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An investigation into theory of mind in individuals with multiple sclerosis:

A systematic review of the psychometric properties of the theory of mind measures used in multiple sclerosis

and

Psychological, interpersonal and social functioning in multiple sclerosis: the role of theory of mind

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Thesis Abstract

Theory of Mind (TOM) is an important ability in guiding social behaviour, with impairments in TOM being associated with psychosocial difficulties. Over recent years, individuals with multiple sclerosis (MS) have been consistently shown to have impaired TOM abilities, however, little is known about the psychosocial impact of these impairments in this population. This thesis has two sections. Initially, a systematic review was completed that assessed and compared the psychometric properties of the TOM measures which have been used with individuals with MS. This highlighted that seventeen different TOM measures have been used with individuals with MS. Through exploring the psychometric properties of these seventeen measures, it was revealed that no measure has been validated on an MS sample and more generally there was little information about the psychometric properties of these measures. Whilst recommendations are tentatively made on TOM measure selection for individuals with MS, the paper discusses the remaining challenges in measure selection, accuracy of measurement and the need for further research into these measures. Secondly, an empirical study explored the relationships between TOM abilities and psychosocial outcomes in individuals with MS. In total, 36 individuals participated, which involved completing neuropsychological tasks of TOM and executive functioning abilities, as well as self-report measures of their psychological, interpersonal and social abilities. Results indicated that TOM was not associated with psychological, interpersonal and several areas of social functioning, however, TOM performance was significantly related to social withdrawal, employment and quality of life. These findings are discussed and areas for future research identified.

A systematic review of the psychometric properties of the theory of mind measures used in multiple sclerosis

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Abstract

Background: Theory of Mind (TOM) abilities are important in guiding an individual's social behaviour and supporting their interactions with others. Impairments in TOM have been linked to poorer psychosocial outcomes, including lower quality of life and depressive symptomology. Individuals with Multiple Sclerosis (MS) have been consistently shown to have impaired TOM. Accurate measurement is critical for identifying impairments and individuals' needs, and for intervention planning.

Objective: This review aimed to summarise the TOM measures that have been used to explore TOM abilities in individuals with MS and to assess and compare the psychometric properties of these measures.

Method: Systematic literature searches were performed in Ovid using the PsycINFO, Embase, Ovid MEDLINE and Epub databases. To be included, studies had to report using at least one TOM measure with an MS sample. The psychometric quality of the measures was assessed using published quality assessment criteria.

Results: In total, twenty-eight studies, which used a range of seventeen different measures of TOM, were included in this review. There was wide variation in the reported psychometric information for the various TOM measures, with large amounts of missing information limiting the ability to review and compare psychometric properties across the TOM measures. Only five of the seventeen measures scored more than half marks on the quality assessment measure. No TOM measure had been specifically validated on an MS sample and only a few validated on other neurological populations.

Conclusions: The most psychometrically established measures of TOM are reported, and recommendations are tentatively made surrounding appropriate measure selection within an MS sample. There are significant gaps in the reported psychometric properties of TOM measures. Future work is necessary to address these gaps and to explore more fully their suitability for use within MS and other neurological populations.

Introduction

There is an ongoing challenge within the field of psychology to develop neuropsychological tests which are accessible to all, but are also able to identify subtle cognitive dysfunction (Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001). One particular neuropsychological domain where this is a challenge is Social Cognition (SC). SC is the umbrella term for a number of cognitive abilities which are used to guide our behaviour and support successful interaction with others (Lysaker, Dimaggio, & Brüne, 2014). One SC ability which has generated a lot of research interest in a variety of populations is Theory of Mind (TOM), which refers to an individual's ability to attribute the mental states of oneself and others (e.g. their beliefs, goals, intentions and emotions; Banati et al., 2010). TOM itself is also a multifaceted construct, used to explain several cognitive skills which are acquired at different developmental stages, including understanding mental states and recognition of social faux pas.

Research has shown that in neurotypical children, these TOM abilities start to develop between the ages of three and four years (Wimmer & Perner, 1983) and continue to develop in a hierarchical fashion. Children initially develop the ability to complete first-order false belief tasks (i.e. those which assess an individual's knowledge that others may have a different mental representation than them and therefore can hold a false belief; Wimmer & Perner, 1983). Then around the age of six and seven years they acquire the capacity to understand and make inferences about another individual's mental state and complete second order false-belief tasks (i.e. those that assess an individual's ability to understand what someone thinks about what another individual thinks; Stone, Baron-Cohen, & Knight, 1998; Wimmer & Perner, 1983). Finally, around the ages of nine to eleven years, children become able to recognise and understand social faux pas (Stone & Baron-Cohen, 1998).

The development of these skills is not only of crucial importance as they drive social behaviour, allow individuals to connect with others, develop relationships and act in "socially appropriate ways" (Kennedy & Adolphs, 2012), but they also have wider implications on an individual's physical and mental health. This has been highlighted through research in a range of populations who are known to have impaired TOM, including individuals with autism spectrum disorder (Baron-Cohen, Leslie, & Frith, 1985; Moran et al., 2011) and schizophrenia

(Harrington, Langdon, Siegert, & McClure, 2005; Lysaker et al., 2014). Research has evidenced relationships between impaired TOM abilities and: depressive symptomology (Wang et al., 2018); lower quality of life (Canty, Neumann, Fleming, & Shum, 2017); and fewer and poorer quality social relations (Brüne, Abdel-Hamid, Lehmkämper, & Sonntag, 2007; Kennedy & Adolphs, 2012). Therefore, the capacity to measure these abilities may help identify individuals who are in need of psychosocial support.

In recent years there has been increased research interest into cognitive functioning, including social cognition abilities in individuals with Multiple Sclerosis (MS). This work has consistently highlighted impaired TOM abilities when compared against matched control samples (Cotter et al., 2016). Research into TOM abilities in MS is ongoing and gaps remain in our understanding in comparison to TOM abilities in other populations, such as individuals with autism spectrum disorder or schizophrenia. Given the significant wider implications of impaired TOM on other health and psychosocial outcomes it is important that accurate, comprehensive and ecologically valid TOM assessments are available for individuals with MS (McDonald et al., 2006). These assessments are relied upon for identifying TOM impairments and informing rehabilitation interventions.

Currently, there are a large number of assessments available to assess TOM abilities at the various developmental levels. Within the MS research to date, a large variety of TOM measures have been used across studies (Cotter et al., 2016). This includes assessments such as the Sally-Ann doll task (Wimmer & Perner, 1983) which assesses false belief, the Reading the Mind in the Eyes Test (Baron-Cohen et al., 2001) which assesses mental inferencing and the Faux Pas Test (Stone, Baron-cohen, & Knight, 1998) assessing faux pas recognition and understanding. Whilst these measures have been tested, adapted, used and evaluated in some populations, it remains unclear which are more suitable for use with individuals with MS, and more generally there remains debate over their development, administration and interpretation (Canty et al., 2017).

Many TOM tasks were developed for use with young children (e.g. the Sally-Ann doll task). Individuals with Autism Spectrum Disorder, who are known to have impaired TOM abilities, have been shown to pass these tasks (see Dziobek et al., 2006), which questions whether

these tasks would be able to identify mild cognitive dysfunction in adults of normal intellectual functioning (Baron-Cohen et al., 2001). Similarly, most TOM tasks primarily target one of the three developmental stages and therefore successful completion of one task does not necessarily generalise across all TOM abilities. This is of crucial consideration when comparing performance across studies, as results will likely be dependent upon the task administered. A further challenge in assessing TOM is the administration burden, given the ongoing debate surrounding the influence of other cognitive abilities (e.g. executive functions and verbal IQ) on task performance (Wade et al., 2018). This means that in clinical practice several tests have to be completed to ensure more accurate conclusions are drawn. Finally, there has been an ongoing drive in recent years to develop more advanced, ecologically valid measures of TOM, given the criticism of earlier tasks that performance is not generalisable to daily life and that researchers were in fact making broad conclusions from tests that measured a very narrow function (Canty et al., 2017). Despite efforts to make tests more ecologically valid there remains some debate regarding the extent to which this has been successful (Lancaster, Stone, & Genova, 2019).

It is important to acknowledge that whilst there are critiques, many of these measures have been validated across a range of populations (Baron-Cohen et al., 2001; Happé, 1994; Stone et al., 1998). However, as these measures have not been validated on a MS sample, it remains unclear which measures are most suitable for use with individuals with MS. Additionally, to date no reviews have been completed to compare and evaluate TOM assessment measures in any population sample, and rather a test's psychometrics have been explored in isolation. Therefore, it remains unclear which measures are the most psychometrically established in the literature. As TOM in MS is an ongoing topic of research interest, the current review had two main aims, to:

1. identify tasks/ tests/ instruments which have been used to assess TOM in individuals with a diagnosis of MS; and
2. assess and compare the psychometric properties of these measures against published quality assessment criteria (Terwee et al., 2007).

Methods

The review protocol was registered on PROSPERO (registration number: CRD42020169274).

Search Strategy

Once the general topic area of Theory of Mind (TOM) assessment in individuals with Multiple Sclerosis (MS) was identified, scoping searches were carried out to ascertain the volume and type of papers/evidence available for inclusion in this review. Following this, systematic literature searches were run in Ovid using the PsycINFO (1806 to January week 2 2020), Embase (Classic and 1947 to 2020 January 17), and Ovid MEDLINE(R) and Epub (Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to January 17th, 2020) databases to identify all papers which assessed TOM abilities in individuals with MS. Searches were limited to studies published in English with human participants. The full search string entered and run in Ovid is outlined in Table 1. The search was completed on 19th January 2020.

Table 1: Advanced Search String Run in Ovid

1	Theory of mind
2	TOM
3	Social cognit*
4	Mentali*
5	1 or 2 or 3 or 4
6	Multiple Sclerosis
7	MS
8	6 or 7
9	5 and 8
10	Removed duplicates from 9

Inclusion and Exclusion Criteria

Studies were included in this systematic review if they met the following criteria: (i) the study population was individuals with MS; (ii) the study utilised an instrument to explicitly and objectively measure TOM abilities; (iii) the study was published in English; and (iv) the study was an empirical paper. Exclusion criteria included: (i) articles studying a paediatric MS population; (ii) review or theoretical articles; and (iii) articles in unpublished grey literature.

Study Selection

In total, the search of OVID retrieved 978 articles (see Figure 1 below for PRISMA flow chart of study selection process). After duplicates were removed on Ovid, citations and abstracts were exported into excel and were screened by the first author. Title, abstract and full text screening was done solely by the first author. Reference lists from identified articles were also screened to ensure no study had been missed or not identified through the search string.

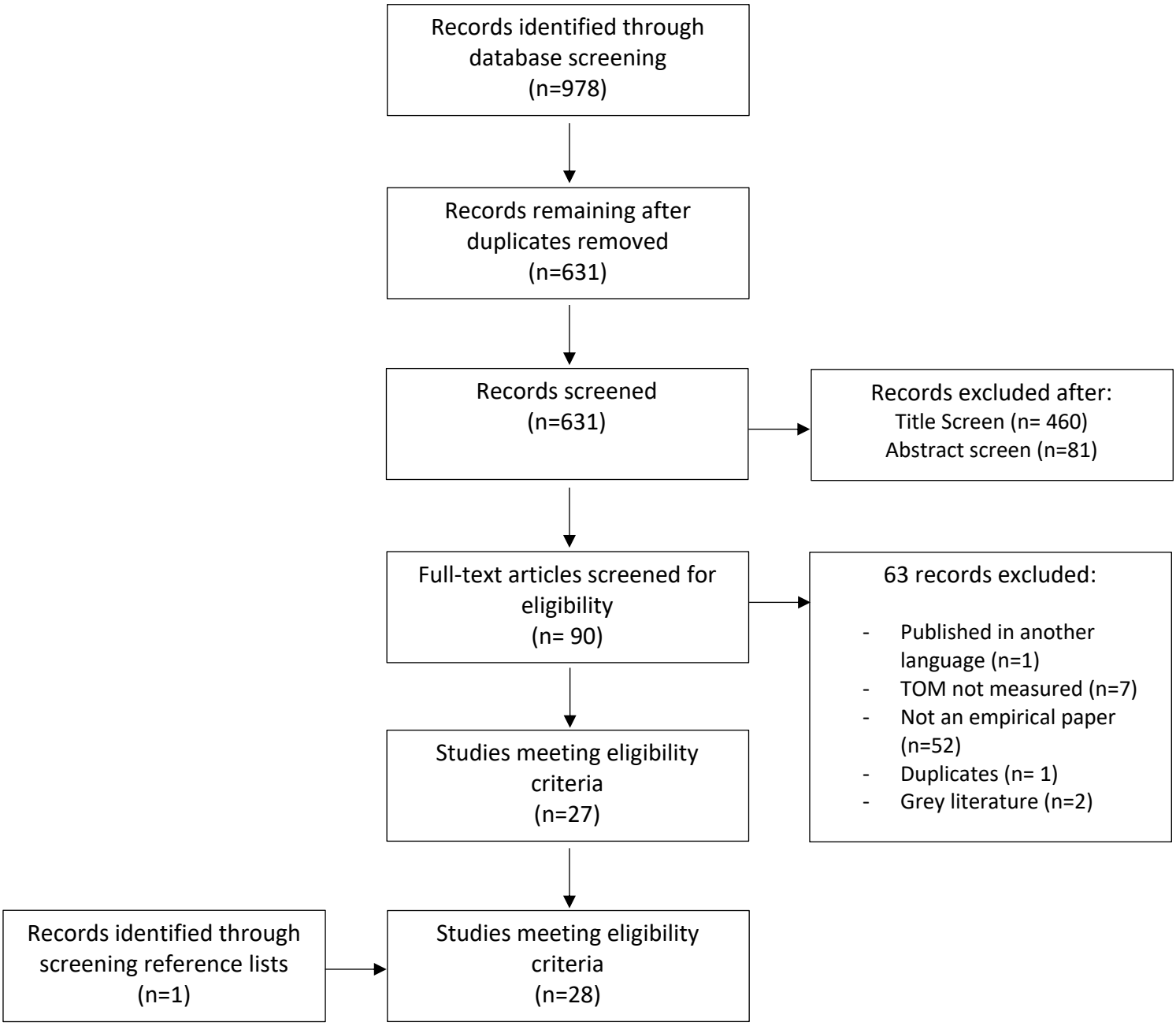

Figure 1: PRISMA flow chart of study selection process

Data Extraction

From each of the studies, descriptive information was gathered on sample size, MS diagnosis type, TOM measures used, date and country. In total, there were 17 different TOM measures/assessments identified across the 28 studies. Additionally, any reported psychometric properties of the TOM measure(s) were recorded.

Following data extraction from the studies measuring TOM in MS, the first author searched the literature for the original, and any subsequent study which aimed to validate each of the identified TOM measures. Original validation papers were identified from reference lists, with further searches for further validation papers being identified through searches on the university database. Specifically, this involved searching within OVID for validation papers for each of the TOM measures. All psychometric data on the TOM measures was extracted and assessed against quality criteria.

Quality Evaluation/ Assessment

The psychometric properties for each measure, reported either in the 28 papers identified through the systematic search or from validation studies, were reviewed and assessed against quality criteria (Table 2), adapted from Terwee et al. (2007). Their quality assessment criteria were used as they were developed specifically for assessing the measurement properties of health questionnaires. Whilst TOM measures are not health questionnaires, Terwee et al. (2007) work is the most closely related, has been used in similar systematic searches (e.g. see Fletcher, Flight, Gunn, Patterson, & Wilson, 2020; Hidding, Altenburg, Mokkink, Terwee, & Chinapaw, 2017; Strauss et al., 2016) and sets out clear definitions of explicit criteria for what constitutes good measurement properties. Two of the criteria assessed by Terwee et al. (2007) were not rated in the current review: “criterion validity” (the extent to which scores on a particular instrument relate to a gold standard) and “responsiveness” (the ability of a questionnaire to detect clinically important changes over time). This was due to there not being a clear gold standard TOM measure to compare against and because the TOM measures are not primarily designed to measure clinically meaningful change over time, respectively.

In comparison with Terwee et al. (2007) who uses (+), (?), (-) and (0) ratings, here numerical values were used, similar to that Strauss et al. (2016), to make the results easier to interpret (see Table 2 for specific criteria). The maximum possible quality assessment score for any measure was 12, with higher scores being indicative of more established and validated measures. A second rater independently completed the quality analysis on a random subsample (29%) of the TOM measures and the inter-rater agreement was 89.58%. Any disagreements in rating were discussed together and a decision made collaboratively.

Table 2: Quality Criteria for Assessment of Psychometric Properties (adapted from Terwee et al., 2007, and scoring informed by Strauss et al., 2016)

Property	Definition	Criteria [a] [b]
Content Validity	The extent to which the concepts of interest are comprehensively represented by the items in the questionnaire	2 A clear description is provided of the measurement aim, the target population, the concepts that are being measured, and the item selection 1 A clear description is lacking OR only target population involved 0 No target population involved OR No information found on target involvement
Internal Consistency	The extent to which items in a (sub)scale are correlated, thus measuring the same concept	2 Cronbach's alpha calculated per dimension AND Cronbach's alpha between 0.70 and 0.95 1 Cronbach's alpha not calculated for each dimension OR doubtful design or method 0 Cronbach's alpha <0.70 or .0.95, despite adequate design or methodology OR No information found on internal consistency
Construct Validity	The extent to which scores on a particular instrument relate to other measures in a manner that is consistent with theoretically derived hypotheses concerning the concepts that are being measured	2 hypotheses are specified in advance AND at least 75% of the results are in correspondence with these hypotheses 1 doubtful design or method (e.g. no hypotheses) 0 Less than 75% of hypotheses confirmed, despite adequate design and method OR No information found on construct validity
Reliability	The extent to which respondents can be distinguished from each other, despite measurement error	2 ICC or weighted Kappa ≥0.70 1 doubtful design or method (e.g. no time interval mentioned) 0 ICC or weighted Kappa <0.70, despite adequate design and method OR No information found on reliability
Floor and Ceiling Effects	The number of respondents who achieved the lowest of highest possible score	2 ≤15% of the respondents achieved the highest or lowest possible scores 1 Doubtful design or method 0 >15% of the respondents achieved the highest or lower possible scores, despite adequate design and methods OR No information found on floor and ceiling effects
Interpretability	The degree to which one can assign qualitative meaning to quantitative scores	2Mean and SD scores presented of at least four relevant subgroups of patients and MIC defined 1 Doubtful design or method OR less than four subgroups OR no MIC defined 0 No information found on interpretation

MIC = minimal important change; SDC = smallest detectable change; LOA = limits of agreement; ICC = Intraclass correlation; SD = standard deviation.

[a] 2 =positive rating; 1 = indeterminate rating; 0= negative rating OR no information available.

[b] Doubtful design or method= lacking a clear description of the design or methods of the study, sample size smaller than 50 subjects (should be at least 50 in every (subgroup) analysis), or any important methodological weakness in the design or execution of the study.

Results

What measures have been used to measure Theory of Mind in individuals with Multiple Sclerosis?

In total, 17 Theory of Mind (TOM) measures were identified from the 28 studies of TOM in individuals with Multiple Sclerosis (MS). These 28 studies were conducted across 13 countries, with sample sizes ranging from 15 to 64 (M=40.71, SD= 15.02). All demographic information from the TOM in MS studies is reported in Table 3. Additionally, a brief summary of each of the 17 TOM measures used with individuals with MS is reported below.

The frequency of TOM measure use varied greatly. The adult eyes test was the most commonly used measure of TOM within the MS population, with 14 of the 28 papers using it. The faux pas, or an adapted version of the faux pas test was the second most common measure used in eight of the papers. In contrast, several measures were only used in one of the papers: Bordeaux social cognition assessment; conversation and insinuations task; emotional attribution task; Genova social cognition scale; mini social cognition and emotional assessment; TOM picture sequencing task and the virtual assessment of mentalising ability.

Baron-Cohen Adult Eyes Test (Baron-Cohen et al., 2001)

This test, also known as the Reading the Mind in the Eyes test (RMET), is made up of 36 photographs showing a set of eyes, each portraying different complex mental states. No other facial features are shown. For each set of eyes, the participant is asked to select one of four emotions which best describes the mental state of the individual in the picture. A point is awarded for each correctly identified mental state, with higher scores being indicative of better performance.

Baron-Cohen Adult Faces Test (Baron-Cohen, Wheelwright, & Jolliffe, 1997)

This task consists of twenty photographs, all of the same actress from the shoulders upwards, who is displaying different complex mental states. The participant has to choose one of two words which are printed below each photograph that best represents the emotion or mental state portrayed by the face. Each correctly identified emotion/mental state is awarded a point, with larger scores denoting better performance.

Bordeaux Social Cognition Assessment Protocol (Etchepare et al., 2014)

The Bordeaux Social Cognition Assessment Protocol is made up of seven recognised tests of Social Cognition. Whilst it assesses TOM using the Faux Pas, Attribution of Intentions and Baron-Cohen's Eye Tests, and facial emotion recognition through the Adult Faces Test, it also measures other social cognition abilities such as emotional awareness, emotional fluency and alexithymia through other subtests. Information for the faces, eyes and faux pas' tests are reported separately (see test description). The attribution of intentions test is made up of 30 comic strips involving human figures. Each comic strip comprises of three pictures which represent a short story. Individuals then choose one of three further pictures which provides a logical end to the story. The protocol for the Bordeaux social cognition assessment is written in French and as far as the author is aware, has not been translated or used within other language populations. Due to the translation barrier, it is not possible to identify if or how the subtest scores are combined into an overall score of social cognition ability.

Conversation and Insinuations (Ouellet et al., 2010)

This is a video task comprising of four clips, each lasting around two minutes. The video is paused approximately every 20 seconds and the individual asked a question about a character's response. Each response included one of the following language acts: irony, faux pas, lies or indirect messages (Ouellet et al., 2010). Individuals have to select the correct answer from four possible answers which appear on the screen.

Emotion Attribution Task (Blair et al., 1995)

The Emotional Attribution Task consists of between 9 and 35 short social stories, depending on the task version. Once each story has been read out, individuals are asked how they think the main character in the story would be feeling. For each correctly identified emotional state individuals are awarded a point, with higher scores illustrating better performance.

False Belief Tasks (Baron-Cohen et al., 1985; Rowe, Bullock, Polkey, & Morris, 2001)

Two of the papers (Henry et al, 2011, 2017) used false belief tasks, which they describe as being based upon the work of Baron-Cohen, Leslie, & Frith, (1985) and Rowe, Bullock, Polkey, & Morris, (2001). They stated using two first-order false belief tasks (assessing an individual's

ability to recognise that someone can hold a mistaken belief that is different from their own true belief), two second-order false belief tasks (assessing an individual's ability to understand what another person thinks another person thinks) and 2 faux pas stories (see below). Following each story being read to them, participants were asked 4 questions to assess their identification and understanding of the false belief or faux pas present. Points were awarded for correct answers, with detection, understanding and total scores being generated.

Faux Pas (Baron-Cohen, O'Riordan, Stone, Jones, & Plaisted, 1999; Stone et al., 1998)

The Faux Pas Recognition Test (Baron-Cohen et al., 1999; Stone et al., 1998) comprises of twenty short vignettes, ten of which detail a situation where a 'faux pa' is present, whilst the other ten are control vignettes. The faux pas and control stories are presented in a random order. If an individual identifies a faux pa to be present within a vignette, they are asked further questions which explore their detection of the faux pa and understanding of the character's intentions and beliefs. Individuals had to answer all questions correctly for each faux pa to gain the point for that faux pa, with a total of 10 points available. One point for each faux pa story, with higher scores being indicative of better understanding of the faux pas.

Faux Pas- Adapted (Henry et al, 2011, 2017)

All nine studies that reported using the Faux Pas' test with individuals with MS used an alternative or adapted version of the standard test developed by Stone et al., (1998). The adaptations made to the faux pas test were unique to and varied by study. This ranged from some studies using as few as two faux pas stories (Henry et al, 2011, 2017) to others using up to five. A few of the studies used only faux pas stories, whilst others also included control stories. It was unclear for several of the studies how many stories they had used from the original measure versus how many they had created. Whilst most of the adapted measures require individuals to identify and explain the faux pas, others only require the individuals to detect the faux pas to get the full scoring credit (e.g. Henrry et al.,2017).

Genova Social Cognition Scale (Martory et al., 2015)

The Genova Social Cognition Scale was developed from existing, recognised measures for use in everyday clinical practice. It comprises of six tasks, five of which assess social cognition and one assesses executive functioning. These include social cognition stories which assess false belief and faux pa recognition; 10 items from the reading the mind in the eyes test; cartoons assessing non-verbal false belief recognition; a social inference task and "absurd stories" which comprises of stories without social aspect. Scores are generated for each test, with full points being given to complete answers and half marks given to incomplete or correct answers without explanation.

Mini Social Cognition and Emotional Assessment (Bertoux et al., 2012, 2014)

This is a shorter version of the Social Emotional Assessment Test. It comprises of an abbreviated version of the Faux Pas test and the Facial Emotion Recognition test. The faux pas component comprises of 10 vignettes, which requires the individual to identify a Faux Pa if it occurred (n=5). The facial emotion recognition test used 35 faces from the Ekman faces test, a test of emotion recognition. Individuals are asked to identify the emotion a face is displaying. Each test is scored individually, as per test scoring instructions, before scores being added together to form a total score.

Movie for the Assessment of Social Cognition (Dziobek et al., 2006)

This test involves watching a 15-minute video about four individuals at a dinner party. The video is stopped on 46 occasions and the participants are asked questions about the characters' thoughts, feelings and intentions. For each correct emotion identification participants are given one point, with all scores being added together to give a total score.

Strange Stories (Happé, 1994)

This task involves the participant reading 24 vignettes where someone says something they do not mean literally. There are 12 categories of stories (e.g. lie, white lie, misunderstanding, sarcasm, double bluff). Individuals' comprehension is initially assessed by asking "is it true what X said?" then the justification is explored by asking "why did X say that?". Additionally, there are 4 control questions which ask about physical events. A total of one point was

available per story and this was awarded based upon the subject's justification of why X said what they did.

Strange Stories- Adapted (Isernia et al., 2019; Raimo et al., 2017)

Two studies (Isernia et al., 2019; Raimo et al., 2017) used alternative versions of the Strange Stories task developed by Happé (1994), however both made reference to this measure in their papers. Both papers used differing numbers of TOM and control stories. Scoring varied across studies with either one or two points being available per story. These were awarded based upon the completeness of the inference of mental state rather than a purely factual answer.

The Awareness of Social Inferences Test (TASIT; McDonald et al., 2006; McDonald, Flanagan, Martin, & Saunders, 2004; McDonald, Flanagan, Rollins, & Kinch, 2003)

The TASIT is a test made up of three parts, the first of which assesses emotional recognition followed by the latter two parts assessing TOM. Part two involves asking individuals to watch a series of vignettes of adults engaging in conversations and then asking them to determine whether their reactions were sincere or sarcastic. Part three asks individuals to decide whether the individual in the clip is deliberately concealing the truth through lying or through use of sarcasm. Questions are asked on what the speaker said, what they intended, how the protagonist would have felt and what was the unsaid message communicated. Scores were awarded for correct answers to each of these questions.

The Theory of Mind Sequencing Task (Brüne, 2003)

The Theory of Mind Sequencing Task comprises of only one story which is made up of four cartoon pictures. Initially, individuals are asked to sequence the pictures before being asked five questions: a first-order false belief question ("what does the monkey think is in the paper bag?") followed by the subsequent reality question ("what is really in the paper bag?"), the a second-order false belief question ("what does the monkey think the maid intends?") followed by being asked the reality question again ("what is really in the paper bag?"), then finally they are asked a tactical deception question ("what does the maid intend?"). There is a maximum of 5 points available for this task.

TOM Video Task (Sullivan & Ruffman, 2004)

The TOM Video Task involves watching 26 silent video clips showing characters' interactions before choosing one of two words which best describes the thoughts or feelings of the character in the video, based on their body language. One point is given per correct answer.

Virtual Assessment of Mentalising Ability (Canty et al., 2017)

This virtual reality TOM assessment involves participants navigating round a shopping centre completing errands before answering a number of questions about the interactions they engage in. There are 10 social interactions, each followed by four multiple choice questions which explore first-order cognitive, second-order cognitive, first order affective and second-order affective TOM. Discretion is given to the examiner whether they wish to use a three-point scale to rate responses (0= impaired mentalising, 1= reduced mentalising, 2= accurate mentalising), or two-point scale to allow comparisons to be made with other TOM measures.

Table 3: Sample Characteristics of Included Studies

Studies measuring TOM in individuals with MS	Country	TOM Tasks	MS Subtype	Number of Participants
Banati et al. (2010)	Hungary	RMET; Faux Pas; Adult Faces	RRMS (37); SPMS (3)	40
Batista, Alves, et al. (2017)	Portugal	RMET; TOM video test	RRMS (50); SPMS (10)	60
Batista et al. (2017)	Portugal	RMET; TOM video test	RRMS (50); SPMS (10)	60
Batista et al. (2018)	Portugal	RMET; TOM video test	RRMS (50); SPMS (10)	60
Chalah et al. (2017)	France	RMET	RRMS (3); PPMS (18); SPMS (17)	38
Chanial et al.(2020)	France	Faux Pas	RRMS (19); PPMS (1); SPMS (1)	21
Ciampi et al. (2018)	Chile	Mini-Social Cognition and Emotional Assessment	PPMS (23); SPMS (20)	43
Czekóová et al. (2019)	Czech Republic	RMET	RRMS (43)	43
Dulau et al. (2017)	France	Bordeaux Social Cognition Assessment Protocol	RRMS (30); PPMS (15); SPMS (15)	60
Genova, Cagna, Chiaravalloti, Deluca, & Lengenfelder, (2015)	USA	TASIT	RRMS (10); PPMS (2); SPMS (2); PRMS (1)	15
Genova et al. (2019)	USA	RMET; Strange stories	RRMS (17); PPMS (3); SPMS (3)	23
Henry et al. (2015)	France	Faux Pas	RRMS (64)	64
Henry, Tourbah, Chaunu, Bakchine, & Montreuil, (2017)	France	False Belief Tasks; Faux Pas tasks	RRMS (31); PPMS (16); SPMS (15)	62
Henry et al. (2011)	France	Faux Pas; False Beliefs Tasks	RRMS (64)	64
Henry et al. (2009)	France	RMET	NR	27
Isernia et al. (2019)	Italy	RMET; Strange Stories; Faux Pas; MASC	RRMS (42)	42
Kraemer et al. (2013)	Germany	MASC	RRMS (25)	25
Lancaster, Stone, & Genova, (2019)	USA	Virtual Assessment of Mentalising Ability	PPMS (11); SPMS (4)	15
Mike et al. (2013)	Hungary	RMET; Faux Pas; Adult Faces	RRMS (44); SPMS (5)	49
Neuhaus et al. (2018)	Switzerland	Geneva Social Cognition Scale	RRMS (25); PPMS (8); SPMS (2)	35
Ouellet et al. (2010)	Canada	Faux Pas; Strange Stories; Conversation and Insinuation Task	RRMS (22); PPMS (5); SPMS (13); NR (1)	41
Phillips et al. (2011)	UK	TOM video task	RRMS (27); PPMS (2); SPMS (3)	32
Pitteri et al. (2019)	Italy	RMET	RRMS (31)	31
Pöttgen, Dziobek, Reh, Heesen, & Gold, (2013)	Germany	MASC	RRMS (31); PPMS (6); SPMS (8)	45
Raimo et al. (2017)	Italy	RMET; Emotion Attribution Task; TOM Picture sequencing task; Adapted Strange Stories	RRMS (36); PPMS (2); SPMS (2)	40
Realmuto et al. (2019)	Italy	RMET	RRMS (45)	45
Roca et al. (2014)	Argentina	Faux Pas	RRMS (5); PPMS (1); SPMS (29)	35
Sofologi et al. (2019)	Greece	TASIT	PPMS (25)	25

MASC= Movie for the Assessment of Social Cognition; NR= not reported; PPMS= Primary Progressive Multiple Sclerosis; PRMS= Primary Relapsing Multiple Sclerosis; RMET= Reading the Mind in the Eyes Test; RRMS= Relapsing Remitting Multiple Sclerosis; SPMS= Secondary Progressive Multiple Sclerosis; TASIT= The Awareness of Social Inference Test; TOM= Theory of Mind

What are the psychometric properties of these measures and which are the most established?

Using the adapted version of the Terwee et al. (2007) quality assessment criteria described in Table 2, the psychometric properties of each of these 17 measures were explored. The results are reported in Table 4, below. There was a lot of missing information in the psychometric information documented. Only five of the seventeen measures scored greater than, or equal to half points (6/12). These were: the adult eyes test, the MASC, strange stories, the TASIT and the Virtual Assessment of Mentalising Ability. In particular, information on reliability (internal consistency and reliability items) was often not reported. The top scoring TOM measures assessed the range of TOM skills including false belief recognition and understanding, inferring of mental state and non-literal language interpretation.

In addition to the information gathered by the quality assessment tool, this review aimed to explore additional psychometric information including e.g. the factor structures of the measures. However, only the RMET has had its factor structure explored. The developers (Baron-Cohen et al., 2001) suggested that all items of the RMET are indications of a single factor model; however, later work has challenged this conclusion, and stated that the one factor structure does not demonstrate a goodness to fit and rather a five factor solution would be more appropriate (Olderbak et al., 2015). Therefore, there are questions regarding the internal consistency of this measure.

It was not possible to complete the quality assessment for five of the identified measures. There were two main reasons for this: a lack of clarity around how the measures have been adapted and psychometrics reported in another language. Firstly, whilst the False Belief, Emotion Attribution and the adapted versions of both the Strange Stories and Faux Pas Tasks were based on earlier studies, the exact stories/items were not available, and were made up of additional or fewer items than the standardised measure. Therefore, it was not possible to gauge psychometric information from earlier work. Secondly, for the Bordeaux Social Cognition Assessment Protocol (PECS-B) and Conversations and Insinuations Task, psychometric properties have been explored but as they were reported in French (see Etchepare et al., 2014) they could not be understood or interpreted.

Table 4: Quality Assessment of Measures

Measure	Reference	Population	Content Validity	Internal Consistency	Construct Validity	Reliability	Floor and Ceiling Effects	Interpretability	Total
Baron-Cohen Adult Eyes Test	Baron-Cohen et al. (2001)	Adults with ASD, and two control group	2	0	2	0	2	1	7
	Olderbak et al. (2015)	Amazon Mechanical Turk	2	0	0	0	1	0	3
Baron-Cohen Adult Faces Task	Baron-Cohen, Wheelwright, & Jolliffe, (1997)	Adults and Adults with ASD	2	0	0	0	0	1	3
The Bordeaux Social Cognition Assessment Protocol (PECS-B)	Etchepare et al. (2014)	"Healthy" French Population	-	-	-	-	-	-	N/K
Emotion Attribution Task	Blair et al. (1995)	-	-	-	-	-	-	-	-
Conversations and Insinuations	Ouellet et al. (2010)	-	-	-	-	-	-	-	N/K
False Belief Task	Baron-Cohen, Leslie, & Frith, (1985); Rowe, Bullock, Polkey, & Morris, (2001)	-	-	-	-	-	-	-	-
Faux Pas	Stone, Baron-cohen, & Knight, (1998)	patients with brain damage/ lesions	1	0	1	0	0	1	3
Faux Pas (Adapted)	-	-	-	-	-	-	-	-	-
Genova Social Cognition Scale	Martory et al. (2015)	Brain injured individuals and control group	2	0	1	0	1	1	5
Mini Social Cognition and Emotional Assessment	Bertoux et al. (2012)	Depression or Fronto-temporal dementia	1	0	1	1	0	0	3
	Bertoux et al. (2014)	Frontotemporal dementia	1	0	0	0	0	0	1
Movie for the Assessment of Social Cognition	Dziobek et al. (2006)	Individual's with Asperger's and controls	2	2	0	2	2	1	9
	Fossati, Borroni, Dziobek, Fonagy, & Somma, (2018)	adolescents, adults and individuals with personality disorder	2	2	1	0	0	1	6
Strange stories	Happé, (1994)	Autism Spectrum Disorder and 3 control groups	2	0	2	0	2	1	7
Strange stories (adapted)	-	-	-	-	-	-	-	-	N/K
TASIT	McDonald, Flanagan, Rollins, & Kinch, (2003)	Neurologically normal population	2	0	1	0	0	1	4
	McDonald, Flanagan, Martin, & Saunders, (2004)	Adults with brain injury	2	1	1	0	0	1	5
	McDonald et al. (2006)	Adults with brain injury	2	1	1	0	2	0	6
The Theory of Mind Picture Sequencing Task	Brüne, (2003)	Individuals with schizophrenia	1	0	1	0	0	1	3
TOM Video Task	Sullivan & Ruffman, (2004)	Older adults and younger adults	2	0	0	0	0	1	3
Virtual Assessment of Mentalising Ability	Canty, Neumann, Fleming, & Shum, (2017)	Healthy adult population	2	2	1	2	0	0	7

N/K= not known, TASIT= The Awareness of Social Inference Test

Discussion

This review aimed to identify the specific measures used to assess Theory of Mind (TOM) in individuals with Multiple Sclerosis (MS), and to explore the psychometric properties of these measures to better understand which are the most psychometrically established within the current literature. Seventeen TOM measures had been used with an MS sample and these assessed TOM abilities across the various levels of the construct. Items exploring an individual's ability to identify and understand another individual's intentions were present across 14 of the measures, faux pas understanding was explored in 8 measures and false belief in 4 of them. Whilst it is important to remember the different TOM constructs measured by the various measures, the review found the Movie for the Assessment of Social Cognition (MASC; Dziobek et al., 2006; Fossati et al., 2018) was the most established measure of TOM in terms of the reported psychometrics, closely followed by the Adult Eyes (Baron-Cohen et al., 2001), strange stories (Happé, 1994) and the Virtual Assessment of Mentalising Ability Tasks (VAMAT; Canty et al., 2017). This does not mean that the other assessment measures are not suitable for purpose or are invalid, but rather that their psychometric properties are less evidenced or reported within the literature.

There are several potential reasons for why some TOM measures appeared to be more psychometrically established than others. It could be that they are not as reliable or valid in measuring the construct they were designed to. In these cases, the measures would have been given a lower rating on the assessment measure as their statistical output was in a less desirable range. However, this was not representative of the majority of lower quality ratings given in this review. Rather, lower scores were more commonly given as no psychometric information was reported. There was a large amount of missing psychometric information for these measures, particularly reliability ratings, floor and ceiling effects, and where measures used were adapted from other established measures (e.g. the adapted faux pas and strange stories tasks). Whilst the authors likely made such adaptations to make the measure more accessible to their target population, there was no psychometric information available to show whether or not this process was successful. This missing information makes it challenging to draw conclusions about which measures assess particular constructs most

effectively. It would be useful for these gaps, as well as the factor structures, of TOM measures to be explored and for more informed conclusions to be drawn.

Although the quantitative information generated from this review is informative in identifying the most psychometrically established TOM assessment measures, qualitatively there are many considerations to be made when interpreting the results and informing of measure selection for individuals with MS. Firstly, no measures have been specifically validated on an MS population, and rather the measures were validated on a range of populations from neurotypical adults, to individuals with Autism Spectrum Disorder (ASD) to individuals with other neurological conditions. This specific review aimed to understand TOM measurement in MS, a neurological condition (Feinstein, 2007); however, none of the more psychometrically sound measures (reported above) were validated on individuals with a neurological diagnosis of any kind. There is a large degree of variability in the cognitive profiles of different neurological conditions (see Husain & Schott, 2016), as well as between neurological and non-neurological (e.g. ASD and controls) conditions. Research has shown the TOM impairments in individuals with MS can be subtle and are not as severe as those identified in individuals with schizophrenia or other neurological disorders (Cotter et al., 2016, 2018). Therefore, it is not clear based upon the current evidence whether these measures would be able to identify any subtle impairments in individuals with MS, if present. This ability of the assessment measures is of vital importance in ensuring accurate measurements as these assessments inform rehabilitation interventions (Canty et al., 2017).

Secondly, many of the most commonly used measures were developed around twenty years ago. In these cases, it seems more likely that measures have become more established in the field due to their frequency of use, rather than their psychometric qualities (Olderbak et al., 2015). This may explain why the Adult Eyes Test has been the most commonly used measure of TOM. It is not to say that these measures are not reliable; however, with little attempts to validate measures since, and on other population samples, it is not clear how sensitive they are to current population demographics and psychosocial behaviours. It would be interesting to assess how much overlap there is between these older and the more recent, psychometrically established measures in their assessment of the same TOM construct.

Future studies may wish to consider using more than one measure of TOM to better understand the concurrent validity across these.

Additionally, this review has highlighted the wide geographical spread of completed studies. This means that many of the measures have either been written/developed in another language or have required translation to be used. In addition to the potential challenges of direct translation of text into another language, there is also cultural variations in "socially appropriate" behaviours and ways of interaction with others (House et al., 2013). This could have potential implications on normative data and scoring as there will likely be some subjective differences in ratings across cultures. Where possible, researchers should consider the population in which measures have been developed as this may impact upon their ability to identify and record TOM abilities across cultures.

One of the key limitations of this review is that it did not explore ecological validity as part of the quality assessment measure. This was partly due to the quality assessment being informed by previous work (Terwee et al., 2007) and only minor adaptations being made. Whilst ecological validity may not be of as great importance in other areas of clinical health measurement (e.g. physical health studies), in TOM this is of crucial importance as TOM abilities have a direct impact on many psychosocial outcomes (Brüne et al., 2007; Kennedy & Adolphs, 2012; Wang et al., 2018). Therefore, it should be a key consideration in the selection of assessment measures used in both research and clinical practice (Sbordone, 2001). In recent years an increased number of measures have been developed, with the primary aim of them being more ecologically valid. This has included using videos of everyday interactions and Virtual Reality technology in the development of measures. The results of this review suggest that some of the more recently developed measures, which aimed to be more ecologically valid (e.g. the MASC and the VAMAT), are amongst the most psychometrically sound, however, to date they have only been validated on a small selection of clinical populations. It is recommended that further research is carried out on these measures to assess their suitability for use with a neurological population, which will promote accurate measurement of TOM abilities in these populations.

In summary, this paper aimed to review the existing psychometric literature on measures of TOM in individuals with MS. Whilst it is not possible to draw firm conclusions on which TOM measures are most suitable for use with individuals with MS, this review tentatively would recommend the use of the MASC in clinical practice due to its higher overall rating, good content validity and adequate interpretability. Additionally, using this alongside the Adult Eye's test would be beneficial in allowing comparisons to be made with existing studies of TOM in MS as it has been the most used measure to date. The VAMAT may be a good choice of measure for research purposes, however, requires further assessment of its interpretability before firmer conclusions can be made surrounding it's suitability for use in clinical practice. In addition to identifying the most established measures in the evidence base, this paper has also highlighted the significant number of existing gaps and the urgent need for further work to better understand the utility and accuracy of TOM measures. This is particularly true for their sensitivity to identifying subtle impairments within neurological populations. Until such work is completed research into TOM in MS can and should continue, however, researchers may wish to give additional consideration to the selection of assessment measures. This may include using multiple measures and also exploring and reporting the internal consistency of the measures used within their sample, as it can vary from sample to sample.

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Appendix A: Guidance for publication in Journal of the International Neuropsychological Society

Guidance taken from: https://www.cambridge.org/core/journals/journal-of-the-international-neuropsychological-society/information/instructions-contributors

Aims and Scope

The *Journal of the International Neuropsychological Society* is the official journal of the International Neuropsychological Society, an organization of over 4,500 international members from a variety of disciplines. The *Journal of the International Neuropsychological Society* welcomes original, creative, high quality research papers covering all areas of neuropsychology. The focus of articles may be primarily experimental, applied, or clinical. Contributions will broadly reflect the interest of all areas of neuropsychology, including but not limited to: development of cognitive processes, brain-behavior relationships, adult and pediatric neuropsychology, neurobehavioral syndromes (such as aphasia or apraxia), and the interfaces of neuropsychology with related areas such as behavioral neurology, neuropsychiatry, genetics, and cognitive neuroscience. Papers that utilize behavioral, neuroimaging, and electrophysiological measures are appropriate.

To assure maximum flexibility and to promote diverse mechanisms of scholarly communication, the following formats are available in addition to a *Regular Research Article: Brief Communication* is a shorter research article; *Rapid Communication* is intended for "fast breaking" new work that does not yet justify a full length article and is placed on a fast review track; *Case Report* is a theoretically important and unique case study; *Critical Review* and *Short Review* are thoughtful considerations of topics of importance to neuropsychology and include meta-analyses; *Dialogue* provides a forum for publishing two distinct positions on controversial issues in a point-counterpoint format; *Special Issue* and *Special Section* consist of several articles linked thematically; *Letter to the Editor* responds to recent articles published in the *Journal of the International Neuropsychological Society*; and *Book Review,* which is considered but is no longer solicited.

Manuscript Submission and Review

The Journal of the International Neuropsychological Society uses online submission and peer review. Paper submissions are not accepted.

The website address for submissions is: http://mc.manuscriptcentral.com/jins. Complete instructions are provided on the website.

Prior to online submission, please consult http://www.nlm.nih.gov/mesh/ for 6 keywords or mesh terms that are different from words in the title. Accurate mesh terms will increase the probability that your manuscript will be identified in online searches. Please follow the instructions carefully to avoid delays. The menu will prompt the author to provide all necessary information, including the manuscript category, the corresponding author including postal address, phone and fax numbers, and e-mail address, and suggested reviewers.

Manuscript Length

In order to increase the number of manuscripts that can be published in the *Journal of the International Neuropsychological Society*, please adhere to the following length requirements. Please provide a word count on the title page for the abstract and manuscript (not including abstract, tables, figures, or references). Manuscripts will be returned if they exceed length requirements.

Critical Review: Maximum of 7,000 words (not including abstract, tables, figures, or references) and a 250 word abstract. Critical Reviews will be considered on any important topic in neuropsychology. Quantitative meta-analyses are encouraged. Critical Reviews must be preapproved by the Editor-in-Chief. For consideration, please e-mail your abstract to jins@cambridge.org.

Manuscript Preparation and Style

The entire manuscript should be typed double-spaced throughout using a word processing program. Unless otherwise specified, the guideline for preparation of manuscripts is the *Publication Manual of the American Psychological Association (6th edition)* except for references with 3 or more authors (see References section). This manual may be ordered from: APA Order Dept., 750 1st St. NE, Washington, DC 20002-4242, USA.

Pages should be numbered sequentially beginning with the Title Page. The Title Page should contain the full title of the manuscript, the full names and institutional affiliations of all authors; mailing address, telephone and fax numbers, and e-mail address for the corresponding author; and the word count for the abstract and manuscript text (excluding title page, abstract, references, tables, and figures). At the top right provide a short title of up to 45 characters preceded by the lead author's last name. Example: Smith-Memory in Parkinson's Disease. This running head should be repeated at the top right of every following page.

Page 2 should include an Abstract and a list of at least six keywords or mesh terms. Note: structured abstracts must be included with papers submitted after January 1, 2014. A structured abstract must include four header labels: Objective, Method, Results, and Conclusions. A total of six mesh terms (http://www.nlm.nih.gov/mesh/) or keywords should be provided and should not duplicate words in the title.

The full text of the manuscript should begin on page 3. For scientific articles, including *Regular Research Articles, Brief Communications, Rapid Communications,* and *Symposia*, the format should include a structured Abstract, Introduction, Method, Results, and Discussion. This should be followed by Acknowledgments, References, Tables, Figure Legends, Figures, and optional Appendices and Supplemental Material.

The use of abbreviations, except those that are widely used, is strongly discouraged. They should be used only if they contribute to better comprehension of the manuscript. Acronyms should be spelled out at first mention. Metric system (SI) units should be used.

Appendices and Supplemental Materials may be submitted. Appendices include material intended for print and should be included with the manuscript file. Supplementary material

will appear only online and should be submitted as a separate file. Supplementary material is replicated as-is.

The Acknowledgements Section should include two parts: a Conflicts of Interest disclosure (see above) and a statement to disclose all Funding sources of financial support for the paper. If no Conflicts of Interest exist, you will be required to state as such ("COI: None." or a similar statement). In documenting financial support, please provide details of the sources of financial support for all authors, including grant numbers. Multiple grant numbers should be separated by a comma and space and where research was funded by more than one agency, the different agencies should be separated by a semicolon with "and" before the final funding agency. Grants held by different authors should be identified using the authors' initials.

Tables and Figures should be numbered in Arabic numerals. Figures should be numbered consecutively as they appear in the text. Figures should be twice their intended final size and authors should do their best to construct figures with notation and data points of sufficient size (recommended ≥ 300 dpi) to permit legible photo reduction to one column of a two-column format. Please upload figure(s) in either a .doc, .jpeg, .tiff, or .pdf format. There is no additional cost for publishing color figures. The approximate position of each table and figure should be provided in the manuscript with call-outs: [INSERT TABLE 1 HERE]. Tables and figures should be on separate pages. Tables should have short titles and all figure legends should be on separate pages. All tables and figures must have in-text citations in order of appearance.

Figures submitted in color will appear online in color, but all figures will be printed in black and white unless authors specify during submission that figures should be printed in color, for which there may be a fee. There is no additional cost for publishing color figures in the print version of the journal for corresponding authors who are INS members. For non-members, the cost for publishing color figures in print version of the journal will be $320 per figure with a cap of $1600 per article.

References should be consistent with the *Publication Manual of the American Psychological Association (6th Edition)*. In-text references should be cited as follows: "...Given the critical role of the prefrontal cortex (PFC) in working memory (Cohen et al., 1997; Goldman-Rakic, 1987; Perlstein et al., 2003a, 2003b)..." with multiple references in alphabetical order. Another example: "...Cohen et al. (1994, 1997), Braver et al. (1997), and Jonides and Smith (1997) demonstrated..."

References cited in the text with two authors should list both names. References cited in the text with three, four, or five authors, list all authors at first mention; with subsequent citations include only the first author's last name followed by et al. References cited in the text with six or more authors should list the first author et al. throughout. In the reference section, for works with up to seven authors, list all authors. For eight authors or more, list the first six, then ellipses followed by the last author's name.

Psychological, Interpersonal and Social Functioning in Multiple Sclerosis: The Role of Theory of Mind

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Word count: 6,322

Abstract

Background: Research has consistently shown Theory of Mind (TOM) impairments in individuals with Multiple Sclerosis (MS), when compared to a matched control group. TOM impairments have been linked to poorer psychosocial outcomes in other clinical populations, however, the association between TOM and psychosocial outcomes in individuals with MS remains unknown.

Objective: This exploratory study aimed to explore the associations between TOM abilities and interpersonal, psychological, and social functioning in individuals with MS.

Method: Thirty-six individuals with a diagnosis of MS completed the Faux Pas and Reading the Mind in the Eyes (RMET) tests of TOM. Neuropsychological assessments of executive abilities and self-report measures of psychological, interpersonal and social functioning were also completed.

Results: Participants performed similar to normative control samples on all TOM and executive functioning measures. Additionally, they did not report impaired social functioning, relationship quality or depressive symptomology. Relationships were identified between TOM abilities and social withdrawal, employment and quality of life.

Conclusions: In summary, relationships were identified between TOM and some areas of social functioning, but not psychological or interpersonal functioning. Compared to previous research, the current sample showed fewer cognitive impairments, therefore, further work exploring these relationships in a more cognitively diverse sample is recommended.

Introduction

Multiple Sclerosis (MS) is a chronic, inflammatory disease of the central nervous system, characterised by demyelination and widespread lesions or plaques on the brain and spinal cord (Feinstein, 2007). The location of these lesions is unpredictable and varies across individuals (Giovannoni et al., 2016). Individuals with MS can, therefore, experience a broad range of symptoms depending upon the location and extent of their myelin damage (Costello & Newsome, 2016). Additionally, symptoms vary by MS diagnostic subtype (Feinstein, 2007), with each having a different disease course. The most prevalent subtype is relapsing-remitting MS (RRMS), which approximately 85% of individuals are initially diagnosed with. Individuals with RRMS experience acute relapses characterised by neurological deterioration, followed by a period of (full or partial) recovery (Feinstein, 2007). Between relapses their presentation remains stable. Some individuals with RRMS will later develop secondary progressive MS (SPMS), which is characterised by progressive deterioration, with or without the relapses. Alternatively, around 15% of individuals are initially diagnosed with primary progressive MS (PPMS), which is characterised by gradual, continuous deterioration in neurological functioning (Feinstein, 2007) with no acute relapses.

Individuals with MS can present with motor, visual, neuropsychological and cognitive difficulties (National MS Society, 2014; Niino, 2016). Whilst previously research into symptomology in MS has primarily focused on physical symptoms, more recently research assessing cognitive symptoms have been gathering more interest (Niino, 2016). Cognitive difficulties are extremely common in individuals with MS, with between 40 and 60% of individuals displaying some form of cognitive impairment (Bobholz & Rao, 2003; Chiaravalloti & DeLuca, 2008; Cotter et al., 2016); although, impairments are more frequently reported in individuals with SPMS (DeLuca, Chelune, Tulsky, Lengenfelder, & Chiaravalloti, 2004). Impairments have been identified across a range of cognitive abilities: between 40 and 60% of individuals with MS display deficits in memory and new learning (Winkelmann, Engel, Apel, & Zettl, 2007); 12 to 25% display difficulties with sustained attention and slower information processing speed (Chiaravalloti & DeLuca, 2008; DeLuca et al., 2004); and up to 19% of individuals have difficulties with executive functioning (Chiaravalloti & DeLuca, 2008; Rao, Leo, Bernardin, & Unverzagt, 1991).

Whilst several neuropsychological characteristics of MS have been extensively researched and evidenced, until recently social cognition (SC) had been less widely explored and understood (Cotter et al., 2016). SC refers to the 'mental operations that underlie social interactions' (Cotter et al., 2018, p.92) and is an umbrella term for a number of cognitive abilities including emotion recognition, theory of mind (TOM), and empathy (Lysaker et al. 2014). SC abilities are important in helping individuals to understand and make inferences about their own and others' thoughts and feelings. This information informs and guides their behaviour, appropriate to their social context. Individuals with MS have been consistently shown to have impaired SC abilities when compared to a matched control sample (see Gleichgerrcht et al., 2015; Henry et al., 2011; Lenne et al., 2014; Ouellet et al., 2010; Phillips et al., 2011). This includes impairments in TOM, which refers to an individual's ability to attribute the mental states of oneself and others (e.g. their beliefs, goals, intentions and emotions; Banati et al., 2010), which is crucial in understanding and predicting others' behaviour. A recent meta-analysis (Cotter et al., 2016) exploring TOM in individuals with MS showed these abilities to be consistently impaired, with the magnitude of these impairments being equivalent to or greater than impairments in other cognitive domains. Although TOM impairments have been evidenced in a range of MS samples and using various measures of TOM, there has been limited research into the impact of these impairments on an individual's daily life and functional abilities (Henry et al., 2011).

The neurocognitive, neuropsychological and social implications of TOM impairments for individuals with MS are not yet known. Several studies have explored the relationship between TOM and neurocognitive abilities. Associations have been identified between TOM and several neurocognitive abilities, specifically executive functioning (Henry et al., 2009), working memory (Genova, Cagna, Chiaravalloti, Deluca, & Lengenfelder, 2016) and processing speed (Henry et al., 2009; Pöttgen, Dziobek, Reh, Heesen, & Gold, 2013). Executive functions include the ability to focus attention, inhibit responses/behaviours and problem solve. All of these abilities likely contribute to TOM abilities as individuals are required to select the social stimulus to focus on, think and problem solve what the other individuals is thinking/feeling and inhibit any inappropriate or automatic behaviours. Ouellet et al. (2010) found TOM impairments to be greater in individuals with more severe neurocognitive impairment, however, other research has shown TOM impairments to exist in the absence of other neurocognitive or neuropsychological difficulties (Pöttgen et al., 2013). There is

variability in the strengths of associations reported between TOM and neurocognitive abilities across studies. This variability may be accounted for by small sample sizes, which increases the likelihood of type 2 errors (e.g. Henry et al., 2009; n=17), and the wide range of TOM measures used across studies. This makes it difficult to interpret research findings and compare results across studies.

The associations between TOM impairments and psychological outcomes for individuals with MS also remains unclear, despite depression symptomology being higher in individuals with MS when compared to a control sample (Cotter et al., 2018). Several smaller studies have completed exploratory analysis into the link between TOM and depressive symptomology, however, no relationship was found. To the researcher's knowledge, there has been no similar research exploring whether there are any relationships between TOM and interpersonal or social functioning in individuals with MS. It would be expected that impairments in TOM would have implications for interpersonal and social functioning due to the role of TOM abilities in facilitating the development of quality interpersonal relationships and subsequent successful social integration (i.e. in helping us tailor our speech to our interlocutor, identify mutual interests and guiding our behaviour; (Bora, Özakbaş, Velakoulis, & Walterfang, 2016)). Additionally, quality interpersonal relationships and social connectedness are thought to be protective against mental health difficulties (Teo, Choi & Valenstein, 2013). Associations have also been consistently highlighted between social interactions and quality of life, well-being and mental health (Schuster, Kessler, & Aseltine, 1990). Therefore it is unsurprising that impaired SC abilities have also been linked to the development and maintenance of mental health concerns (Penton-Voak et al., 2017). This has not been explored within an MS sample, but similar associations would be expected.

Research has consistently evidenced social difficulties (e.g. isolation, reduced independence) and cognitive impairments (e.g. slower processing speed, impaired TOM) in individuals with MS (Feinstein, 2007), however, the associations between them remain unclear. This exploratory study aims to explore and better understand the associations between these difficulties. This research is important in enhancing mental well-being in individuals with MS, as having a more comprehensive understanding of these impairments will inform rehabilitation interventions.

Presently, these gaps in the research literature mean it is not possible to ascertain which areas of an individual's functioning rehabilitation interventions should focus on. SC rehabilitation interventions are not evidenced or routinely offered to individuals with MS, although, preliminary research into SC interventions with individuals with schizophrenia has led to improvements in TOM abilities and had a positive impact upon social functioning (see Kurtz, et al., 2016). However, prior to future work exploring SC interventions for individuals with MS, a more comprehensive understanding of the implications of SC impairments in this population is sought. The current study aims to address this by exploring the associations between TOM abilities and social, emotional, neurocognitive and interpersonal functioning in individuals with MS. As this study is exploratory, it is not possible for prior hypotheses to be established and rather any significant findings will generate new hypotheses for future research to investigate.

Methods

Participants

A power calculation, using GPower, revealed that 103 participants were required to detect a medium effect (beta= .8, alpha= .05) from a regression model with 7 predictor variables. The study recruited 39 individuals with Multiple Sclerosis (MS). Three individuals subsequently withdrew from the study. All three individuals completed the testing session but did not return their self-report questionnaires: one due to health concerns; one continually forgot to return the questionnaires and these were not received by the end date of the study; and finally the researcher was unable to make contact with the third individual post testing. Therefore, the final sample included 36 individuals with MS. All individuals had previously received a formal diagnosis of MS from a neurologist. Individuals were recruited through either the Physical Rehabilitation Service (NHS Fife) or the Anne Rowling Clinic (NHS Lothian), and identified by an MS nurse or research assistant from pre-existing service databases. Inclusion criteria were: (1) a diagnosis of MS and (2) aged between 18 and 65 years. Exclusion criteria were: (1) English as a second language, (2) no capacity to give informed consent, (3) history of substance abuse, (4) any diagnosis that would affects social or cognitive functioning (e.g. Autism Spectrum Disorder, Brain Injury, Dementia, Learning Disability, Psychosis) and (5) significant visual perceptual or verbal comprehension impairment.

Measures

The assessment measures used in this study were selected based upon their suitability and previous usage within an MS sample. For example, no assessment measures completed in person required the individuals to write, because motor impairments are often present in individuals with MS. Additionally, where available, the psychometric properties of the measures were identified, considered and informed the measure selection, with the more psychometrically established measures being chosen for inclusion. At present most of the measures considered/selected, with the exception of Quality of Life (QoL; Vickrey, 1995) and depression (Sacco et al., 2016) reported below, had not been validated with an MS sample. The general lack of validation evidence within MS samples meant measure selection was informed by the psychometric evaluations in other samples and the prior use of measures with an MS sample.

Affective Theory of Mind Measures

Two measures of affective TOM were used, *the Reading the Mind in the Eyes Test* (RMET; Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001) and *Faux Pas Recognition Test* (Baron-Cohen, O'Riordan, Stone, Jones, & Plaisted, 1999; Stone, Baron-Cohen, & Knight, 1998). The RMET involves 36 administration items, each of which consists of an image of a pair of eyes, surrounded by four words detailing an emotion or mental state (see Appendix B for sample items). The participants were given a booklet containing all administration items and asked to select which emotion printed around the eyes best described the mental state or feeling expressed through the eyes. The Faux Pas Recognition Test (Stone et al., 1998) comprises of twenty short vignettes, ten of which detail a situation where a 'faux pas' is present, whilst the other ten are control vignettes (see Appendix C for sample items). The faux pas and control stories are presented in a random order. Printed copies of the stories were provided to the participants and they were asked if a faux pa was present. If the participant identified a faux pa to be present within a vignette, they were asked 5 further questions which explored the participant's detection of the faux pa and their understanding of the character in the story's intentions and beliefs. One point was available for each of the faux pas stories, and individuals had to answer all 6 questions correctly to get the point. This scoring method was described in the test development paper (Baron-Cohen et al., 1999) and has been used in more recent studies which have used the original faux pas test (see Lecce, Ceccato, & Cavallini, 2019; Tenenbaum & Leonard, 2020).

Whilst both the RMET and the Faux Pas Recognition Test have not been validated specifically on a MS sample, neither have other TOM measures (Gibson, Calia, Newman, & Harper, 2020). This has resulted in a wide range of TOM measures being used with individuals with MS (see Cotter et al., 2018; Gibson et al., 2020). Both the RMET and the Faux Pas Recognition Test have been used to assess social cognition in previous research with individual's with MS (e.g. Banati et al., 2010; Ouellet et al., 2010).

Neuropsychological Measures

The *Test of Pre-Morbid Functioning* (TOPF; Wechsler, 2011) is a reading test which aims to estimate an individual's pre-morbid cognitive function. Specifically, participants were given a card with 70 words printed on it, each of which have atypical grapheme to phoneme translations, and asked to read each aloud. The raw score was translated into an IQ estimate

using normative data tables. It has been shown to have high reliability (*r* ranging from .96-.99) and concurrent validity with the WAIS-IV full-scale IQ (*r=.70;* Holdnack & Drozdick, 2009)

The *Verbal and Category Fluency* (Delis, Kaplan, & Kramer, 2001) test from the Delis Kapan Executive Function Systems (D-KEFS) is a measure of executive functioning and specifically assesses an individual's mental flexibility. Participants were given either a letter of the alphabet or semantic category (e.g. animals) and asked to generate as many words as possible within a minute, starting with that letter or fitting into the semantic category. There is one further subtest which asked individuals to switch between giving answers across two semantic categories (e.g. a piece of fruit, then piece of furniture then another piece of fruit and so on). All correct responses are summed together to generate total scores, which are transformed into standard scores (M=10, SD=3). Internal consistencies of the verbal fluency scale were good to strong (.77- .90) , whilst the category and switching fluency subscales ranged from poor to good (.61- .76 and .43- .68, respectively; Delis et al., 2001). Test-retest reliability for the verbal fluency (.67- .88) and category fluency (.70- .82) subscales was good, however, was poor for the switching subscale (.49- .65; Delis et al., 2001).

The *Hayling Sentence Completion Test* (Burgess & Shallice, 1997) is a test of two parts. The initial part assesses initiation and response speed. Participants were asked to complete a sentence as quickly as possible. The second part assesses inhibition and response suppression, with participants being asked to complete sentences using a completely unrelated word. The test has been shown to have good test re-test reliability (.76; Burgess & Shallice, 1997) and adequate convergent validity with other measures of executive functioning (see Wood & Liossi, 2007).

The *Brixton Spatial Anticipation Test* (Burgess & Shallice, 1996) is a measure of rule detection and set shifting. Participants were presented with a box consisting of ten circles, one of which is blue. The blue circle moves according to certain patterns and the participant had to follow the pattern and predict where the blue circle will move to on the next page. Similar to the Hayling Sentence Completion test, test re-test reliability has been shown to be good (.71) and the Brixton has also demonstrated adequate convergent validity with other executive measures (see Wood & Liossi, 2007).

Self-Report Measures

The *Beck's Depression Inventory II* (BDI-II; Beck, Steer, & Brown, 1996) is a measure of depression symptomology. It is a 21 item self-report questionnaire, which focuses primarily on the psychological, rather than physical symptoms of depression. Therefore, the participants' scores are less likely to be influenced by the physical symptoms of MS than other measures of depression symptomology. The items are rated on a 4-point scale from 0 to 3. A total score is generated by summing all item scores, with higher scores being indicative of higher levels of emotional distress. The BDI-II has been found to have good internal consistency (Cronbach's alpha= .89), good convergent and divergent validity with individuals with MS (Sacco et al., 2016).

The *Multiple Sclerosis Quality of Life- 54* (Vickrey, 1995) is a quality of life measure specifically developed for use with individuals with MS. It consists of 54 questions making 12 subscales, which combine to form two composite scores for both physical and mental health. For each question, participants are asked to rate their responses using Likert scales of varying ranges. Higher scores are indicative of better perceived quality of life. This measure has been less widely used in research but has been shown to have good internal consistency, with Cronbach's alphas ranging from .75 to .96 (Vickrey, Hays, Harooni, Myers, & Ellison, 1995) and evidenced validity.

The *Revised Dyadic Adjustment Scale* (RDAS; Busby, Christensen, Crane, & Larson, 1995) is a 14-item measure of relationship quality, subdivided into three subscales: dyadic satisfaction, dyadic cohesion and dyadic consensus. Individual item scores are summed to make subscale scores, with higher scores being suggestive of better relationship quality. It is a shorter version of the original Dyadic Assessment Scale (Spanier, 1976). Internal consistency has been shown to be good (Cronbach's alpha ranging from .80 to .90), as well as construct validity, with the RDAS correlating with other measures of relationship quality (Busby et al., 1995).

The *Social Functioning Scale* (SFS): Individual Version (Birchwood, Smith, & Cochrane, 1990) is a measure of social functioning. The SFS is designed to assess more fundamental elements of social functioning, as seen in chronic disorders. It comprised of 79 items which make up seven subscales: social engagement; interactional behaviour; prosocial activities; recreational activities; independence-competence; independence- performance and employment. Total

raw scores are translated into standardised scores using the normative table, with higher scores being indicative of higher levels of social functioning. It was developed for use with individuals with schizophrenia and has been shown to have good internal consistency (Cronbach's alpha ranging from .69 to.85; Birchwood, et al., 1990) and construct validity, with scores on the SFS correlating with negative symptoms which contribute to deficits in social functioning (*r*=-.44).

The *DEX Questionnaire* (Wilson, Alderman, Burgess, Emslie, & Evans, 1996) is a 20 item questionnaire designed to assess for behaviours associated with dysexecutive syndromes including emotional or personality changes, motivational changes, behavioural changes and cognitive changes. There are two versions of this questionnaire, a self-rated and independent rated, made up of 20 items which are rated on a 5-point scale. Total scores are calculated by summing scores on individual items, with higher scores being indicative of greater difficulty. The DEX has been evaluated to have good reliability and validity (Chaytor & Schmitter-Edgecombe, 2007) and has been extensively used in other neurological populations (e.g. Traumatic Injury).

Proxy Measures

Proxy measures were completed by a participant's family member or close friend. They were asked to complete informant versions of the SFS and the DEX questionnaire, alongside the Revised Dyadic Adjustment Scale. Details of which are reported above. The informant versions of both measures are identical to the self-rated version, the only exception is that there is a couple of questions about employment on the self-report version of the SFS. There are no additional psychometric properties reported for the informant measure of either scale.

Procedure

The study (see Appendix D for protocol) received a favourable ethical opinion from the South East Scotland Research Ethics Committee 1 (Appendix E) and site-specific approvals from NHS Fife and NHS Lothian Research and Development departments (Appendixes F and G). All participants provided informed written consent to participate in the study (Appendixes H and I). In addition, each consenting participant was invited to contact a relative or friend who had the opportunity to observe everyday behaviour to complete proxy measures, with 27 of the 36 participants consented to this.

Participants were sent the self-report measures, and where appropriate proxy measures, in the post for them to complete at home prior to their scheduled appointment with the researcher to complete neuropsychological testing. Participants were tested individually at an outpatient department within NHS Fife or NHS Lothian board areas. The battery of tests took between 60 and 90 minutes to complete. Most participants were able to complete the test battery in one session, whilst 2 required the testing to be completed over 2 shorter sessions. This was either due to participant's time restraints or fatigue. To reduce any order effects and limit the impact of fatigue on test performance, the administration order of the tests was varied across participants, through a simple rotation of test order.

Data Analysis

Statistical analyses were performed using SPSS software (Version 22.0, IBM Corp., Armock, NY, USA). Graphs were used to identify any significant outliners and any typographical errors with data input. Descriptive statistics are reported as means $\pm$ SD. Pearson's correlations were preformed within the whole sample to explore relationships between demographic variables (e.g. individuals time since diagnosis, age, years in education and physical ability index) and TOM abilities, to identify if they had any effect on TOM abilities. Mann-Whitney U tests were used to explore differences in TOM abilities by gender and MS diagnosis type. Only RRMS and SPMS were included in this analysis as only one participant had a diagnosis of benign MS. Non-parametric analyses were used due to the sample being subdivided into smaller groups and the variables not being normally distributed.

Exploratory Pearson's correlations explored relationships between TOM, executive functioning scores and outcome variables measured by the standardised questionnaires. As several of the outcome variables were reported by both the participant and their significant other, Wilcoxon tests were used to detect any differences in reporting of psychosocial outcomes. The outcome of the Wilcoxon tests was used to determine whether further analyses were required to analyse these variables separately, or if separate comparisons were not required (e.g. if reports were not significantly different).

Further exploratory analyses were completed to investigate the relationship between TOM abilities and psychosocial outcomes through applying linear regression models. Regression

model predictors were entered for specific outcome variables based upon the outcomes of the Pearson's correlations between TOM, executive functioning and outcome variables, and the existing literature. Within models fixed effects were TOM and executive functioning scores.

Results

Descriptive Statistics

Of the 36 individuals who participated, 27 had a diagnosis of RRMS, 8 SPMS and 1 Benign MS. There were 29 females and 7 males; the mean age was 45.53 ± 9.23; the mean years in education was 15.89 ± 4.17; mean EDSS (Expanded Disability Status Scale, a measure of disability in MS) was 4.24 ± 1.54; mean time since diagnosis was 9.39 years ± 8.39).

Descriptive statistics for each measure and comparisons with normative data are reported in Table 1. Individuals did not display impairments on the TOM or executive functioning assessments. Additionally, they reported subclinical levels of depressive symptomology, better social functioning and fewer dysexecutive behaviours than non-clinical adult samples.

Table 1: Comparisons between MS psychometric test and self-report questionnaire scores with normative data sample

Measure	Sample Scores (m± SD)	Normative data	
		Score classifications (m± SD)	Normative Group
RMET	25.36 ±5.43	26.2 ±3.6	Adults, adult students and IQ- matched controls (n=205)[a]
Faux Pas	5.36 ±2.54	N/K[b]	
TOPF	IQ= 104 ±8.48	IQ=100 ±15	Adults demographically matched to census data (n=248)[c]
Verbal Fluency	SS= 10.03 ± 3.59	SS=10 ±3	Non-clinical adults (n=1050)[d]
Category Fluency	SS= 11.22 ± 3.61	SS=10 ±3	Non-clinical adults (n=1050)[d]
Switching Fluency	SS= 11.44 ±4.44	SS=10 ±3	Non-clinical adults (n=1050)[d]
Hayling	6 ±1.22	Average range	Non-clinical adults (n=121)[e]
Brixton	6.97 ±2.15	Average-high average range	Non-clinical adults (n=121)[e]
DEX Questionnaire	19.75 ±14.33	22.13 ±8.86	Non-clinical individuals- no history of head injury, central nervous diseases or mental illness (n=93)[f]
BDI	13.89 ±9.57	Minimal symptoms	Hospital/clinic outpatients (n=500)[g]
MS QoL- Physical Health	52.21 ±.46	[h]	
MS QoL- Mental Health	66.03 ±20.59	[h]	
RDAS	48 ±11.42	52.3 ±6.6	Non-clinical couples, scoring up 107 on dyadic adjustment Scale (n=144)[i]
SFS Withdrawal	110.8 ±13.40	100 ±15	Non-clinical sample recruited through relatives of individuals with schizophrenia (n=100)[j]
SFS Interaction	132.88 ±16.67	100 ±15	Non-clinical sample recruited through relatives of individuals with schizophrenia (n=100)[j]
SFS Performance	116.38 ±12.72	100 ±15	Non-clinical sample recruited through relatives of individuals with schizophrenia (n=100)[j]
SFS Competence	113.66 ±10.77	100 ±15	Non-clinical sample recruited through relatives of individuals with schizophrenia (n=100)[j]
SFS Recreation	117.20 ±15.30	100 ±15	Non-clinical sample recruited through relatives of individuals with schizophrenia (n=100)[j]
SFS Prosocial	115.29 ±12.36	100 ±15	Non-clinical sample recruited through relatives of individuals with schizophrenia (n=100)[j]
SFS Employment	110.62 ±12.59	100 ±15	Non-clinical sample recruited through relatives of individuals with schizophrenia (n=100)[j]

a= Baron-Cohen et al. (2001), b= two citations for test do not report appropriate control group (no control in Stone et al., (1998) and older control group (m=57.1±5.1 years) in Gregor et al., (2002) paper) c= Wechsler, (2011), d= Delis et al. (2001), e= Burgess & Shallice (1997), f=original test did not have control group complete DEX, therefore, therefore normative data taken from Chan, (2001), g= Beck et al. (1996), h= not able to report as measure designed for MS sample specifically, i= Busby et al., 1995, j= Birchwood, et al. (1990)

Relationships between demographic variables and TOM abilities

Pearson's correlations between scores on the RMET and: age, EDSS score, years in education and time since diagnosis were all non-significant, *p* ranging from .096- .539 (Table 2). The faux pas test negatively correlated with age and positively with years in education. Faux pas test performance was not significantly associated with time since diagnosis or EDSS scores (Table 2).

On the RMET, women's (mean= 26 ±5.68, Mdn=27) performance did not significantly differ from men's (mean= 22.71 ±3.4, Mdn= 22) performance (U= 63, z= -1.55, *p*= .131, *r*= .257). Similarly, on the faux pas test there was no significant difference (U= 57, z=-1.783, *p*= .078, *r*= -.300) between female (mean= 5.69 ±2.42, Mdn= 6) and male (mean= 4 ±2.77, Mdn= 4) participants' performance. Performance on the RMET did not significantly differ across diagnosis types (U= 61, z= -1.851, *p*= .064, *r*= -.313), RRMS (mean= 26.41 ±5.19, Mdn= 27) and SPMS (mean= 22.25 ±5.50, Mdn= 22). Similarly, scores on the faux pas test (RRMS (mean= 5.78 ±2.38, Mdn= 6), SPMS (mean= 3.88 ±2.85, Mdn= 3.50)), did not significantly differ by diagnosis type (U=64.5, z= -1.721, *p*= .085, *r*= -.291).

Table 2: Correlations between TOM ability and demographic variables

	RMET		Faux Pas	
	r	*p*	*r*	*p*
Age	-.158	.192	-.511	.001
EDSS	-.282	.096	-.277	.101
Years in Education	.161	.349	.408	.014
Time since diagnosis	.106	.539	-.134	.436

Relationships between TOM and cognitive abilities, and psychosocial outcomes

Individuals' performance on the two measures of TOM did not significantly correlate with one another (*r*= .214, *p*= .211). Performance on the RMET was significantly related to an individual's estimated IQ (*r*= .336, *p*= .045), verbal fluency (*r*= .441, *p*= .008) and switching fluency (*r*= .443, *p*= .007), whilst performance on the faux pas test significantly correlated with estimated IQ (*r*= .363, *p*= .029), Hayling (*r*= .332, *p*= .048), Brixton (*r*= .458, *p*= .005), verbal fluency (*r*= .414, *p*= .013), category fluency (*r*= .592, *p*= .000) and switching fluency (*r*= .474, *p*= .003) scores. Performance on the RMET was not correlated with any of the participant reported outcome variables (*p* ranged from .063- .942), however, faux pas performance was

significantly related to participants' reported social withdrawal (*r*= .355, *p*= .036), employment (*r*= .475, *p*= .005) and physical health related quality of life (*r*= .405, *p*= .014). There was no significant difference in scores reported on all dual rated (participant and significant other) outcome measures: the RDAS (T= 132, *p*= .606, *r*= -.072), DEX (T= 237, *p*= .244, *r*= .159) or the seven SFF subscales (*p* ranges from .234- .954).

Regression Analyses

Three exploratory regression models were run, one for each of the three outcome variables which significantly correlated with Faux Pas performance (Table 3). There were seven predictors within each model: faux pas, TOPF, verbal fluency, category fluency, switching fluency, Hayling and Brixton scores.

The first model, which explored the relationships between TOM and cognitive abilities and social withdrawal, was non-significant (F(7,26)= 2.316, *p*= .056). Similarly, a regression run to predict employment social functioning scores based on TOM and cognitive abilities was non-significant (F(7, 24)= 2.312, *p*= .059). Finally, the model calculating physical health related quality of life based on TOM and cognitive abilities was significant (F(7,27)= 2.772, *p*= .026), with the predictors explaining 41.8% of the variance in this outcome. However, TOM was not a significant predictor (*p*=.366), with the only significant predictors in this model being verbal (*p*= .036) and switching fluency (*p*= .034) scores.

Table 3: Linear regression model results

Variable	SFS Withdrawal					SFS Employment					Physical Health QoL				
	B	SE	Beta	*t*	*p*	*B*	SE	Beta	*t*	*p*	*B*	SE	Beta	*t*	*p*
Faux Pas	.397	1.159	.073	.343	.735	1.208	1.071	.246	1.128	.270	1.600	1.741	.191	.919	.366
TOPF	-.205	.300	-.118	1.686	.499	.187	.292	.122	.639	.529	.153	.440	.061	.346	.732
Verbal Fluency	-.351	.837	-.092	-.420	.678	-.843	.765	-.246	-1.102	.281	-2.803	1.269	-.468	-2.209	.036
Category Fluency	-.528	.874	-.143	-.604	.551	.684	.799	.205	.856	.400	.690	1.339	.117	.516	.610
Switching Fluency	1.333	.713	.442	1.871	.073	.962	.699	.309	1.376	.182	2.344	1.050	.486	2.233	.034
Hayling	3.558	1.883	.328	1.891	.070	1.200	1.742	.123	.689	.497	3.047	2.867	.175	1.063	.297
Brixton	1.239	1.145	.190	1.082	.289	.292	1.051	.051	.278	.784	.928	1.733	.091	.536	.596
(Constant)	94.595	31.658		2.988	.006	65.148	30.524		2.134	.043	-2.101	46.141		-.46	.964
R^2	.384					.403					.418				

Discussion

This study aimed to explore the associations between TOM abilities and psychosocial outcomes in individuals with MS. Comparisons made between scores on all TOM and executive functioning tasks with normative data gathered from non-clinical adult samples, suggested that these abilities were not impaired in the current MS sample. Similarly, when comparing self-reported scores on psychosocial questionnaires with test normative data from control samples, no difficulties were identified on any subscale of the SFS, depressive symptomology was in the non-clinical range, and fewer dysexecutive behaviours were reported than in a control sample (Chan, 2001). Performance on one of the TOM measures, RMET, was not significantly related to any of the psychosocial outcomes, whilst the other measure (Faux Pas test) only correlated, with weak to moderate effect, to three of the psychosocial variables. Specifically, social withdrawal, employment and physical health related quality of life. However, regression analyses suggested that these variables (faux pa performance and executive abilities) did not explain a significant amount of variance in two of these measure scores. As this is an exploratory study, these results should be interpreted with caution, as the type one error rate is inflated due to the multiple tests used in the analysis. Further studies are required to replicate these findings.

The findings from this study were largely unexpected given the theoretical literature and the established links between TOM abilities and psychosocial outcomes in other populations (Couture, Penn, & Roberts, 2006; Penton-Voak et al., 2017). However, this may be partially explained by the unexpected lack of cognitive impairments and psychosocial difficulties reported by the current sample. These impairments/difficulties have been evidenced in individuals with MS in previous research (Chiaravalloti & DeLuca, 2008; Cotter et al., 2016; Pompeii, Moon, & McCrory, 2005), but the current results suggested no impairments, or better psychosocial outcomes than control samples. Through considering effect sizes, correlation coefficients and r squared values it is unlikely that the lack of reported difficulties and significant effects found can primarily be explained by the study being underpowered. Most effect sizes were small (<.300), therefore would not be greatly sensitive to change with increasing participant numbers.

Whilst it is possible that the results are a true reflection of no impairments or associations between variables being present, there are an additional three main factors to consider when interpreting the results: the sample recruited, the assessment measures used, and analyses conducted. The sample was recruited through signposting from clinicians and also through a research database and website, with the majority being recruited from the latter. This may have biased the sample by predominately attracting individuals with higher education qualifications, an interest in academia and taking part in research. In comparing the current sample demographics with those included in previous research where TOM impairments were identified (e.g. Chanial et al., 2020; Henry et al., 2011; Ouellet et al., 2010; Raimo et al., 2017), the current sample averaged two or more years extra in education. It is thought that greater cognitive abilities prior to a diagnosis of a neurological condition are somewhat protective in the slowing of neurological deterioration (Sumowski et al., 2014). This, alongside the large cognitive demands of participating in this study may have recruited a sample of individuals with less significant cognitive difficulties. However, in contradiction, the sample did not include individuals who were within two years of receiving their diagnosis and there were no individuals with PPMS, but a large subgroup of the sample was individuals with SPMS, who more frequently report cognitive impairments (DeLuca et al., 2004). Therefore, a larger spread of cognitive difficulties would have been expected than was seen.

Based on the knowledge that executive functioning may impact upon TOM task performance (Henry et al., 2009), the decision was made to include executive measures in the study. Unfortunately, given the already high task burden on individuals, further tests exploring a wider range of cognitive abilities were not included. This information may have been informative and allowed for a more complete and comprehensive understanding of the cognitive profiles of the individuals included in the study. It would be interesting for future research to consider other cognitive abilities such as attention and processing speed.

A further consideration is the ability and sensitivity of the assessments used to measure the constructs they are intended to measure. There remains a lack of research into the reliability, validity and suitability of TOM measures use in individuals with MS (Gibson et al., 2020). Whilst the TOM measure selection for this study was based upon their psychometrics properties in other samples and prior use with individuals with MS, it is possible that they are

not sensitive enough to identify subtle difficulties within an MS samples. This is one potential explanation for the similarity in RMET scores between this sample and the normative data sample. Further work is essential to better understand the suitability of TOM measures more generally for use with individuals with MS so these abilities can be accurately measured and better understood. Similarly, some of the psychosocial outcome measures (e.g. the RDAS and SFS) have not been used with individuals with MS. Given the novel nature of the research questions addressed by this study within an MS sample, it was challenging to identify appropriate measures and again this was based upon psychometric properties within non-neurological, non-clinical samples. This makes it challenging to judge whether the current reports are a true reflection of the psychosocial characteristics of the sample, or the measures used.

Finally, in understanding the findings, the analyses run need to be considered. The exploratory nature of this paper resulted in multiple analyses being run to explore the associations between a large variety of variables. Therefore, the results need to be considered with caution given that associations may be overestimated, and it was not possible to accurately calculate the family-wise error rate. Additionally, the limitations of the regression analysis are recognised. Given the large number of potential predictors and small sample size, the correlation analyses were used, alongside theoretical knowledge of executive contributors to TOM performance, to inform predictor input. It is recognised that predictor selection through this means can be challenging as the relationship between predictors and outcomes varies upon the other predictors in the model (Field, 2013, p.323). Whilst one model (physical health QoL) came out significant and the other two near significance, it is possible that the model fit, and estimates were influenced by the large predictor to participant ratio. This is emphasised by the lack of significant relationships for single predictors within the model and low R^2 values considering the number of predictors. Whilst the sample size was similar to that used in other studies in this research area, further research using a larger sample is required to better understand the associations between these variables.

Additionally, the smaller than desirable sample size had implications when interpreting the analyses exploring subtype and gender variations in TOM abilities. The effect sizes suggest

that the analyses have likely been impacted by low power and therefore it is not possible to reliably conclude that there is no difference across subtypes or genders. It would be informative for further research to be completed to explore any variations in TOM and/or cognitive abilities, and their associations with psychosocial outcomes across gender and MS subtypes.

In conclusion, this study aimed to explore the associations between TOM abilities and several psychosocial outcomes in individuals with MS. However, within the current sample TOM impairments and psychosocial difficulties were not commonly reported, similar to previous research and limited relationships between variables found. However, initial findings suggest there may be links between TOM abilities and some areas of social functioning, in individuals with MS. Future confirmatory studies should aim to explore this hypothesis in larger, and more cognitively diverse samples. Additionally, it is recommended that research into the psychometrics and suitability of TOM measures within this population is conducted, to ensure accurate assessments are completed and abilities fully understood.

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Appendices

Appendix A: Guidance for publication in Journal of the International Neuropsychological Society

Guidance taken from: https://www.cambridge.org/core/journals/journal-of-the-international-neuropsychological-society/information/instructions-contributors

Aims and Scope

The *Journal of the International Neuropsychological Society* is the official journal of the International Neuropsychological Society, an organization of over 4,500 international members from a variety of disciplines. The *Journal of the International Neuropsychological Society* welcomes original, creative, high quality research papers covering all areas of neuropsychology. The focus of articles may be primarily experimental, applied, or clinical. Contributions will broadly reflect the interest of all areas of neuropsychology, including but not limited to: development of cognitive processes, brain-behavior relationships, adult and pediatric neuropsychology, neurobehavioral syndromes (such as aphasia or apraxia), and the interfaces of neuropsychology with related areas such as behavioral neurology, neuropsychiatry, genetics, and cognitive neuroscience. Papers that utilize behavioral, neuroimaging, and electrophysiological measures are appropriate.

To assure maximum flexibility and to promote diverse mechanisms of scholarly communication, the following formats are available in addition to a *Regular Research Article: Brief Communication* is a shorter research article; *Rapid Communication* is intended for "fast breaking" new work that does not yet justify a full length article and is placed on a fast review track; *Case Report* is a theoretically important and unique case study; *Critical Review* and *Short Review* are thoughtful considerations of topics of importance to neuropsychology and include meta-analyses; *Dialogue* provides a forum for publishing two distinct positions on controversial issues in a point-counterpoint format; *Special Issue* and *Special Section* consist of several articles linked thematically; *Letter to the Editor* responds to recent articles published in the *Journal of the International Neuropsychological Society*; and *Book Review,* which is considered but is no longer solicited.

Manuscript Submission and Review

The Journal of the International Neuropsychological Society uses online submission and peer review. Paper submissions are not accepted.

The website address for submissions is: http://mc.manuscriptcentral.com/jins. Complete instructions are provided on the website.

Prior to online submission, please consult http://www.nlm.nih.gov/mesh/ for 6 keywords or mesh terms that are different from words in the title. Accurate mesh terms will increase the probability that your manuscript will be identified in online searches. Please follow the instructions carefully to avoid delays. The menu will prompt the author to provide all necessary information, including the manuscript category, the corresponding author including postal address, phone and fax numbers, and e-mail address, and suggested reviewers.

Manuscript Length

In order to increase the number of manuscripts that can be published in the *Journal of the International Neuropsychological Society*, please adhere to the following length requirements. Please provide a word count on the title page for the abstract and manuscript (not including abstract, tables, figures, or references). Manuscripts will be returned if they exceed length requirements.

Regular Research Article: Maximum of 5,000 words (not including abstract, tables, figures, or references) and a 250 word abstract. Regular Research Articles are original, creative, high quality papers covering all areas of neuropsychology; focus may be experimental, applied or clinical.

Manuscript Preparation and Style

The entire manuscript should be typed double-spaced throughout using a word processing program. Unless otherwise specified, the guideline for preparation of manuscripts is the *Publication Manual of the American Psychological Association (6th edition)* except for references with 3 or more authors (see References section). This manual may be ordered from: APA Order Dept., 750 1st St. NE, Washington, DC 20002-4242, USA.

Pages should be numbered sequentially beginning with the Title Page. The Title Page should contain the full title of the manuscript, the full names and institutional affiliations of all authors; mailing address, telephone and fax numbers, and e-mail address for the corresponding author; and the word count for the abstract and manuscript text (excluding title page, abstract, references, tables, and figures). At the top right provide a short title of up to 45 characters preceded by the lead author's last name. Example: Smith-Memory in Parkinson's Disease. This running head should be repeated at the top right of every following page.

Page 2 should include an Abstract and a list of at least six keywords or mesh terms. Note: structured abstracts must be included with papers submitted after January 1, 2014. A structured abstract must include four header labels: Objective, Method, Results, and Conclusions. A total of six mesh terms (http://www.nlm.nih.gov/mesh/) or keywords should be provided and should not duplicate words in the title.

The full text of the manuscript should begin on page 3. For scientific articles, including *Regular Research Articles, Brief Communications, Rapid Communications,* and *Symposia*, the format should include a structured Abstract, Introduction, Method, Results, and Discussion. This should be followed by Acknowledgments, References, Tables, Figure Legends, Figures, and optional Appendices and Supplemental Material.

The use of abbreviations, except those that are widely used, is strongly discouraged. They should be used only if they contribute to better comprehension of the manuscript. Acronyms should be spelled out at first mention. Metric system (SI) units should be used.

Appendices and Supplemental Materials may be submitted. Appendices include material intended for print and should be included with the manuscript file. Supplementary material

will appear only online and should be submitted as a separate file. Supplementary material is replicated as-is.

The Acknowledgements Section should include two parts: a Conflicts of Interest disclosure (see above) and a statement to disclose all Funding sources of financial support for the paper. If no Conflicts of Interest exist, you will be required to state as such ("COI: None." or a similar statement). In documenting financial support, please provide details of the sources of financial support for all authors, including grant numbers. Multiple grant numbers should be separated by a comma and space and where research was funded by more than one agency, the different agencies should be separated by a semicolon with "and" before the final funding agency. Grants held by different authors should be identified using the authors' initials.

Tables and Figures should be numbered in Arabic numerals. Figures should be numbered consecutively as they appear in the text. Figures should be twice their intended final size and authors should do their best to construct figures with notation and data points of sufficient size (recommended ≥ 300 dpi) to permit legible photo reduction to one column of a two-column format. Please upload figure(s) in either a .doc, .jpeg, .tiff, or .pdf format. There is no additional cost for publishing color figures. The approximate position of each table and figure should be provided in the manuscript with call-outs: [INSERT TABLE 1 HERE]. Tables and figures should be on separate pages. Tables should have short titles and all figure legends should be on separate pages. All tables and figures must have in-text citations in order of appearance.

Figures submitted in color will appear online in color, but all figures will be printed in black and white unless authors specify during submission that figures should be printed in color, for which there may be a fee. There is no additional cost for publishing color figures in the print version of the journal for corresponding authors who are INS members. For non-members, the cost for publishing color figures in print version of the journal will be $320 per figure with a cap of $1600 per article.

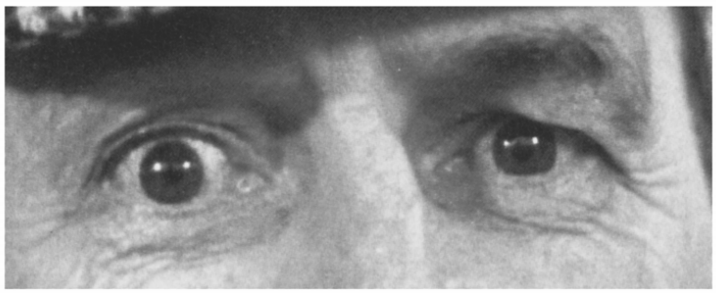
References should be consistent with the *Publication Manual of the American Psychological Association (6th Edition)*. In-text references should be cited as follows: "...Given the critical role of the prefrontal cortex (PFC) in working memory (Cohen et al., 1997; Goldman-Rakic, 1987; Perlstein et al., 2003a, 2003b)..." with multiple references in alphabetical order. Another example: "...Cohen et al. (1994, 1997), Braver et al. (1997), and Jonides and Smith (1997) demonstrated..."

References cited in the text with two authors should list both names. References cited in the text with three, four, or five authors, list all authors at first mention; with subsequent citations include only the first author's last name followed by et al. References cited in the text with six or more authors should list the first author et al. throughout. In the reference section, for works with up to seven authors, list all authors. For eight authors or more, list the first six, then ellipses followed by the last author's name.

Appendix B: Sample items from the Reading the Mind in the Eyes Test (Baron-Cohen et al., 2001)

Example 1:

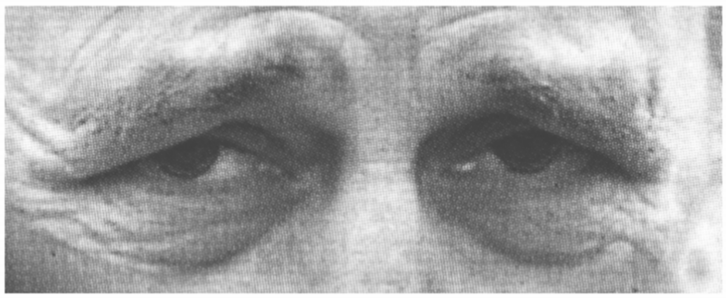
jealous panicked



arrogant hateful

Example 2:

terrified upset



arrogant annoyed

Appendix C: Sample Items from the Faux Pas Test (Baron-Cohen et al., 1999; Stone & Baron-Cohen, 1998)

Faux Pa Stories

Story 2. Helen's husband was throwing a surprise party for her birthday. He invited Sarah, a friend of Helen's, and said, "Don't tell anyone, especially Helen." The day before the party, Helen was over at Sarah's and Sarah spilled some coffee on a new dress that was hanging over her chair.
"Oh!" said Sarah, "I was going to wear this to your party!"
"What party?" said Helen.
"Come on," said Sarah, "Let's go see if we can get the stain out."

Story 7. Sally is a three-year-old girl with a round face and short blonde hair. She was at her Aunt Carol's house. The doorbell rang and her Aunt Carol answered it. It was Mary, a neighbour.
"Hi," Aunt Carol said, "Nice of you to stop by."
Mary said, "Hello," then looked at Sally and said, "Oh, I don't think I've met this little boy. What's your name?"

Control Stories

Story 1. Vicky was at a party at her friend Oliver's house. She was talking to Oliver when another woman came up to them. She was one of Oliver's neighbours. The woman said, "Hello," then turned to Vicky and said, " I don't think we've met. I'm Maria, what's your name?"
"I'm Vicky."
"Would anyone like something to drink?" Oliver asked.

Story 9. Joanne had had a major role in last year's school play and she really wanted the lead role this year. She took acting classes, and in the spring, she auditioned for the play. The day the decisions were posted, she went before class to check the list of who had made the play.
She hadn't made the lead and had instead been cast in a minor role. She ran into her boyfriend in the hall and told him what had happened. "I'm sorry," he said. "You must be disappointed."
"Yes," Joanne answered, "I have to decide whether to take this role."

Appendix D: Study Protocol

Study Protocol

Psychological, Interpersonal and Social Functioning in MS: The Role of Theory of Mind

	The University of Edinburgh College of Arts, Humanities and Social Sciences 55 George Square Edinburgh EH8 9JU
Protocol authors	Rachel Gibson
Chief Investigator	Rachel Gibson (Trainee Clinical Psychologist)
Sponsor number	CAHSS1809/07
REC Number	RECSES01 19/SS/0006
Version Number and Date	Version 2, 10/02/2019

Amendment classification and number:	**Summary of change(s)**
Version 2	Following attending SESREC01 the protocol was updated to: detail that individuals would be offered breaks and refreshments; report total study commitment time; and that sealed, addressed envelopes will be provided. Additionally, the recruitment protocol for NHS Lothian was changed to be similar to that of NHS Fife.

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Background

Multiple Sclerosis

Multiple Sclerosis (MS) is the most common cause of neurological disability in young people in the UK (MS Society, 2018), with around 100,000 individuals having a diagnosis of MS. MS is a chronic, inflammatory disease of the central nervous system, characterised by demyelination (Feinstein, 2007).

MS is a heterogeneous condition with symptoms varying depending upon the location and extent of the myelin damage (Feinstein, 2007). Symptoms also vary by MS subtype, with each subtype being characterised by a different disease course. The most prevalent subtype is relapse-remitting MS (RRMS), which approximately 85% of individuals are initially diagnosed with. Individuals with RRMS experience acute relapses characterised by neurological deterioration, followed by a period of (full or partial) recovery (Feinstein, 2007). Between relapses their presentation remains stable. Some individuals with RRMS will later develop secondary progressive MS (SPMS), which is characterised by progressive deterioration, with or without the relapses. Alternatively, around 15% of individuals are initially diagnosed with primary progressive MS (PPMS), which is characterised by gradual, continuous deterioration in neurological functioning (Feinstein, 2007), with no acute relapses. Similar to RRMS, many of these individuals will go onto develop SPMS. Whilst previously research into symptomology in MS has focused on physical symptoms, more recently cognitive symptoms have been gathering more interest (Niino, 2016b).

Cognitive Functioning in MS

Demyelination leads to a slower transmission of electrical signals between neurons in the brain, and if demyelination continues it can progress to axonal damage (Feinstein, 2007). Given that neurological damage is present in all individuals with MS, they are more vulnerable to developing neuropsychological impairments. Research has shown that neuropsychological impairments are common in individuals with MS, with up to 70% of individuals displaying some form of cognitive impairment (Cotter et al. 2016). Whilst cognitive dysfunction has been shown in all MS subtypes, the extent of this is thought to vary by MS subtype. For example in one study, individuals with RRMS have been shown to experience greater cognitive impairments than individuals with PPMS (Niino, 2016b). Given that cognitive dysfunction has been shown to be a predictor of lower social engagement and poorer quality of life in individuals with MS (Niino, 2016b; Sartori & Edan, 2006), it is important that all areas of cognitive function are researched and their links to social outcomes are better understood.

Several neuropsychological characteristics in MS are well-established in the literature (e.g. impairments in processing speed, working memory, and executive functioning; Bobholz & Rao, 2003; Feinstein, 2007; Niino, 2016), however, less research has explored the sixth core domain of neurocognitive functioning (Henry, et al. 2015), social cognition (SC; Cotter et al. 2016). SC refers to the 'mental operations that underlie social interactions' (Cotter et al. 2018) and is an umbrella term for a number of cognitive abilities including emotion recognition, theory of mind (TOM), and empathy (Lysaker et al. 2014). As SC impairments have been linked to the development and maintenance of mental health concerns (Penton-Voak et al. 2017), it is important more research explores these abilities to help enhance metal well-being in individuals with MS.

Social Cognition/ Theory of Mind in MS

There is consistent evidence of SC impairments in individuals with MS, across a range of SC abilities (see Gleichgerrcht et al. 2015; Henry et al. 2011; Lenne et al. 2014; Ouellet et al. 2010; Phillips et al. 2011). One of the most researched SC abilities is theory of mind (TOM), which refers to an individual's ability to attribute the mental states of oneself and others (e.g. their beliefs, goals, intentions and emotion; Banati et al. 2010) which is crucial in both understanding and predicting behaviour. Research into TOM in individual's with MS has consistently shown this ability to be impaired when compared against healthy controls. Specifically, a recent meta-analysis (Cotter et al. 2016) which explored TOM and emotion recognition abilities in individuals with MS, found both to be impaired when compared against healthy controls. The magnitude of these impairments was either equivalent to or greater than other cognitive domains (e.g. memory, language and planning).

Whilst the magnitude of SC impairments has been explored in individuals with MS, there has been very little research exploring the impact of these SC deficits on an individual's functioning (Henry et al., 2011). One study which explored emotion perception deficits in MS (Phillips et al., 2011) found associations with reduced psychological and social quality of life. Whilst there has been limited research exploring the relationship between TOM and depressive symptomology in individuals with MS, no relationship has been found (Cotter et al. 2016). To the researcher's knowledge, there has been no similar research exploring the relationship between TOM and interpersonal or social functioning. Given that there are many social (e.g. isolation, reduced independence) and cognitive (e.g. slower processing speed, impaired TOM) symptoms commonly seen in individuals with MS (Feinstein, 2007), it is surprising that the relationships between these have not been explored. Additionally, given that TOM is an important skill required for engaging in social interaction and adapting behaviour to our environment, it is possible that impairments in TOM abilities mat be partially associated with the poorer relationship quality and lower quality of life in individuals with MS (Henry, Tourbah, Chaunu, Bakchine, & Montreuil, 2017). This study aims to explore this relationship, which may be informative in improving the clinical management and rehabilitation interventions available to individuals with MS.

Given that RRMS is initially the more prevalent MS subtype (Feinstein, 2007), it is not surprising that to date, the majority of research into SC in MS has recruited primarily individuals with RRMS. Specifically, data from a recent meta-analysis (Cotter et al., 2016) highlighted that 77% of all participants in SC research had a RRMS diagnosis, with the remaining 23% having an alternative MS diagnosis. Therefore, little is known about the homogeneity of TOM impairments across MS subtypes. Given that individuals with RRMS have been shown to have greater cognitive impairments than individuals with other MS diagnoses (Niino, 2016b), there is reason to suggest that TOM impairments may not be homogenous across MS subtypes either. To date, no study has been able to make any comparisons (even exploratory) on TOM abilities across MS subtypes. This would be a valuable addition to the research base (Phillips et al., 2011), to help better understand the varying clinical presentations of MS subtypes.

It is well known that greater pre-exist cognitive abilities (cognitive reserve) are a protective factor against cognitive dysfunction (Sumowski & Leavitt, 2013). A one year longitudinal study showed cognitive and brain reserve (brain mass) were protective factors for both memory and processing speed in individuals with MS (Sumowski et al. 2014). Whilst a recent pilot study (N=15) found a positive

relationship between cognitive ability (IQ) and performance on a SC test battery in individuals with MS (Genova, et al. 2016), this relationship has not been explored on other measures of SC or replicated on a larger sample.

TOM Based Interventions

There has been some promising findings for TOM based interventions in other clinical populations (Kurtz, et al. 2016), primarily individuals with schizophrenia. Kurtz et al. (2016) also specifically explored the effectiveness of TOM based interventions across 13 studies, with 10 evidencing positive improvements following intervention (Cohen's d=0.7), including improved TOM and social functioning. There is currently no research on TOM interventions within a MS population. This may partly be explained by the limited TOM research and remaining gaps in the knowledge base for individuals with MS. The current study hopes to address some of these gaps, which is required prior to future work exploring possible interventions for SC impairments in individuals with MS.

Rationale for Study

Whilst research has highlighted impaired TOM (Cotter et al., 2016), impaired social functioning (Feinstein, 2007), reduced quality of life (Phillips et al., 2011) and reduced relationship quality (King & Arnett, 2005) in individuals with MS, no study has explored the relationships between these variables. Given that TOM is important for effective social interactions and adapting behaviour appropriately to an audience, it is possible that impairments to TOM are associated with the lower relationships quality and quality of life reported in individuals with MS. This is a significant gap in the existing knowledge base as without fully understanding the links between neuropsychological and psychosocial variables in individuals with MS, it is not possible to ascertain which areas of functioning rehabilitation interventions should focus on. Whilst this study does not aim to explore or evidence TOM interventions, it is hoped that thought aiming to explore any possible relationship between TOM and social, emotional and interpersonal functioning we can inform future research into potential interventions and enhance clinical management of this population.

Additionally, the majority of research to date has explored TOM abilities in individuals with RRMS, however, there is research to suggest there may be differences in cognitive impairments across subtypes. This study also aims to explore whether TOM abilities are homogeneous across MS subtype.

Study Objectives

Primary Objective

- Is Theory of Mind associated with psychological, social and interpersonal functioning in individuals with Multiple Sclerosis (MS)?

Secondary Objectives

- Is there a difference in TOM performance across different MS subtypes? Specifically, Relapse-Remitting MS and Primary Progressive MS.
- Is there a relationship between estimated cognitive abilities pre-diagnosis and TOM abilities in individuals with MS?

Study Design

The study will use a questionnaire based, within-group design. This particular design was chosen because impairments in Theory of Mind (TOM) in individuals with MS have been consistently shown in the literature by comparing test performance with individuals without MS (between-group studies), therefore it was not felt necessary to further replicate this here. The study will implement a cross-sectional design as the primary aim is to explore the relationships between TOM and other functional abilities, rather than to explore the trajectory of impairments over the disease course. As this is a student project, the project will be completed, and written up ahead of May 2020.

Procedure

Potential participants will be identified using methods described below (see section 5.1). Potential participants will either consent to the research team contacting them by phone or they will call into the research team themselves. During the initial phone call, the potential participant will have the opportunity to ask any questions they may have about the project, the PI will gain verbal consent from the individuals if they wish to participate and arrange an appointment for the individual to attend to complete the neuropsychological assessments.

Participants will be sent out several self-report questionnaires in the post, which they will be asked to complete at home prior to attending their assessment appointment. If they forget to complete these, they will have the opportunity to complete them when they attend for their appointment or they will be sent home with a stamped addressed envelope to return them in. Additional to the self-report questionnaires, there are a few questionnaires which require a significant other to complete (e.g. family or friend). During the initial phone call, consent will be sought from participants for these measures to be sent out. If the participant consents to these measures being completed, they will be sent out alongside the participant's self-report measures, for the participant to distribute to the appropriate person to complete. These will either be returned when the participant attends for their assessment appointment, or they can be returned in the stamped addressed envelope provided. If these are not returned at this time, the participant will be reminded of these and asked for them to be completed and returned.

The participant will be required to attend one 90-minute assessment appointment, during which all neuropsychological assessment measures will be completed. As individuals with MS can experience fatigue, this will be monitored by the PI during the appointment, through direct questioning and observation of behaviour and body language. If required they will be able to take a break during testing, when refreshments can be provided, or testing can be completed over multiple sessions, to reduce participant burden and limit the impact of fatigue on test performance. Additionally, to distribute the potential impact of fatigue across the various measures, the order of the tests will vary across participants, with the tests continually rotating in order of presentation with each participant. This will also limit the possibility of any order effects.

The appointments will be held within outpatient hospital clinics and GP practices within the participant's NHS board area. Where possible in NHS Fife, the appointment will be offered with the participants preferences (location/time) in mind. In NHS Lothian, appointments will be primarily held at the Anne Rowling Clinic. At this appointment, before testing has commenced, written consent will be obtained from all participants. Individuals will then be asked to complete a battery of neuropsychological tests, which will assess their TOM and their executive abilities (e.g. attention,

planning, problem solving). The specific tests/measures/questionnaires are detailed below (see section 6).

Participants are only required to attend one appointment and therefore at most, participants will be involved in the study for a few months. However, study duration will be dependent upon the individual and PI's availability and when an assessment appointment can be booked in.

Study Participants

Number of Participants

The required sample size was determined using the primary research objective, which will be answered using regression analysis. The G*Power programme (Faul, Erdfelder, Buchner, & Lang, 2009) was used to calculate sample size. For a multivariate linear regression, with three predictor variables, a sample size of 61 is required. Power was set at 0.8, alpha at 0.017 (to control for multiple comparisons) and the effect size was set as medium. Through reviewing previous research which has explored SC in individuals with MS, medium to large effect sizes have been shown in studies which have primarily aimed to explore the magnitude of SC impairments within this population (see Cotter et al. 2016; Genova et al. 2016; Phillips et al. 2011). Taking this into consideration, alongside the lack of research into the impact of impaired SC on functional abilities, the effect size was set as medium.

The study aims to recruit from two sites: Fife Rehabilitation Service (NHS Fife) and NHS Lothian's Anne Rowling Clinic. It is hoped that they will recruit around 40 and 20 participants, respectively. As this is a student project, this places some restrictions on the recruitment window for this project. The PI aims to facilitate as long a recruitment window as is feasible, hopefully around 12 months.

Within NHS Fife, there is a database with over 700 individuals with a diagnosis of MS, who are within the specified age category. In NHS Lothian, they see around 50 individuals a week in the MS clinic. Staff from both research sites are optimistic about being able to achieve/ recruit the required sample size.

Inclusion Criteria

- A pre-existing, formal diagnosis of Multiple Sclerosis (MS) from a neurologist or other medical professional. Specifically, the study will aim to recruit individuals who are at least two years post diagnosis or have had two relapses (if RRMS).
    - It is hoped that by recruiting individuals who are a 2+ years post diagnosis or have had 2+ relapses, there will be a greater possibility of recruiting individuals with varying degrees of TOM impairments. Additionally, in the earlier stages of the disease course, an individual's cognitive functioning may be less stable; they may be adjusting psychologically and emotionally to receiving their diagnosis; as well as beginning treatment (e.g. modification therapy). Therefore, those who have recently been diagnosed will not be considered for recruitment.
- Aged between 18 and 65 years. MS is typically diagnosed between 20 and 40 years of age.
    - As individuals under the age of 18 years may represent a different clinical population, they will not be recruited into the study.
    - Due to time constraints, it is not possible for the study to screen individuals for cognitive decline. Whilst the research team recognises that not all individuals over 65

years will experience cognitive impairment, the age cut-off minimises the risk of age-related decline acting as a confounding variable.

Exclusion Criteria

The exclusion criteria listed below will be considered when recruiting all potential participants into the study. Information related to the exclusion criteria will be gained through information held in the database and/or the individual's medical records. If the information is not available through theses means, the PI will ask and gather this information prior to completing testing. In ambiguous situations, decisions on excluding participants will be discussed in supervision with the field supervisor.

- Individuals for whom English is not their first language
    - As the psychometric tests used within this study were normed on an English-speaking population, the norms would not be representative or appropriate for use with individuals for whom English is not their dominant language.
- Individuals who are unable to provide informed consent.
    - It is possible that individuals who are unable to provide informed consent may have significant cognitive impairments. Taking this into consideration, the testing environment would likely be both challenging and distressing for them, therefore, it would be unethical to include them in the test sample.
- History of substance misuse.
    - Substance misuse is known to impact upon an individual's thinking, problem solving and perception (American Psychiatric Association, 2013). Therefore, it would not be possible to ascertain whether any cognitive impairment was due to substance misuse or a product of their MS.
- Diagnosis (current or historical) which affects social or cognitive functioning (e.g. Autism Spectrum Disorder, Brain Injury, Dementia, Learning Disability, Psychosis).
    - As the above conditions are known to affect cognitive and social functioning, it would not be possible to fully understand the contribution of an individual's MS on their functioning in isolation of the cognitive and social impairments of the above conditions.
- Current or historic severe aphasia.
    - As several of the psychometric tests used in this study rely on verbal responses, individuals with aphasia will not be included as their aphasia would likely influence test performance.
- Individuals with significant hearing or visual impairments which would impact on their ability to adequately complete testing.
    - Similar to reasons detailed above, any visual or hearing impairment may impact upon test administration and subsequently test performance. Unfortunately, it is not possible for tests to be adapted as this may confound the results.

Participant Selection and Enrolment

NHS Fife

Within the Fife Rehabilitation Service (NHS Fife), potential participants will be identified from an existing database, which holds data on over 700 individuals with an MS diagnosis. This database is owned and managed by one of the MS Nurses within the team, and they have consent to contact individuals contained within the database for research purposes. This individual will be responsible for identifying potential participants at this site. Individuals who have been more recently seen in the service, who meet the inclusion criteria, will be invited to participate initially. This is because on the database their information will be the most up to date and more representative of their current presentation. Should too few individuals opt in to participating, additional invites will be sent out, working backwards chronologically from their discharge date. Potential participants will be sent a letter from the MS nurse which will include a reply slip for them to complete and return to her should they wish to participate in the research study. They can also phone the PI directly. If participants do not wish to participate, they are encouraged to inform the MS nurse, to prevent them receiving further information about the study.

NHS Lothian

At the NHS Lothian site (Anne Rowling Clinic), potential participants will be identified by their neurologist or MS nurse during clinic appointments. Potential participants will already be enrolled with 'Rowling Care', which is a register of individuals known to the Anne Rowling Clinic who are willing to be contacted about ongoing research. When an individual who is registered with Rowling Care and meets the inclusion criteria for the study, attends for a clinic appointment they will be informed by the clinician (neurologist or MS nurse) about the study and given a participant information sheet and letter of invitation. Individuals will be able to express an interest in the study in two ways. Specifically, they will be able to inform the clinician at the clinic or if the individual requires additional time to consider their participation, they will be able to return a reply slip attached to the bottom of the letter of invitation to the neurologist from the clinic. Their details will then be given to the PI who will contact them to discuss participation, answer any questions they have and arrange an appointment for neuropsychological testing.

Consenting Participants

Only individuals who are able to provide informed consent will be invited to take part in the study. The decision on whether an individual has capacity will be determined by the most recent assessment made by an individual from the participants direct care team. Particularly at the NHS Lothian site, the direct care team will be identifying potential participants for the study, therefore, an individual's capacity will be considered at this point. In NHS Fife, this will be a previous or current member of the individual's care team.

Potential participants will initially be sent out or given a written information sheet about the study and given the opportunity to consider whether they wish to take part. In NHS Fife, as information will be sent in the post, there will be no formally specified time period for them to consider their decision. As individuals with MS can experience relapse, this may impact their ability to take part (during and 3 months post relapse), however, once their functioning has stabled they may wish to participate. Therefore, by not specifying a time frame this allows the individual to consider participating when their health allows them to. In NHS Lothian, individuals will be able to consider participation until their follow-up clinic appointment. It is unlikely that past this point that individual will opt in as their follow-

up appointment would allow them to ask questions and be directed to the PI to answer these. The recruitment window for this study will be approximately one year, due to it being a student project. Only towards the end of this period may the time allocated for the potential participant to consider their decision be more limited.

Once potential participants have had the time to consider their decision, they will then either call the PI to express interest or will be called by the PI if they have informed another clinical member of staff that they wish to participate. At this point verbal consent will be gained over the phone by the PI and an appointment arranged with the participant for them to attend to complete the neuropsychological testing. At this appointment, the PI will provide the potential participant with the opportunity to go over the participant information sheet and answer any questions they have about participating in the study. All questions will be answered and following this, should the potential participant still wish to take part, a written consent form will be completed.

Withdrawal of Study Participants

Participants are free to withdraw from the study at any point or a participant can be withdrawn by the investigator. For example, if they lose capacity during study or if tasks are too demanding and cause them significant distress. The participant will be withdrawn from all aspects of the trial, including data gathered up to this point which will not be included in the analysis.

Partners and/or Significant Other

Identifying Participants

As mentioned in section 3.2, participant's partners and/or significant other will be invited to take part in the study. Specifically, this will involve them completing a few questionnaires, which ask about the primary participant's social engagement and the quality of the relationship they have with them.

Individuals will be identified by the primary participant, the individual with MS. They will be informed that the chosen individual should know them well and have regular contact with them. During the initial phone call with the primary participant, the PI will: discuss the selection of a partner and/or significant other with the primary participant; and go through the inclusion and exclusion criteria to ensure the individual selects an individual who meets the criteria. Specifically, the PI will send out a participant information sheet and the other-report measures for the significant other, alongside the information sent to the primary participant. The primary participant will be asked to distribute the information to their partner and or significant other.

Inclusion Criteria

- Will have known the primary participant for at least one year
- Have regular contact with the primary participant (at least once a week)
- Be able to provide informed consent

Exclusion Criteria

- Individuals who are unable to comprehensively understand the information contained in the questionnaires. For example: individuals with a learning disability or individuals who are not fluent in English, as translations cannot be provided.
- Individuals who are unable to provide informed consent

Withdrawal of Study Participants

Participants are free to withdraw from the study at any point or a participant can be withdrawn by the investigator. For example, if they are unable to understand or complete the measures. The participant will be withdrawn from all aspects of the trial, including data gathered up to this point which will not be included in the analysis. Their withdrawal will not impact upon the primary participant's involvement in the study.

Study Assessment

The neuropsychological tests and the questionnaires which the participants will be asked to complete are detailed in the table below. Total commitment time for the primary participants is between two hours and two hours fifteen minutes. For significant others, total commitment time is up to thirty minutes.

Assessment/questionnaire	**Description of task**	**Time to administer**	**Who will administer task and where**
Reading the Mind in the Eyes Test (RMET).	RMET is a measure of affective TOM. The individual is shown 36 sets of eyes and have to choose the emotion shown by the eyes.	20	The principal investigator will conduct the procedure, in an outpatient appointment with the individual
Faux Pas Recognition Test	This is a measure of cognitive and affective TOM. The individual is read 20 stories and asked to identify any faux pas.	20	The principal investigator will conduct the procedure, in an outpatient appointment with the individual
The Test of Premorbid Function (TOPF).	The TOPF is a reading test which aims to estimate an individual's pre-morbid cognitive function. The individual is required to read 70 words which have atypical grapheme to phoneme translations	5	The principal investigator will conduct the procedure, in an outpatient appointment with the individual
Verbal and Category Fluency.	This is a measure of mental flexibility. Individuals are given a letter of the alphabet or semantic category and asked to generate as many words as possible in 1 minute	15	The principal investigator will conduct the procedure, in an outpatient appointment with the individual
Hayling Sentence Completion Test	This is a sentence completion task. Part 1- measures response speed and initiation by asking the individual to complete a sentence	10	The principal investigator will conduct the procedure, in an outpatient appointment with the individual

	Part 2- measures response suppression by asking the individual to complete the sentence but this time with a completely unrelated word		
The Brixton Spatial Anticipation Test	This task measures rule detection and set shifting. Individuals are shown 10 circles, one of which is blue. They have to predict the location of the blue circle on the next page, following set rules.	15	The principal investigator will conduct the procedure, in an outpatient appointment with the individual
Beck's Depression Inventory	This is a 21 item, self-report measure of depression symptomology.	5	This will be completed by the participants at home, prior to attending for the neuropsychological testing appointment.
The Multiple Sclerosis Quality of Life- 54	This is a 54 item, self-report measure of quality of life.	10	This will be completed by the participants at home, prior to attending for the neuropsychological testing appointment.
The Social Functioning Scale	This questionnaire assesses social functioning. It is specifically designed for use in chronic conditions, focusing primarily on independence, social engagement, friendships and daily activities.	15	This will be completed by the participants at home, prior to attending for the neuropsychological testing appointment. It will also be completed by a friend/relative if available.
The DEX questionnaire	This is a 20 item questionnaire designed to assess for behaviours associated with dysexecutive syndromes including emotional or personality changes, motivational changes, behavioural changes and cognitive changes.	10	This will be completed by the participants at home, prior to attending for the neuropsychological testing appointment. It will also be completed by a friend/relative if available.
The Revised Dyadic Adjustment (RDAS)	This is a 14 item questionnaire which assesses relationship quality.	10	This will be completed by the participants at home, prior to attending for the neuropsychological testing appointment. It will also be completed by a friend/relative if available.

Data Collection

As this study is a cross-sectional study, data will only be collected at a single time point. As detailed above, participants will complete a range of standardised assessment measures and questionnaires. From all of these measures and questionnaires standardised scores will be generated. All data will be collected by the PI.

Where possible, the PI will aim to maximise the completeness of data collection using several methods:

- Participants will be asked to complete questionnaires ahead of their assessment appointment, to help distribute and limit the potential test burden on participants. Additionally in doing so, a second opportunity (at the testing session) is provided for participants to complete the questionnaires and for these to be assessed for missing values by the PI.
- Where possible, testing will be completed during one session and if the individual appears to be experiencing fatigue they will encouraged to take a break. Whilst the PI recognises that not all individuals will be able to complete testing in one sitting, this will be completed where possible as this would limit the opportunity for participants to drop-out (e.g. not being able to or remembering to attend a second appointment). Also, one session places less demand on the participants, both placing less pressure on their time and limiting travel costs.
- Finally, a participant's significant other will be asked to complete two questionnaires. These will also be sent out ahead of the testing appointment as participants will be able to return these in person when they attend their appointment, where the PI can check for missing data. If they do not return them at this time, the PI will remind the participant about these and gather contact details to call them should an additional reminder be required or if measure are to be completed over the phone. Only one addition reminder will be given, so as not to place too much pressure on the individual to complete them.

Source Data Documentation

Source documents include all the record forms for the neuropsychological tests, and all the paper questionnaires completed by the participants and their significant others. Additionally, relevant sections of the participants medical records will be reviewed.

Statistical and Data Analysis

Sample Size Calculation

The required sample size was determined using the primary research objective, which will be answered using regression analysis. The G*Power programme (Faul et al., 2009) was used to calculate sample size. For a multivariate linear regression, with three predictor variables, a sample size of 61 is required. Power was set at 0.8, alpha at 0.017 (to control for multiple comparisons) and the effect size was set as medium. Through reviewing previous research which has explored SC in individuals with MS, medium to large effect sizes have been shown in studies which have primarily aimed to explore the magnitude of SC impairments within this population (see Cotter et al. 2016; Genova et al. 2016; Phillips et al. 2011). Taking this into consideration, alongside the lack of research into the impact of impaired SC on functional abilities, the effect size was set as medium

Proposed Analyses

The data will be analysed within SPSS. Missing data will be excluded from the analysis. Prior to running any analyses, all variables will be checked for outliers and homogeneity of variance. The primary aim of the analysis is to explore the relationship between variables of SC and functional outcomes.

1. Demographics

Initially, descriptive statistics will run on the data. This will also include t-tests and correlations (Pearson correlations if data is parametrically distributed and Spearman correlations if the data is non-parametrically distributed) to identify any possible relationships between demographic information and cognitive or functional variables.

2. Primary research question

To explore the relationship between cognitive variables (e.g. measures of TOM and executive functioning) and functional outcomes, regression analyses will be used. Specifically, three regression models will be run, one for each of the outcome variables: psychological, social and interpersonal functioning. The predictor variables will be TOM, executive functioning and pre-morbid functioning.

3. Secondary research questions

T-test calculations and potentially and ANOVA will be completed to explore whether there are any differences between MS subtypes on cognitive variables. These results will be interpreted with caution, as they will have lower statistical power; however, this exploratory analysis will hopefully be able to inform of future research directions.

Additionally, t-tests will be run to answer the second, secondary research question which explores whether there is a relationship between pre-morbid IQ and cognitive abilities. Specifically of interest is whether there is a relationship between pre-morbid IQ and TOM abilities. Detail the variables to be used for assessment and how these will be reported (e.g. means, standard deviations, medians etc.)

Risks

There is a medium likelihood of the test burden being too demanding on participants due to the testing session being too long/ taxing. However, the number/range of tests selected is required to adequately measure the constructs being explored through this study. In order to minimise the possible test burden, the neuropsychological tests selection was based on their suitability for use with individuals with MS, and those which have previously been used for research in this area. Additionally, participants will be offered a break within the session, or if required testing will be spread over multiple sessions to reduce the burden testing places on them.

There is a low likelihood that participants may experiences high levels of psychological distress during testing. Participants will be informed in advance what will be involved in the study, and it may involve subject areas that they find distressing. The PI is experienced in supporting individuals who are experiencing high levels of psychological distress. Whilst there is a low likelihood of this occurring, the researcher will have contact details for unscheduled care assessment services, as well as other local support services. Participants will also have a five minute debrief at the end of the testing appointment where they can provide feedback on their testing experience and ask any questions.

As with any study using personal data, data-protection or confidentiality must be strongly considered. The likelihood of confidentiality being broken, or patient identifiable data being lost is very low. All paper documentation (e.g. neuropsychology record forms, questionnaires) will be transported from the appointment location to the physical rehabilitation psychology office in a locked bag. The paper records will remain there in a locked filing cabinet for the duration of the study. Data from the paper documents will be anonymised and entered into a spreadsheet which will be held in the secure NHS Fife drive.

It is possible that test results may reveal more severe difficulties than was previously known. Prior to beginning teasing, potential participants will be made aware of the limits to confidentiality. If a case arises where the participants test results raise concern, this will be communicated to the participant and they will be informed that this information will be passed onto the most appropriate clinician involved in their case (e.g. their GP, neurologist) for them to consider and respond to. Confidentiality will not be broken without the participant being aware of the presence of concerns.

Oversight Arrangements

Inspection of Records

Investigators and institutions involved in the study will permit trial related monitoring and audits on behalf of the sponsor, REC review, and regulatory inspection(s). In the event of audit or monitoring, the Investigator agrees to allow the representatives of the sponsor direct access to all study records and source documentation. In the event of regulatory inspection, the Investigator agrees to allow inspectors direct access to all study records and source documentation.

Study Monitoring and Audit

The ACCORD Sponsor Representative will assess the study to determine if an independent risk assessment is required. If required, the independent risk assessment will be carried out by the ACCORD Quality Assurance Group to determine if an audit should be performed before/during/after the study and, if so, at what frequency.
Risk assessment, if required, will determine if audit by the ACCORD QA group is required. Should audit be required, details will be captured in an audit plan. Audit of Investigator sites, study management activities and study collaborative units, facilities and 3rd parties may be performed.

Good Clinical Practice

Ethical Conduct

The study will be conducted in accordance with the principles of the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice (ICH GCP).
Before the study can commence, all required approvals will be obtained and any conditions of approvals will be met.

Investigator Responsibilities

The Investigator is responsible for the overall conduct of the study at the site and compliance with the protocol and any protocol amendments. In accordance with the principles of ICH GCP, the following areas listed in this section are also the responsibility of the Investigator. Responsibilities may be delegated to an appropriate member of study site staff.

Informed Consent

The Investigator is responsible for ensuring informed consent is obtained before any protocol specific procedures are carried out. The decision of a participant to participate in clinical research is voluntary and should be based on a clear understanding of what is involved.

Participants must receive adequate oral and written information – appropriate Participant Information and Informed Consent Forms will be provided. The oral explanation to the participant will be performed by the Investigator or qualified delegated person, and must cover all the elements specified in the Participant Information Sheet and Consent Form.

The participant must be given every opportunity to clarify any points they do not understand and, if necessary, ask for more information. The participant must be given sufficient time to consider the information provided. It should be emphasised that the participant may withdraw their consent to participate at any time without loss of benefits to which they otherwise would be entitled.

The participant will be informed and agree to their medical records being inspected by regulatory authorities and representatives of the sponsor(s).

The Investigator or delegated member of the trial team and the participant will sign and date the Informed Consent Form(s) to confirm that consent has been obtained. The participant will receive a copy of this document and a copy filed in the Investigator Site File (ISF).

Study Site Staff

The Investigator must be familiar with the protocol and the study requirements. It is the Investigator's responsibility to ensure that all staff assisting with the study are adequately informed about the protocol and their trial related duties.

Data Recording

The Principal Investigator is responsible for the quality of the data recorded in the CRF at each Investigator Site.

Investigator Documentation

The Principal Investigator will ensure that the required documentation is available in local Investigator Site files ISFs.

Confidentiality

Participants' personal data will be contained on the consent forms, record forms and questionnaires. These will be stored in a locked filing cabinet in the Psychology office of the NHS Fife Rehabilitation

Service. Access to the cabinet will require a key, which only the PI, field supervisor and two other psychologists within the team will have access too.

Additionally, participants' data will be stored anonymously on the secure network, using pseudonyms in place of personally identifiable data. In accordance with the Data Protection Act (2018), only data specifically required for this study will be recorded, it will be reviewed regularly during the study and after 5 years, and only kept for 10 years. A separate file, which links participants to the pseudonyms applied will be stored separately from the spreadsheet including patient data.

The data collected in this study will only be used for the purposes of this study, to answer the research questions and will not be passed onto third parties, or be identifiable from the dissemination of the results. The Investigator and study site staff involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

Data Protection

All Investigators and study site staff involved with this study will comply with the requirements of the Data Protection Act 2018 with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. Access to collated participant data will be restricted to individuals from the research team treating the participants, representatives of the sponsor(s) and representatives of regulatory authorities.

Computers used to collate the data will have limited access measures via user names and passwords.

Published results will not contain any personal data that could allow identification of individual participants.

Study Conduct Responsibility

Protocol Amendments

Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the participant in the case of an urgent safety measure, must be reviewed and approved by the Chief Investigator.

Amendments will be submitted to a sponsor representative for review and authorisation before being submitted in writing to the appropriate REC, and local R&D for approval prior to participants being enrolled into an amended protocol.

Management of Protocol Non-Compliance

Prospective protocol deviations, i.e. protocol waivers, will not be approved by the sponsors and therefore will not be implemented, except where necessary to eliminate an immediate hazard to study participants. If this necessitates a subsequent protocol amendment, this should be submitted to the REC, and local R&D for review and approval if appropriate.

Protocol deviations will be recorded in a protocol deviation log and logs will be submitted to the sponsors every 3 months. Each protocol violation will be reported to the sponsor within 3 days of becoming aware of the violation. All protocol deviation logs and violation forms should be emailed to QA@accord.scot

Deviations and violations are non-compliance events discovered after the event has occurred. Deviation logs will be maintained for each site in multi-centre studies. An alternative frequency of deviation log submission to the sponsors may be agreed in writing with the sponsors.

Serious Breach Requirements

A serious breach is a breach which is likely to effect to a significant degree:

(a) the safety or physical or mental integrity of the participants of the trial; or

(b) the scientific value of the trial.

If a potential serious breach is identified by the Principal Investigator or delegates, the co-sponsors (seriousbreach@accord.scot) must be notified within 24 hours. It is the responsibility of the co-sponsors to assess the impact of the breach on the scientific value of the trial, to determine whether the incident constitutes a serious breach and report to research ethics committees as necessary.

Study Record Retention

Following completion of the study, the PI will remove all personal data within 6 months. As this is a student project, there will be a VIVA post completion, therefore, if additional changes are required the personal data will not already be removed.

The anonymous research data will be stored for 3 years. The original paper record forms will be stored in a locked filing cabinet at the Physical Rehabilitation department, NHS Fife. Both the PI and field supervisor will have access to the raw data. The data will also be stored on an electronic file on the NHS Fife server, on a secure drive, owned by the PI. Should the PI leave the organisation, the dataset will be managed by the PI's field supervisor.

When the retention period has elapsed, study documentation will not be destroyed without permission from the sponsor.

End of Study

The end of study is defined as the last participant's last visit.

The Investigators or the co-sponsor(s) have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the REC, and R+D Office(s) and co-sponsors within 90 days, or 15 days if the study is terminated prematurely. The Investigators will inform participants of the premature study closure and ensure that the appropriate follow up is arranged for all participants involved. End of study notification will be reported to the co-sponsors via email to resgov@accord.scot.

A summary report of the study will be provided to the REC within 1 year of the end of the study.

Insurance and Indemnity

The co-sponsors are responsible for ensuring proper provision has been made for insurance or indemnity to cover their liability and the liability of the Chief Investigator and staff.

The following arrangements are in place to fulfil the co-sponsors' responsibilities:

- The Protocol has been designed by the PI and researchers employed by the University and collaborators. The University has insurance in place (which includes no-fault compensation) for negligent harm caused by poor protocol design by the Chief Investigator and researchers employed by the University.
- Sites participating in the study will be liable for clinical negligence and other negligent harm to individuals taking part in the study and covered by the duty of care owed to them by the sites concerned. The co-sponsors require individual sites participating in the study to arrange for their own insurance or indemnity in respect of these liabilities.
- Sites which are part of the United Kingdom's National Health Service will have the benefit of NHS Indemnity.

Reporting, Publications and Notifications of Results

When recruited into the study, individuals will be asked whether or not they wish to be informed of the findings upon completion. Participants who opt into this will be sent a written summary of the research findings. Any staff, families and third sector organisations who take part in the study will also be offered information on the study results.

In NHS Fife there is a bi-annual research conference run by the psychology department. The results of this study will be disseminated there. Additionally, the findings will be presented to the neuropsychology service as part of their regular in-service educational programme.

It is hoped that this study will be published in a relevant peer-reviewed neuropsychology journal (e.g. the Journal of the International Neuropsychological Society, Neuropsychology), and relevant conferences post completion. No personal identifiable data will be included in publications or presentations.

Authorship Policy

Ownership of the data arising from this study resides with the study team.

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Appendix E: Letter of Favourable Ethical Opinion from South East Scotland Research Ethics Committee

Lothian NHS Board

South East Scotland Research Ethics Committee 01

Waverley Gate
2-4 Waterloo Place
Edinburgh
EH1 3EG

www.nhslothian.scot.nhs.uk

Date 13 February 2019

Enquiries to : Sandra Wyllie
Extension: 35473
Direct Line: 0131 465 5473
Email: Sandra.Wyllie@nhslothian.scot.nhs.uk

13 February 2019

Dr Clara Calia
School of Health in Social Science
University of Edinburgh
Medical School, Teviot Place
EH8 9AG

Dear Dr Calia

Study title:	**Psychological, Interpersonal and Social Functioning in Multiple Sclerosis: The Role of Theory of Mind**
REC reference:	**19/SS/0006**
Protocol number:	**CAHSS1809/0**
IRAS project ID:	**250096**

Thank you for your letter of 10 February 2019 , 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.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact hra.studyregistration@nhs.net outlining the reasons for your request.

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.

Conditions of the favourable opinion

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

study.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission 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, at www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

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

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

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from the HRA. Guidance on where to register is provided on the HRA website.

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).

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Approved documents

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

Document	*Version*	*Date*
Covering letter on headed paper [Covering letter following REC review]	1	10 February 2019
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Professional indemnity confirmation]		31 July 2018
GP/consultant information sheets or letters [GP Letter]	2	16 January 2019
IRAS Application Form [IRAS_Form_05122018]		05 December 2018
Letters of invitation to participant [Letter of invitation]	2	23 January 2019
Letters of invitation to participant [Letter of invitation- NHS Lothian]	1	10 February 2019
Letters of invitation to participant [Letter of invitation- significant other]	2	23 January 2019
Participant consent form [Participant consent form]	2	23 January 2019
Participant information sheet (PIS) [Participant Information Sheet]	2	23 January 2019
Participant information sheet (PIS) [Participant information sheet for significant other]	2	23 January 2019
Research protocol or project proposal [Study Protocol]	2	10 February 2019
Summary CV for Chief Investigator (CI) [CI CV]	1	13 October 2018
Summary CV for student [Student CV]	1	11 October 2018
Summary CV for supervisor (student research) [Emily Newman CV]	1	12 October 2018
Summary of any applicable exclusions to sponsor insurance (non-NHS sponsors only) [Clinical Trail Liability]	1	31 July 2018
Summary of any applicable exclusions to sponsor insurance (non-NHS sponsors only) [Employers liability insurance]	1	01 August 2018
Summary of any applicable exclusions to sponsor insurance (non-NHS sponsors only) [Policy confirmation]	1	24 July 2018
Summary of any applicable exclusions to sponsor insurance (non-NHS sponsors only) [Professional Indemnity Confirmation]	1	31 July 2018
Validated questionnaire [DEX Informant form]		
Validated questionnaire [DEX Self rater form]		
Validated questionnaire [MSQOL-54 form]		
Validated questionnaire [Revised Dyadic Adjustment Scale]		
Validated questionnaire [Social functioning scale]		
Validated questionnaire [BDI]		
Validated questionnaire [Brixton Test]	1	13 December 2018
Validated questionnaire [Hayling Test]	1	13 December 2018
Validated questionnaire [Verbal Fluency Test]	1	13 December 2018
Validated questionnaire [Test of Premorbid Function Test]	1	13 December 2018
Validated questionnaire [Reading the Mind in the Eyes Test]	1	12 April 2018
Validated questionnaire [Faux Pas Test]	1	12 April 2018

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.

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

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

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 Training

We are pleased to welcome researchers and R&D staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

19/SS/0006	**Please quote this number on all correspondence**

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

Yours sincerely

Kyle Gibson

Dr Kyle Gibson
Chair

Email:sandra.wyllie@nhslothian.scot.nhs.uk

Enclosures: "After ethical review – guidance for researchers"
Copy to: *Charlotte Smith, Ms Amanda Wood, NHS Fife*

Appendix F: NHS Fife Research and Development Approval

Medical Director

Hayfield House
Hayfield Road
KIRKCALDY
KY2 5AH

NHS Fife

Miss Rachel Gibson
Trainee Clinical Psychologist
Psychology Dept
Lynebank Hospital
DUNFERMLINE

21 February 2019

Our Ref *18-083 250096 19/SS/0006*
Enquiries to *Aileen Yell*
E-mail *aileenyell@nhs.net*
Telephone *01383 623623 Ext 20940*
Website *www.nhsfife.org*

Dear Miss Gibson

Project Title: Psychological, interpersonal and social functioning in MS

Thank you for your application to carry out the above project. Your project documentation (detailed below) has been reviewed for resource and financial implications for NHS Fife and I am happy to inform you that NHS permission for the above research has been granted on the basis described in the application form, protocol and supporting documentation. The documents reviewed were:

Document	Version	Date
Significant Other Consent Form	1	28 November 2018
IRAS R&D Form	5.9.1	29 November 2018
GP Letter	2	16 January 2019
REC provisional favourable opinion letter		16 January 2019
Letter of Invitation to Participant	2	23 January 2019
Letter of Invitation – Significant Other	2	23 January 2019
Participant Information Sheet	2	23 January 2019
Participant Consent Form	2	23 January 2019
Participant Information Sheet for Significant Other	2	23 January 2019
Protocol	2	10 February 2019
Study-Wide Governance Report		13 February 2019
REC final favourable opinion letter		13 February 2019
IRAS SSI Form	5.11	20 February 2019

The terms of the approval state that you are the Principal Investigator authorised to undertake this study within NHS Fife, with assistance from Dr Alan Harper and Mrs Debbie McCallion.

I note that the favourable ethical opinion applies to all NHS sites taking part in the study therefore no separate Site Specific Review is required in this case. The sponsors for this study are University of Edinburgh. Please note that it is the responsibility of the Sponsor to ensure that adequate and appropriate insurance is maintained throughout the course of the study.

Details of our participation in studies will be included in annual returns we are expected to complete as part of our agreement with the Chief Scientist Office. Regular reports of the study require to be submitted. Your first report should be submitted to Dr A Wood, R&D Manager, R&D Department, Queen Margaret Hospital, Whitefield Rd, Dunfermline, KY12 OSU (Amanda.wood3@nhs.net) in 12 months time and subsequently at yearly intervals until the work is completed. A Lay Summary will also be required upon completion of the project.

{ NHS Fife was awarded the Carbon Trust Standard in February 2010 and is the first Scottish NHS Board to achieve this accolade.

NHS
Fife

In addition, approval is granted subject to the following conditions:-

All research activity must comply with the standards detailed in the UK Policy Framework for Health and Social Care Research http://www.nhsresearchscotland.org.uk/uploads/tinymce/uk-policy-framework-health-social-care-research.pdf, health & safety regulations, data protection principles, other appropriate statutory legislation and in accordance with Good Clinical Practice (GCP).

Any amendments which may subsequently be made to the study should also be notified to Aileen Yell, R&D Research Coordinator (aileenyell@nhs.net) , as well as the appropriate regulatory authorities. Notification should also be given of any new research team members post approval and/or any changes to the status of the project.

This organisation is required to monitor research to ensure compliance with the Research Governance Framework and other legal and regulatory requirements. This is achieved by random audit of research. You will be required to assist with and provide information in regard to monitoring and study outcomes (including providing recruitment figures to the R&D office as and when required).

As custodian of the information collated during this research project you are responsible for ensuring the security of all personal information collected in line with NHS Scotland IT Security Policies, until the destruction of this data. Permission is only granted for the activities for which a favourable opinion has been given by the REC (and which have been authorised by the MHRA where appropriate).

The research sponsor or the Chief Investigator or local Principal Investigator at a research site may take appropriate urgent safety measures in order to protect research participants against any immediate hazard to their health or safety. The R&D office (aileenyell@nhs.net) should be notified that such measures have been taken. The notification should also include the reasons why the measures were taken and the plan for further action. The R&D office should be notified within the same time frame of notifying the REC and any other regulatory bodies.

I would like to wish you every success with your study and look forward to receiving a summary of the findings for dissemination once the project is complete.

Yours sincerely

DR FRANCES ELLIOT
Medical Director
NHS Fife

Appendix G: NHS Lothian Research and Development Approval

University Hospitals Division

NHS Lothian

Queen's Medical Research Institute
47 Little France Crescent, Edinburgh, EH16 4TJ

FM/FM/approval

21 February 2019

Research & Development
Room E1.16
Tel: 0131 242 3330

Email:
accord@nhslothian.scot.nhs.uk

Director: Professor Tim Walsh

Miss Rachel Gibson
NHS Fife
NHS Fife Psychology Department
Lynebank Hospital
Halbeath Road
Dunfermline
KY11 4UW

Dear Miss Gibson

Lothian R&D Project No: 2019/0047 **REC No:** 18/NI/0229

Title of Research: Psychological, Interpersonal and Social Functioning in Multiple Sclerosis: The Role of Theory of Mind

Sponsor Reference: CAHSS1809/0

Participant Information Sheet:
Version 2, dated 23 January 2019
[Significant Other] Version 2, dated 23 January 2019

Consent Form:
Version 2, dated 23 January 2019

Protocol: Version 2, dated 10 February 2019

I am pleased to inform you this letter provides Site Specific approval for NHS Lothian for the above study and you may proceed with your research, subject to the conditions below.

Please note that the NHS Lothian R&D Office must be informed of any changes to the study such as amendments to the protocol, funding, recruitment, personnel or resource input required of NHS Lothian.

Substantial amendments to the protocol will require approval from the ethics committee which approved your study and the MHRA where applicable.

Please keep this office informed of the following study information, **which is a condition of NHS Lothian R&D Management Approval**:

1. Date you are ready to begin recruitment, date of the recruitment of the first participant and the monthly recruitment figures thereafter.
2. Date the final participant is recruited and the final recruitment figures.
3. Date your study / trial is completed within NHS Lothian.

I wish you every success with your study.

Yours sincerely

Fiona McArdle

Ms Fiona McArdle
Deputy R&D Director

Cc Ms Lyn McDonald, Site Director, Royal Infirmary of Edinburgh
Dr Andrew Flapan, Associate Medical Director, Royal Infirmary of Edinburgh

Appendix H: Participant Information Sheet

THE UNIVERSITY of EDINBURGH

NHS SCOTLAND

(**This NHS logo will be changed for each recruitment site**)

University of Edinburgh
School of Health in Social Science
Medical School (Doorway 6)
Teviot Place
EH8 9AG

Participant Information Sheet: Significant Other

Psychological, Interpersonal and Social Functioning in Multiple Sclerosis: The Role of Theory of Mind

V2: 23/01/2019

You are being invited to participate in a research study. Before you decide whether you would like to take part we would like you to understand the purpose of this study and what your participation would involve. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?

Theory of mind refers to an individual's ability to understand that other people have their own thoughts/ opinions/ beliefs which can differ from our own. Theory of mind is important in social interactions as it allows us to adapt our behaviour and know what information to communicate to others, building on what they already know. Our research wants to find out if an individual's theory of mind abilities impact upon their mood, relationship quality and social engagement in individuals with Multiple Sclerosis (MS).

Why have I been invited?

Our study will be recruiting individuals with a diagnosis of MS, who are known to the NHS Fife Rehabilitation Service/ NHS Lothian Anne Rowling Clinic (delete as appropriate). As your partner/ family member/ friend (delete as appropriate) has previously been, or are currently being seen within this service they were invited to participate. As part of their involvement in the study, we asked their permission to contact you to gain additional information for the study.

Do I have to take part?

No, you do not have to take part. If you decide to take part you are still free to withdraw at any time and without giving a reason. Your participation is voluntary.

What will I have to do?

Taking part would involve you being asked to complete a few questionnaires (which are enclosed here) at home, which ask about your partner's/ family member's/ friend's (delete as appropriate) relationships, behaviours and social activities. These will take around 30 minutes to complete. Full details on how to complete the questionnaires are included and attached to the front of the questionnaire booklet.

If you wish to take part after reading this information sheet, please complete the enclosed questionnaires and return them in the stamped addressed envelope provided.

What are the possible disadvantages or risks of taking part?

There are few risk or disadvantages associated with taking part and you will be able to withdraw from the study at any time, without specifying a reason.

It is possible that sensitive topics could arise when completing the questionnaires, which you may find distressing. If you have any concerns about the material or find completing the questionnaires distressing, you can contact Rachel Gibson (Principle Investigator) on 01383 562 402 to discuss these further.

Finally, it is possible that the pattern of task results may cause the research team to be concerned about your partner/ family member/ friend (delete as appropriate). Whilst the likelihood of this is low, if the research team were to have any concerns, this would be discussed with your partner/ family member/ friend (delete as appropriate). Information would also be passed onto their GP who will be able to discuss the concerns with them. Otherwise, we are unable to provide individual feedback.

What are the possible benefits of taking part?

It is hoped that eventually this research will help us to better understand the impact of theory of mind abilities on daily functioning in individuals with MS. It is hoped that this will inform future research studies, which in turn may enhance treatments and case management.

Will my participation be kept confidential?

All information which is collected from you about your partner/ family member/ friend (delete as appropriate) during the course of the research will be kept strictly confidential. Their identifiable data will be kept and stored securely within the NHS on a secure drive, which only the research team will have access to. Identifiable data will be stored separately from the data used in the data analysis. Your partner/ family member/ friend (delete as

appropriate) will be given a unique participant number, which only the research team will have access to.

In addition, data collected during the study may be looked at by individuals from the Sponsor (the University of Edinburgh) or from the NHS organisations, where it is relevant to your taking part in this research.

You can find out more about how we use your information and our legal basis for doing so in our Privacy Notice at: https://www.ed.ac.uk/records-management/privacy-notice-research and https://www.nhsfife.org/nhs/index.cfm (and clicking on the "Data Protection Notice" tab at the bottom of the page).

For further information on the use of personal data by NHS sites, please link to the Health Research Authority (HRA) website: https://www.hra.nhs.uk/information-about-patients/

What if I want to stop the study?

Whether you take part is up to you and your decision, and your partner/ family member/ friend (delete as appropriate) will still be able to participate. You may change your mind about being in the study and withdraw from the study at any time.

What will happen to the results of the study?

The results of this study will be reported as part of a doctorate student thesis project but no names will be included and it will not be possible for you to be identified.

We hope that the results of this study will be published in a scientific journal or presented at a conference, but again no names will be included and it will not be possible for you to be identified.

Your partner/ family member/ friend (delete as appropriate) has been asked whether they wish to be provided with a summary of the research findings upon completion of the study. If they have requested to be provided with a written summary, this will be posted to them upon completion.

Who has reviewed the study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee. A favourable ethical opinion has been obtained from SESREC01. NHS management approval has also been obtained

What if I have further questions?

Thank you for taking the time to hear about our study. We would be really pleased to talk to you about it some more if you have any questions. If you have any further questions about the study please contact Rachel Gibson on 01383 565 402 or email s1025432@ed.ac.uk.

If you would like to discuss this study with someone independent of the study team please contact: Susan McKenzie (Consultant Clinical Psychologist, NHS Fife) on: 01592 226 767.

What if there is a problem?

If you wish to make a complaint about the study please contact NHS Fife:

Patient Relations Department
1st Floor, Hayfield House
Hayfield Road
Kirkcaldy
Fife
KY2 5AH

Phone: 01592 648 153
Email: patientrelations.fife@nhs.net

If you wish to raise a complaint on how we have handled your personal data, you can contact our Data Protection Officer who will investigate the matter. If you are not satisfied with our response or believe we are processing your personal data in a way that is not lawful you can complain to the Information Commissioner's Office (ICO) at https://ico.org.uk/.

Data Protection Officer contact information:
University of Edinburgh
Data Protection Officer
Governance and Strategic Planning
University of Edinburgh
Old College
Edinburgh
EH8 9YL
Tel: 0131 651 4114
dpo@ed.ac.uk

Appendix I: Consent Form

THE UNIVERSITY of EDINBURGH

*(*This NHS logo will be changed for each recruitment site*)*

NHS SCOTLAND

University of Edinburgh
School of Health in Social Science
Medical School (Doorway 6)
Teviot Place
EH8 9AG

Participant Consent Form
CONSENT TO PARTICIPATE IN A RESEARCH STUDY
V2 23/01/2019:

Participant identification ID ☐

Study: **Psychological, Interpersonal and Social Functioning in Multiple Sclerosis: The Role of Theory of Mind**

Investigator: Rachel Gibson (Trainee Clinical Psychologist, University of Edinburgh)

Please initial box

1. I confirm that I have read and understand the information sheet (V2, 23/01/2019) for the above study and have had the opportunity to consider the information and ask questions.* ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.* ☐
3. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from the regulatory authorities and from the Sponsor(s) (the University of Edinburgh) or from the NHS Board(s) where it is relevant to my taking part in this research. I give permission for those individuals to have access to my records.* ☐
4. I agree to my GP being informed of my participation in this study.* ☐
5. I agree to take part in the above study.* ☐
6. I wish to be informed of the study findings upon completion. ☐

_____	_____	_____
Name of Participant	Date	Signature
_____	_____	_____
Name of Person taking consent	Date	Signature

* Mandatory fields
Original (x1) to be retained in site file. Copy (x1) to be included in patient notes. Copy (x1) to be retained by the participant.

Full Thesis References

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