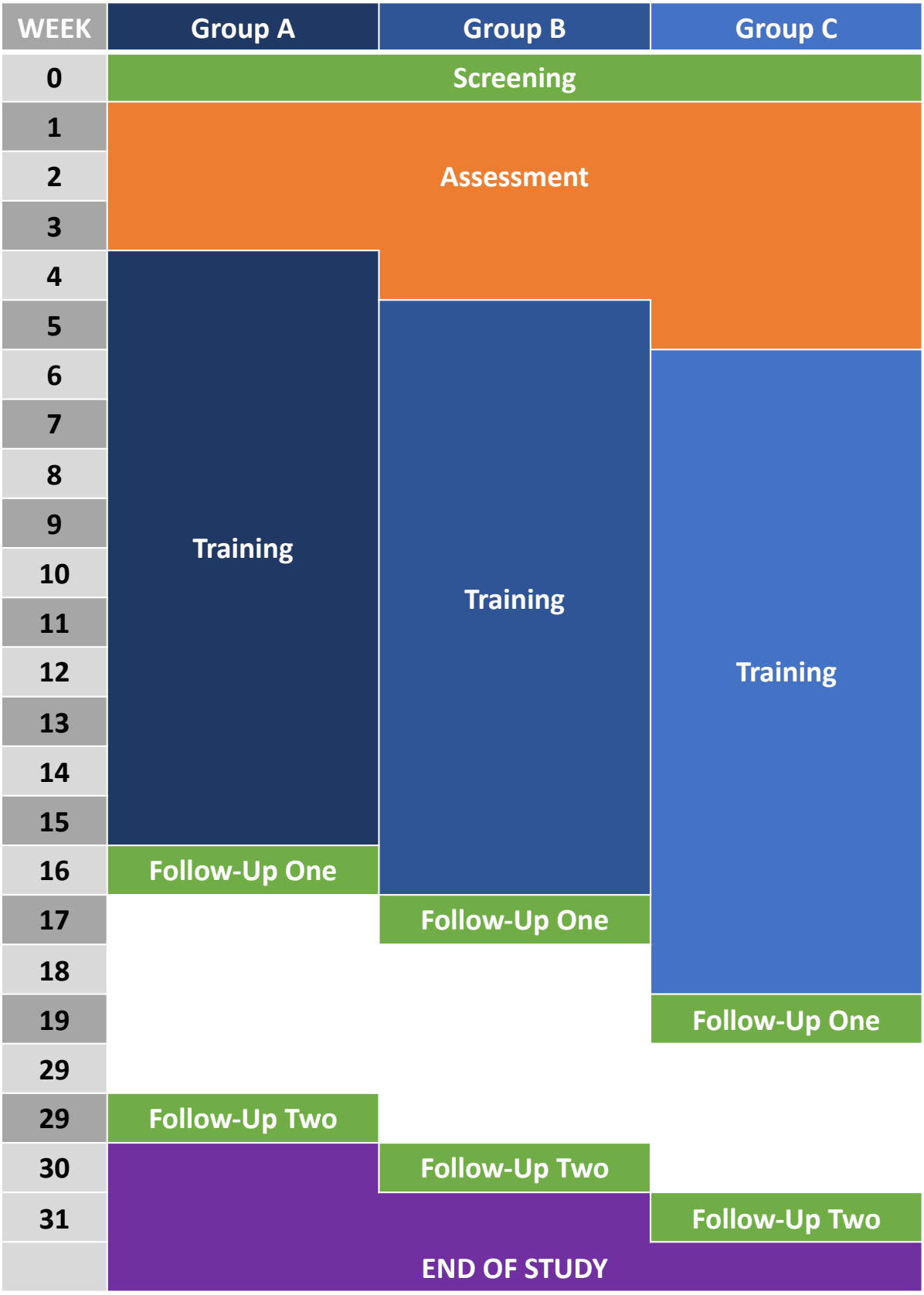
- Training - After the assessment, you will enter the 12-week phase where you begin to use the online SMART programme. You will be asked to use the SMART programme for around 45 minutes, once a week, for 12 weeks. In this 12-week phase you will also be required to continue with the five-minute questionnaire you were completing in the assessment phase above. There will be an additional bi-weekly questionnaire during this training phase; this questionnaire will also take about five minutes and can be completed online. You will also receive a

phone call from the researcher once a week to check in on how you are doing. The phone call will last around 10 minutes and will be audio recorded. In the 6th week of the training you will complete the same tests you will have completed in the assessment phase. Once the 12 weeks are completed you will be asked to stop using the SMART programme. All elements of the training phase can be completed at home.

- Follow Up One – The week after you finish with the SMART programme you will be asked to complete the series of questionnaires and tests again. After the assessment you will be asked to partake in a feedback interview, lasting approximately 30 minutes. The feedback interview will be conducted by the researcher, over the phone, will focus on your experience of the study and will be audio recorded.

- Follow Up Two – Three months after Follow Up One you will be asked to complete the same process described above for Follow Up One. The only difference at this point is that there will be no feedback interview.

- At the completion of the follow up two phase, you have finished with the study and will not be required to do anything more. Overall, from your first visit to your last, you would be involved in the study for up to 31 weeks (inclusive of the three-month break between Follow-Up 1 and Follow-Up 2).


WEEK
Group A
Group B
Group C
0
Screening
1
2
3
Assessment
4
5
6
7
8
9
10
11
12
13
14
15
Training
Training
Training
16
Follow-Up One
17
Follow-Up One
18
19
Follow-Up One
29
29
Follow-Up Two
30
Follow-Up Two
31
Follow-Up Two
END OF STUDY

Expenses and payments

Participants will be paid an inconvenience allowance to participate in the study; you will be provided at £25 shopping voucher card received at increments at set timepoints throughout the study. £5 at *Assessment,* £10 at *Follow-Up One*, and the final £10 at *Follow-Up Two*. As a key area we are investigating is the acceptability and usability of the program you would receive this gift car irrespective of the amount you have engaged with the programme.

What are the possible disadvantages and risks of taking part?

As SMART is a new programme it is hard to say if there any disadvantages or risks to taking part. The research on SMART has not highlighted any risks. The programme has been shown to a group of people with MS and it was stated that the programme is hard, long, and challenging. This difficulty may cause some people discomfort or frustration.

What are the possible benefits of taking part?

We cannot promise the study will help you but the information we get from this study may help improve care in this area in the future. The study will further help in the understanding of cognitive rehabilitation for people with MS and in understanding of the effects of the SMART programme.

What happens when the research study stops?

At the end of the study, your data, and the others that took part, will be used to see if there were any changes in your scores due to the programme being used. Your data relating to age, gender, how long you have had MS etc. will be used to see if there are any relations between those factors and any possible changes that occur.

What if there is a problem?

If you have a concern about any aspect of the study, you should ask to speak to the researchers who will do their best to answer your questions. The researchers' contact details are given at the end of this information sheet. If you remain unhappy and wish to complain formally, you can contact the Patient Advice and Liaison Service (PALS) on 0800 183 0204 or email PALS@nuh.nhs.uk.

In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against the University of Nottingham but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you.

Will my taking part in the study be kept confidential?

We will follow ethical and legal practice and all information about you will be handled in confidence.

If you join the study, we will use information collected from you during the course of the research. This information will be kept **strictly confidential**, stored in a secure and locked office, and on a password protected database at the University of Nottingham. Under UK Data Protection laws the University is the Data Controller (legally responsible for the data security) and the Chief Investigator of this study (named above) is the Data Custodian (manages access to the data). This means we are responsible for looking after your information and using it properly. Your rights to access, change or move your information are limited as we need to manage your information in specific ways to comply with certain laws and for the research to be reliable and

accurate. To safeguard your rights we will use the minimum personally – identifiable information possible.

You can find out more about how we use your information and to read our privacy notice at:

https://www.nottingham.ac.uk/utilities/privacy.aspx.

The data collected for the study will be looked at and stored by authorised persons from the University of Nottingham who are organising the research. They may also be looked at by authorised people from regulatory organisations to check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant and we will do our best to meet this duty

Your contact information will be kept by the University of Nottingham for 1 year after the end of the study so that we are able to contact you about the findings of the study and possible follow-up studies (unless you advise us that you do not wish to be contacted). This information will be kept separately from the research data collected and only those who need to will have access to it. All other data (research data) will be kept securely for 7 years. After this time your data will be disposed of securely. During this time all precautions will be taken by all those involved to maintain your confidentiality, only members of the research team given permission by the data custodian will have access to your personal data.

In accordance with the University of Nottingham's, the Government's and our funders' policies we may share our research data with researchers in other Universities and organisations, including those in other countries, for research in health and social care. Sharing research data is important to allow peer scrutiny, re-use (and therefore avoiding

duplication of research) and to understand the bigger picture in particular areas of research. Data sharing in this way is usually anonymised (so that you cannot be identified) but if we need to share identifiable information we will seek your consent for this and ensure it is secure. You will be made aware then if the data is to be shared with countries whose data protection laws differ to those of the UK and how we will protect your confidentiality.

Although what you say to us is confidential, should you disclose anything to us which we feel puts you or anyone else at any risk, we may feel it necessary to report this to the appropriate persons.

What will happen if I don't want to carry on with the study?

Your participation is voluntary and you are free to withdraw at any time, without giving any reason, and without your legal rights being affected. If you withdraw we will no longer collect any information about you or from you but we will keep the information about you that we have already obtained as we are not allowed to tamper with study records and this information may have already been used in some analyses and may still be used in the final study analyses. To safeguard your rights, we will use the minimum personally-identifiable information possible.

As this study is exploring how people feel about the SMART programme we would still very much like to hear your opinion on this prior to your withdrawal. As such, if you notify us that you wish to withdraw the researcher will ask you if you would like to complete the feedback interview. This is voluntary but, as stated, you may be asked to complete it at withdrawal.

What will happen to the results of the research study?

The results from this study will be written up for a Doctoral Thesis. This thesis aims to be published in an academic journal. Results from the study can be requested from the researcher, contact details can be found at the end of this document. As your data will have been anonymised you will not be identifiable in the results.

Who is organising and funding the research?

This research is being organised by the University of Nottingham and is being funded by the University of Nottingham.

Who has reviewed the study?

All research in healthcare is looked at by independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by Nottingham 2 Research Ethics Committee.

Further information and contact details

Rupert Burge – smartstudy@nottingham.ac.uk

Appendix D: Consent Form

CONSENT FORM

(Final Version 1.1 : 11.08.20)

Title of Study: **SMART Rehab: Exploring the effects of Strengthening Mental Abilities with Relational Training on Cognitive Functioning for People with Multiple Sclerosis**

IRAS Project ID: **270463**

Name of Researcher: **Rupert Burge**

Please read the following **five** statements carefully and select the most appropriate response.

1. I confirm that I have read and understand the information sheet version number **2.4** dated **11.08.20** for the above study and have had the opportunity to ask questions.

YES	NO

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care or legal rights being affected. I understand that should I withdraw then the information collected so far cannot be erased and that this information may still be used in the project analysis.

YES	NO

3. I understand that relevant data collected in the study may be looked at by authorised individuals from the University of Nottingham, the research group and regulatory authorities where it is relevant to my taking part in this study. I give permission for these individuals to have access to these records and to collect, store, analyse and publish information obtained from my participation in this study. I understand that my personal details will be kept confidential.

YES	NO

4. I understand that the interview will be recorded and that anonymous direct quotes from the interview may be used in the study reports.

YES	NO

5. I agree to take part in the above study.

YES	NO

Please enter you initials below to signify you have read and agreed to the above statements.

Please enter todays date (dd/mm/yyyy).

Appendix E: Interview Schedule

Feedback Interview Questions

(Draft Version 1.1 17.01.20)

Study title: SMART Rehab: Exploring the effects of Strengthening Mental Abilities with Relational Training on Cognitive Functioning for People with Multiple Sclerosis

IRAS Project ID: 270463

Name of Researcher: Rupert Burge

Semi-structured interview schedule for Feedback Interview.

To last approximately 30 minutes.

Interview to be audio recorded and transcribed by researcher.

1. **What was your experience of using the SMART programme?**
2. **What changes would you propose to the SMART programme?**
3. **What was your experience of the measures / tests used in the study?**
4. **What changes would you make to the measures / tests used?**
5. **Do you feel that have experienced any changes throughout the study (cog / mood / fatigue etc)?**
6. **If so, what do you attribute these changes to?**
7. **What changes would you make to the design of the study?**

Appendix F: Meta-correlation analysis results for RBANS Subtests.

Subtest	Correlation (*r.*)	Confidence Interval	Heterogeneity (I^2)	*z*	Sig. (2-tailed)
List Learning	.69	.52 - .80	54.20	13.43	<.001
Story	.74	.28 - .92	32.81	6.24	<.001
Figure Copy	.52	.43 - .59	.00	21.50	<.001
Line Orientation	.72	.33 - .90	93.92	6.88	<.001
Picture Naming	.64	.30 - .83	87.78	7.29	<.001
Semantic Fluency	.64	.40 - .80	77.72	9.79	<.001
Digit Span	.68	.40 - .85	87.60	8.80	<.001
Coding	.87	.57 - .97	95.20	8.20	<.001
List Recall	.65	.35 - .83	61.07	8.15	<.001
List Recognition	.50	.37 - .61	3.18	14.95	<.001
Story Recall	.62	.37 - .78	57.39	9.39	<.001
Figure Recall	.68	.57 - .76	18.20	20.40	<.001

SMART Rehab: Strengthening Mental Abilities with Relational Training in MS

Rupert Burge, David L Dawson, Nima G Moghaddam, & Roshan das Nair

Trent Doctorate in Clinical Psychology

The University of Nottingham
UNITED KINGDOM · CHINA · MALAYSIA

UNIVERSITY OF LINCOLN

INTRODUCTION

Multiple Sclerosis is a progressive neurodegenerative disease where 40-70% experience cognitive difficulties[1]. There is a rationale in developing interventions as no 'gold standard' exists[2].

Derived Relational Responding has been proposed to underpin a range of human intelligent behaviours[3]. Training of relational responding with SMART has shown significant increases across a range of IQ tests[4-5].

Objectives

1.Examine the effect of SMART on objective and subjective cognitive functioning and secondary outcomes (mood, fatigue, QoL).
2.Explore acceptability, practicality, and feasibility of the intervention.
3.Explore relational responding as a process of change.

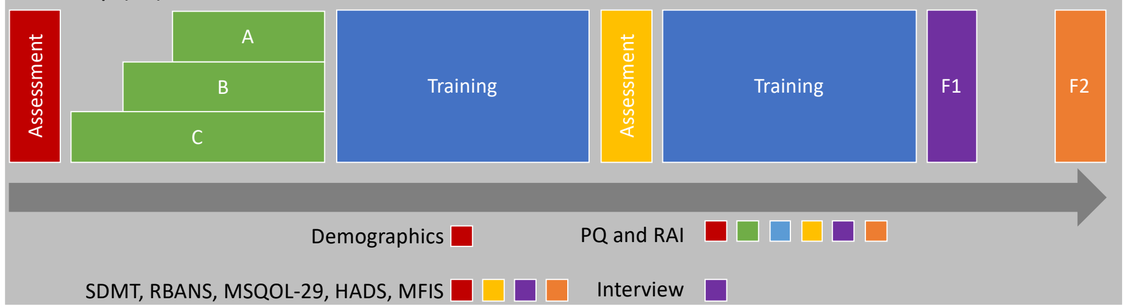
INTERVENTION

SMART – 45 minutes per week for 12 weeks. Online program. Participants trained in Derived Relational Responding skills that increase in complexity as they progress. Presented with multiple exemplars consisting of non-sense words. The training uses *Same/Opposite and More/Less* relations.

NUK is opposite to **ZEQ**
ZEQ is opposite to **BIL**
BIL is the same as **BEL**
*Is **NUK** opposite to **BEL**?*

DESIGN

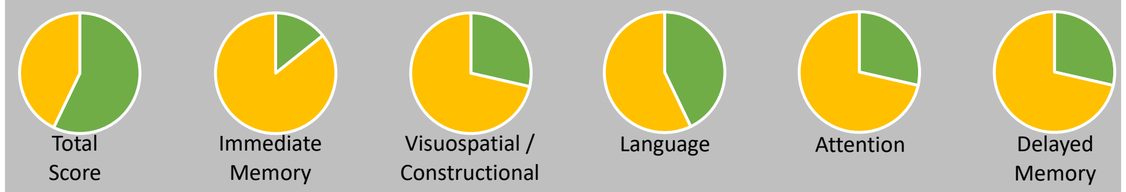
A multiple baseline single case experimental design was used. We aimed to recruit nine participants with three in each of the three baselines (A – three weeks, B – four weeks, C – five weeks). Full assessment at start of baseline, halfway through training, one week follow-up (F1) and three month follow-up (F2).



RESULTS

Pie charts show percentage of total participants changes. Green – Positive Reliable Change. Yellow – No Reliable Change.

RBANS



SDMT

- **Participants –** Six women and two men (N=8) aged between 36-75 years were recruited from local MS Patient and Public Involvement group. One withdrew at mid-assessment.
- **Subjective Functioning –** No improvements observed on Personal Questionnaire.
- **Relational Abilities Index –** Only one participant did not show increasing relational skills.
- **Secondary –** Mood, Quality of Life, and Fatigue remained fairly stable over the study**.**

FEEDBACK INTERVIEWS

- Majority reported positive experience of intervention.
- Face-to-face testing preferrable to online assessments.
- Increase in intervention intensity and duration recommended.
- Three reported cognitive improvement attributed to the study.

DISCUSSION

The majority of participants showed reliable improvements in the SDMT and this also represented a clinically significant improvement for 100% of participants who were in a clinically impaired range at intake. Improvements were most frequently seen in RBANS Total Score.

Subjective reports did not corroborate with objective assessments and these findings are echoed elsewhere[6]. Findings question Personal Questionnaire sensitivity or objective assessment's ecological validity.

No discernible relationship between the trained relational skills and outcomes could be established. Relational skills' role in mediating cognitive improvements is inconclusive. Further examination of the process of change is required.

Feedback interviews and no reported iatrogenic effects provide supporting evidence to develop this promising intervention.

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