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The Contribution of Perceived Memory and Information Processing Deficits on Multiple Sclerosis Cognitive Difficulties

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Abstract

MS is one of the major causes of disability in young adults within western countries. More than half of people with MS develop a cognitive impairment, which might be considered as the major quality of life determinant. Although there have been developed several cognitive batteries, cognitive impairment is often overlooked. Information processing speed (IPS) and memory difficulties are the most common cognitive impairments in MS. The Multiple Sclerosis Neuropsychological Questionnaire (MSNQ) is a valid self-report measure of global cognitive difficulties for people with MS. The Attentional Functional Index (AFI) and the Prospective and Retrospective Memory Questionnaire (PRMQ) are self-report measures for perceived cognitive functioning assessing perceived effectiveness in common activities which require attention/IPS and memory. However, it is little known about MS variability between these patterns isolated and co-occurring cognitive deficits. This study aimed to analyse how information processing and prospective and retrospective memory deficits contribute to self-report of cognitive difficulties on the MSNQ and the nature of this relationship. 76 participants with MS completed a series of MS, demographic, and cognition questionnaires along with the MSNQ, the AFI, and the PRMQ on-line. A within-subjects correlation and multiple regression analysis with MSNQ as the dependent variable and AFI and PRMQ as the independent variables were undertaken. The results indicated a significant correlation ($p< .01$), with a good prediction for the model ($p< .05$, R2 =73). It was concluded that perceived memory ($p<.001$), and IPS ($p=0.5$) deficits contribute to self-report of cognitive deficits on the MSNQ separately within the MS population. Findings, limitations, and future implications were discussed.

Keywords: Multiple sclerosis • Cognition• Memory • Information Processing Self- Report• Cognitive Battery

Introduction

Multiple Sclerosis affects the brain and the spinal cord causing a wide range of physical, physiological, psychological, and neuropsychological symptoms. These might cause serious disability as well as severely reduce quality of life. Cognitive dysfunction prevalence in MS, such as memory impairment or information processing speed difficulties, has been recognised as one of the major problems. Therefore, it continues to be investigated from clinical, neuropsychological, and individual perspective. However, research has shown discrepancies on their findings and some areas have not yet been explored.

Multiple Sclerosis (MS)

Multiple sclerosis (MS) is a common demyelinating autoimmune disease that attacks any region of the central nervous system (CNS), which consists of the brain, the spinal cord, and the optic nerves [1-2]. According to the statistics, MS is one of the major causes of long term non-traumatic neurological diseases and disability in young adults within western countries. MS has a typical early onset of 20 to 40 years of age [3-6]. Although many studies report that the majority of MS patients are female, the gender bias in MS remain uncertain. The disease' symptoms take place when a person's immune system attacks the myelin of the neurons, which consists of a fatty substance that coats the neurons' axon to protect the nerve fibre. These attacks cause inflammation, neurodegeneration, and tissue damage which disrupts the neural signals produced by the nerve impulse. This may obstruct the communication between the brain and the rest of the organism. As a result of these individual CNS lesions, people with MS suffer from several neurological and non-neurological symptoms [6-8]. MS symptoms might be visual, physical, cognitive and psychological. Some examples of these symptoms are lack of balance, loss of sensation, bladder dysfunction, difficulty in walking, fatigue, numbness, blurred or double vision, sexual problems, tingling, or spasticity. The symptoms usually occur unpredictably and differ among individuals [1,9].

MS clinical presentation varies according to the area of the CNS affected and the organism's ability to recover from these attacks, also referred to as remissions. Therefore, MS may present in different forms. The first form, known as Clinically Isolated Syndrome (CIS), is characterised by the appearance of a first or several isolated episodes of typical MS neurological symptoms caused by inflammation and demyelination in the CNS without the disease's manifestation. However, these symptoms increase the risk of developing MS. Early treatment of CIS might delay the disease's onset [10,11]. Current neuroimaging advances have contributed to the improvement of MS diagnosis and evaluation, giving raise to the concept of Radiologically Isolated Syndrome (RIS). Like CIS, RIS is an early MS risk indicator where abnormal brain activity is detected on MRI without an outwarding symptomatology of the disease [11]. The second form is named Relapsing-Remitting (RR) MS. In this presentation, attacks or relapses occur from time to time followed by a period of recovery. The duration of the symptoms might range from days or weeks to years. There is a wide range of medication for treating this form. Primary Progressive (PP) MS is another presentation characterised by a gradual degeneration followed by mild or any recovery. Individuals diagnosed with this type of MS might sometimes experience relapses on top of the progression. In this form, most medicines have resulted ineffective [4-10]. However, most current advances have allowed to offer a limited option [12]. While research continues to develop new treatments [13]. Lastly, Secondary Progressive (SP) MS, is a transitional presentation that normally occurs 10-20 years after RR MS. It is very similar to PP MS, after a relapse people who do not fully recover are prone to move to this stage. In contrast with PP MS, medical treatments are moderately effective in this stage [1,10].

According to studies, the etiology of the disease has not yet been identified [14], but risk factors appear to be associated with both genetic and environmental components [1]. For example, prevalence and migration studies suggested that the prevalence of the disease increases with higher latitudes and varies between ethnicity and race, being the Caucasian European group at higher risk [1,5]. Research have suggested further environmental and genetic factors, such as smoking exposure, certain vitamins deficiency (vitamin D) [15] obesity, decrease in UV radiation exposure, and both MHC and non- MHC (Major Histocompatibility Complex) genes, being the Human Leukocyte Antigen (HLA) considered the strongest genetic risk factor in MS genetic onset [15].

MS diagnosis is generally suggested by the manifestation of the symptoms of the patients, but it is accurately concluded by means of several neurological assessments, blood tests, and radiological and laboratory investigations, including brain and spinal Magnetic Resonance Imaging (MRI), cerebrospinal fluid (CSF) analysis, and visual evoked potentials (VEP) [16,1].

Nowadays, researchers have not found a cure for MS. However, there is a wide variety of treatments available to help MS patients to cope with and manage the disease, as well as to reduce the symptoms. These treatments include pharmacological or non-pharmacological interventions and lifestyle changes, along with mental and well-being therapies. Some examples of these MS interventions and treatments are disease-modifying drugs, steroids or corticosteroids, deep brain stimulation, occupational therapy, neurorehabilitation, whole body cryostimulation, physical therapy and exercise, or alternative/complementary therapies and medicine— such as yoga, acupuncture, relaxation or meditation, herbal remedies, massages [17], and diet and dietary supplements— [17-18].

Cognition in MS

In addition to typical physical, neurological and neuropsychiatric symptoms in MS, including a broad range of abnormalities in mood, affect and behaviour such as stress, anxiety, panic attacks, bipolar disorder, substance misuse, and depression, cognitive impairment is also very common but often overlooked. According to the statistics, more than half of all people with MS might develop difficulties with cognition. These difficulties may also interact with and enhance the neuropsychiatric and physical symptoms, for example, by increasing fatigue or affecting mood and overall motivation.

Cognition refers to a broad range of high-level brain processes and functions. These functions may include the ability to learn and remember information, to plan and organise tasks, to solve different problems or challenges, to focus —maintain and shift attention, to understand and use language, to perceive the environment accurately, and to perform calculations. It is known that processing speed has a main influence on other types of cognitive processes. However, cognitive dysfunction occurs when all these abilities are negatively affected or difficult to perform due to changes in processing speed. When a person reports a cognitive problem, he or she describes a change in function from a previous level, what it means, a cognitive decline [19].

Within people with MS, certain cognitive functions are more likely to be affected than other ones. Generally, these changes in cognitive function are mild and may involve one or two areas. However, in fewer people with MS these changes are more challenging. These functions might be classified as: Information processing memory, attention and concentration, executive functions, visuospatial functions, and verbal fluency [20,17]. Cognitive impairment in MS may reduce life satisfaction and health-related quality of life of patients [21]. Also, it may be considered the most important determinant of employment status and associated societal costs of people with the disease. Additionally, other activities and characteristics such as driving safety, household tasks completion, social activity, physical independence, rehabilitation progress, coping, and treatment adherence are usually highly affected [22,2].

Neural Bases of Cognitive Dysfunction in MS.

Magnetic Resonance Imaging (MRI) plays an essential role in MS diagnosis and disease surveillance, therefore, the field of MS is nowadays at the top of novel and innovative MRI technology. This novel technology provides multiple tools for investigating MS-related cognitive deficits [23]. According to early research, cognitive deficits in MS were linked to greater lesion load. However, subsequent studies showed the importance of white and grey matter lesions, these lesions location [24] microstructural injury [25]. structural brain damage cortical and subcortical [26-28]. Brain atrophy, and discrepant patterns of cerebral activation with fMRI[29]. For instance, there have been found neuroanatomical correlates of cognitive deficits in MS (e.g., thalamus) [26, 27]. Although these correlates of cognition could be useful tools for predicting disease-related cognitive deficits, they are also important for gaining knowledge of precise neural bases in order to identify therapeutic targets for their treatment [20]. However, whether such correlates directly underlie deficits, or are reliable representatives of overall or other cerebral damage —which mediate links to cognition— remains unclear. For example, the thalamus has been shown to be highly susceptible to retrograde degeneration [29], thus, it may have better scan-to-scan reliability than other structures [20]. However, using thalamic volume as a summary measure of disease burden across people with MS with different CNS damage, even if thalamic change does not directly underlie a specific cognitive impairment (e.g., memory or attention).

According to Sumowski [20] advances in ultra-high-field MRI, myelin and molecular imaging —imaging of demyelination and remyelination and non-conventional MRI techniques used to examine microstructural cerebral changes would provide more ways to investigate cognitive deficits due to MS [30-33].The most promising neuroimaging methods to date includes diffusion tensor imaging (DTI); [34] a type of MRI technique that enables the measurement of water diffusion rates between cells to produce a microstructural map of the brain [34] found this technique to provide supplementary disability progression information over 4 years in MS. However, larger prospective longitudinal studies with multi-modality neuroimaging to accurately document temporal correlations of specific cognitive deficits with changes in specific brain structures and functions are still required. Longitudinal studies may help support cross-sectional links between memory deficits and hippocampal changes [23].

MS Cognitive Assessment

There are several cognitive batteries or tests specifically developed for MS [35]. These include tests of processing speed, memory, and other functions individually administered by trained professionals. For example, information processing speed is typically assessed as the amount of work performed within a time frame or time limit (e.g., number of items completed) whereas episodic memory is assessed as the amount of information learned and recalled (e.g., words, visual stimuli) using several tests [35-37]. These tests were developed by a panel or committee of experts composed of twelve neuropsychologists and psychologists from different countries representing the main cultural groups influential in MS research; United States, Canada and United Kingdom. They reunited few decades ago in order to propose a minimal neuropsychological examination for clinical monitoring of MS patients and research, as well as to identify strategies for improving neuropsychological assessment of MS patients. With this purpose, the experts reviewed and discussed the relevant literature on MS-related cognitive dysfunction, as well as they considered psychometric factors relevant to neuropsychological assessment [38]. Peer-reviewed articles covering a broad spectrum of cultures and scales addressing MS-vulnerable cognitive aspects were selected. Each article was rated by two committee members and candidates based on psychometric qualities, such as reliability, validity and sensitivity, international application, ease of administration, feasibility in the specified context, and acceptability to patients [22]. This exhaustive research resulted in the development of the Minimal Assessment of Cognitive Function in MS (MACFIMS). The MACFIMS is a 90-minute battery composed of seven neuropsychological tests that covers the five most common cognitive impairments in MS. These impairments include processing speed and working memory, learning and memory, executive function, visual-spatial processing, and word retrieval [36,7]. Additionally, the battery of tests is supplemented by an instrument of measurement of the estimated pre-morbid cognitive ability.

However, measures for assessing other factors that may potentially confound interpretation of neuropsychological data, for example, visual, sensory and motor impairment, fatigue, and depression— are offered, as well as strategies for improving future neuropsychological assessment of people with MS. Further paths for improvement were found by [20]. The researchers critically evaluated some of these tests, which are the most widely used. As a result, they identified the Symbol Digit Modalities Test (SDMT), the Brief Visuospatial Memory Test-Revised (BVMT-R), and the Selective Reminding Test or California Verbal Learning Test–II (CVLT-II) as the most sensitive tasks for cognitive monitoring in MS nowadays. However, limitations of these tasks were also found. For example, patients referred for specific clinical or research questions beyond monitoring often require more comprehensive evaluations. Also, despite of the briefness of MS batteries based on neuropsychological standards, most of them require even 15 minutes of one-on-one testing for every patient, which might not result very practical in terms of MS care standard. The researchers proposed series of possible alternatives such as the usage of computerised. It was concluded that computerised could be the main key of innovation that would improve most important areas of neuropsychological monitoring in MS cognition. These may include better detection of cognitive decline, large datasets from representative samples to advance understanding of prevalence, time course, and risk factors for decline, and greater feasibility of post market studies of disease-modifying therapy effects on cognition [20].

On the other hand, the need for cost-effective screening techniques that identifies neuropsychological impairment in people with MS, as well as the requirement of cognitive testing with subsequent interpretation by a neuropsychologist of existing methods, lead to the development of a brief self-report. This was elaborated by pooling 80 items based on literature review and consultation with healthcare professionals. The set was then reduced to 15 items through analytical methods. As a result the MS Neuropsychological Screening Questionnaire (MSNQ) emerged. This is a brief five-minute test that includes patient and informant-report form [38] selected 50 MS patients and their caregivers to complete the MSNQ. Additionally, a comprehensive neuropsychological test battery was also administered. Subsequently, the reliability of the MSNQ and correlations between both patient- and informant-report scores and objective neuropsychological testing were analysed. The result of the analyses indicated that both forms of the test were strongly correlated with a more general cognitive complaints questionnaire. Also, a cut-off score of 27 on the informant form of the MSNQ separated patients based on a neuropsychological summary score encompassing measures of processing speed and memory [38].

MS patients are often characterized by studies as as cognitively impaired based on overall performance across multiple tests that measure several or specific cognitive functions. However, this could lead to heterogeneity of impaired groups of patients with different isolated or co-occurring cognitive deficits. This may challenge the interpretation of results and confront comparisons across studies, especially those aiming to identify neural correlates of cognitive impairment. Moreover, cognitive impairment might differ across specific cognitive domains. Therefore, it is suggested that future research should better characterise groups as impaired in isolated or combined as well as to use utilize purer measures for each cognitive domain [20].

Self-Report Cognition and Quality of Life in MS

A self-report study is a type of method in which participants or respondents are able to answer questionnaires, surveys or polls without interference. Researchers obtain participants' views or opinions about their own attitudes, feelings or beliefs through this method [39]. Numerous studies have indicated that people with brain damage are prone to underestimate neuropsychological (NP) impairment when self-report ratings are compared to informant ratings. Research suggest that these discrepancies have not been well examined in MS [40-42]. Moreover, evidence also showed a greater underestimate or less self-awareness of cognitive dysfunction and unemployment within people with MS [42].

Perceived cognitive impairment (PCI) might be considered as the major health-related quality of life (QoL) and work outcomes determinant [43-45]. According to [40]. self-reported cognitive measures may be an indicative for objective cognitive impairment in MS population. [46] examined the specific contribution of cognitive impairment to daily living problems in multiple sclerosis using either cognitively intact or cognitively impaired MS patients trough neuropsychological testing. Results showed that cognitively impaired MS patients were more likely unemployed and less likely engaged in fewer social and avocational activities. They also reported more sexual dysfunction, experienced greater difficulty in performing routine household tasks, and exhibited more psychiatric symptoms than cognitively intact patients.

However, researchers find difficult to assess the PCI accurately due to the variability in how it is defined, either by longitudinal clinical assessment or by individual self-report of perceived symptoms [47-48].Moreover, it is complex to prevent or treat cognitive deficits in MS effectively through pharmacological interventions [49]. Therefore, lifestyle modification such as physical activity, better diet, and avoiding unhealthy behaviours (such as smoking or alcohol consumption) might be a supplementary and protective strategy given their strong association against age-related cognitive decline in the general population [49]. A cross-sectional analysis study found several factors positively associated with PCI using specific definitions in people with MS. These factors increased in magnitude directly and proportionally as their specific definition, including associations for smoking and body mass index. In contrast, physical activity, dietary quality and use of vitamin supplements were inversely associated with PCI [43]. In addition, these factors along with body mass index (BMI) and meditation have also been associated with MS onset [50-51], as well as with general health.

Information Processing and Memory in MS.

According to many studies, people with MS often report difficulties in executive function, verbal fluency, and visuospatial analysis, although additional difficulties in multitasking and word-finding are also very characteristic [52-53]. Cognitive decline often emerges at an early stage of the disease [54]. Whereas impairment is more prevalent [21-20] and may differ qualitatively among people with progressive forms of the disease against RR MS. However, the most common deficits in MS correspond to slowed Cognitive Processing Speed or Information Processing Speed (IPS) impairment and episodic memory decline [55].

Information processing is the core concept of cognitive psychology, which sees individuals as information processors similarly to computers (i.e, as machines that collect information and follow a program to reproduce such information). The IPS approach is based on a number of basic assumptions which include the idea that information present in the environment is processed and transformed systematically through several systems (e.g. attention, perception, and memory). This theory also focuses on the specific processes and structures that underlie cognitive performance [56]. IPS is measured through different methods. However, the most widely used to analyse the relationship between IPS and the clinical and social support variables of people with MS are the Symbol Digit Modalities Test (SDMT) and the Paced Auditory Serial Addition Test (PASAT) [57].

On the other hand, studies have also had empirically demonstrated that Long-term memory (LTM) is one of the principal multiple cognitive functions affected by MS. The LTM deficits have often been associated to retrieval failure [58]. However, increased self-reported memory impairments were significantly correlated with higher levels of normative dissociation experiences as well as with several psychiatric symptoms such as depression, anxiety, and neuroticism rather than neuropsychological variables in people with MS [59].

Some researchers often use alternative classifications to refer to LTM based on the temporal direction of the memories. Retrospective Memory (RM) refers to the process of recalling past memories or episodes (e.g., people, words, events). It includes semantic, episodic and autobiographical memory, and declarative memory [60-61], whereas Prospective memory (PM) is employed when the content is to be intentionally remembered in the future ("remembering to remember"). PM is often triggered by a cue and it may be either event-based when the action is reminded by a specific event–, or time-based –when the action or event is planned on a specific time [62- 63].

There is considerable evidence that cognitive impairment in MS extend to activities requiring PM [64-65] and that MS is associated with impaired retrospective memory [66]. For example,[67] investigated the ability to remember and perform delayed intentions in a sample of individuals with Multiple Sclerosis (MS) in comparison to a neurologically intact control group through a task division model. Performance on the PM component and the RM component were examined. The results showed significantly poorer performance of the MS group in both components. However, findings suggested that failure in PM might be primarily attributable to RM deficits, showing that both PM and RM rely on each other [63].

However, although IPS and memory are correlated in MS these cognitive functions are also highly correlated in healthy population, probably due to general ability [68]. Therefore, conclusions about direct relationships between decline in processing speed, memory, and any other cognitive function regardless of premorbid ability or disease-related mediators, might be premature and potentially misleading [20]. Moreover, although MS leads to deficits in several cognitive domains in the group level [36,53] it is little known about the disease's variability of cognitive deficits in a patient-level expression, for example, patterns of isolated deficits in comparison to co-occurring deficits. In addition, it is not known whether deficits in one cognitive function or domain contribute to dysfunction in other domains, for example, whether IPS contributes to memory. All these factors may lead to groundless expectations or assumptions, such as the idea that treatment of one function may improve correlate functions [20].

Research Question, Objective, and Hypothesis

The MSNQ is a validated self-report measure of global cognitive difficulties for people with MS. The two most prevalent cognitive impairments in MS occur in information processing speed (IPS) and memory. However, it is not known how difficulties in these two cognitive domains separately affect self-report of cognitive difficulties on the MSNQ. Furthermore, it has been suggested that IPS underlies all cognitive deficits [20], and so, they may have a disproportional effect on MS patients' MSNQ responses. The Attentional Functional Index (AFI) is a useful self-report instrument for perceived cognitive functioning that measures perceived effectiveness in common activities which requires attention and working memory. These activities include, in particular, the ability to formulate plans, carry out tasks, and function effectively in daily life [69]. On the other hand, The Prospective and Retrospective Memory Questionnaire (PRMQ) is another self-report instrument developed by [70], in order to test prospective short term and long term memory, as well as retrospective short term and long term memory. Understanding the relationship between these measures and how the affect global MS cognition will help find or develop a tailored questionnaire that a person with MS could fill in, providing more information about personal experience, and more insights on the mechanisms underlying independent and global perceived cognitive dysfunction in MS. This will, additionally, enable health professionals assess additional cognitive impairment associated risks (e.g. poor disease management, like adherence to treatment) and allow to provide better support to individuals.

Therefore, it is expected that the Multiple Sclerosis Neuropsychological Screening Questionnaire (MSNQ) will be more closely associated with the Attentional Functional Index (AFI) and less closely with the Prospective and Retrospective Memory Questionnaire (PRMQ) by analysing their relationship. Additionally, this study explores MS population reported cognition awareness.

Method

Participants

Participants were N=76 adult male and female individuals with MS from the United Kingdom. All participants were recruited on-line through different

MS organisations. All participants were English speakers. Additionally, demographical data was collected for statistical purposes.

Material

The material employed was a demographic questionnaire informing of participants' ethnicity, nationality, age, gender, academic level, and occupation; an Informed Consent Form providing details of the study and specifying its aims and purposes, and a specially constructed set of questions about cognition services.

Participants completed The Multiple Sclerosis Neuropsychological Screening Questionnaire (MSNQ), a valid 15-item self-report measure developed to screen patients for cognitive deficits and neuropsychological impairment in daily activities on MS population [38].

In order to measure participants 'self-report memory we employed The Prospective and Retrospective Memory Questionnaire (PRMQ) [61] a valid 16-item self-report questionnaire assessing prospective and retrospective memory impairment, On a 5-point scale (Very Often, Quite Often, Sometimes, Rarely, Never) participants are asked to indicate their perceived memory errors frequency [70].

The Attentional Functional Index, was employed in order to analyse information processing. It is a 13-item self-report measure with 3 sub-scales designed to assess cognitive function and perceived effectiveness or performance on tasks requiring attention and working memory, particularly, the ability to formulate plans, carry out tasks, and function effectively in daily life. Its construct gained validation using exploratory principal component factor analysis with varimax rotation on a breast cancer study and has demonstrated usefulness for assessment of perceived cognitive functioning [2].

All the material questionnaires and data were administered and collected via on-line through Qualtrics. Additionally, SPSS Statistics was employed for data analysis.

Procedure

All questionnaires were on-line administered through Qualtrics. Participants were provided with a direct link to the study and followed on screen procedures. Data was treated anonymously, as well as confidentially stored, and analysed using SPSS Statistics in computers with access restricted to researchers.

Design

A correlational or regression design (within subjects) were memory, with two levels- prospective and retrospective-, and attention were the independent variables (IV) and the MSNQ (neuropsychological screening) the dependent variable (DV)

Statistical Analysis Plan (SAP)

- **Outcome Measures (Dependent Variable)**

Self-reported cognitive impairment on the MSNQ [38].

- **Independent Variables**

Perceived information processing speed deficits; Attentional Functional index [69].

Perceived memory deficits; Prospective and Retrospective Memory Questionnaire [61]

- **Confounders**

Demographic: Sex, Age, Socio-economic status, education. Physical and cognitive factors: type of MS, general fitness, and self-cognition awareness, for example; ability to write, ability to communicate if unable to write, or ability to understand questions and process information.

Statistical Analyses

1. Data primary observations: Descriptive statistics, tests of normality, homogeneity, multicollinearity, outliers (check and exclusion).

2. Correlation (within-subjects): Statistical relationship between IV (MSNQ scores) and DVs —MS population self-reported information processing speed deficits scores and self-reported prospective and retrospective memory scores. It will be determined if the correlations are statistically significant.

3. Multiple Linear Regression: Participants' self-reported scores reversed if required and coded appropriately of information processing speed will be analysed in order to determine whether these and other variables predict the MSNQ score.

These analyses were designed to address the research question or hypothesis; whether perceived attention or IPS and memory deficits are associated with the MSNQ. These analyses also explained the nature and the power of these relationships. In addition, confounders were explored through a visual evaluation (graphs, plots…) of interaction between the outcome questionnaires scores and demographical data, divided into subgroups or subcategories (i.e. sex, age, type of MS…). Data was confidentially stored for future replication in order to obtain more representative results, and for subsequent observations.

Results

Responses from a total number of 186 adult male and female participants with MS were collected in the study. However, only N=76 cases of all completed respondents were included in the analyses. Thus, missing values were excluded using Listwise deletion. Despite the fact that no outlier was detected (Figure 1), the descriptive statistics indicated slightly asymmetrical data distribution (Figure 2) with a negative skewness (Skp) value between -0.5 and 0.5 considered generally acceptable for all predictors; and an approximately normal or symmetrical distribution for the dependent variable [Table1]. Nevertheless, given the low Skp. coefficient values, which suggests an approximately symmetrical distribution, no transformation was considered to be required.

The relationship between the MSNQ scores (M= 47.38, SD= 13.02) —the DV—, and both the PRMQ (M= 54.17, SD= 16,51) and the AFI (M= 925.71, SD= 333.87) scores—the IVs or predictors— was explored in order to

Figure 1. Regression scatter-plot.

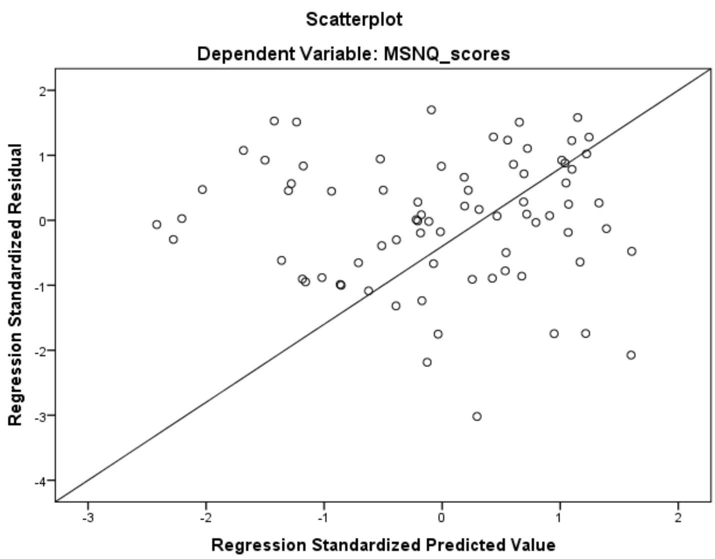

Figure 2. Regression Histogram: Frequencies and distribution of sample (N=76).

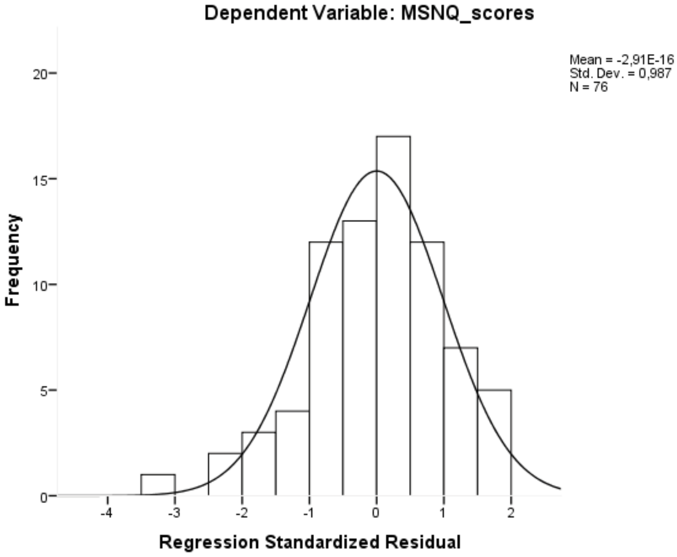

Table 1. Descriptive Statistics. Tests of Symmetry for Data Distribution (Normality).

	Skewness	Kurtosis
MSNQ scores	-0.01	-0.88
PRMQ scores	-0.41	-0.7
AFI scores	-0.34	-0.78

determine whether either information processing speed and prospective and retrospective memory deficits contribute to self-report of cognitive difficulties in MS population [Figure 1].

Correlational analyses were executed to test the statistical relationship between the three variables. The results of the analysis were statistically significant indicating a strong positive correlation between MSNQ scores and PRMQ scores; r (76) = .85, p< .01. Similarly, MSNQ scores and AFI scores showed a strong significant relationship; r (76) =.63, p< .01. On the other hand, Pearson's correlation also suggested a strong significant relationship between the predictors; r (76) =.63, p<.01. This suggests that self-reported prospective and retrospective memory and information processing speed are significantly associated with self-reported cognitive deficits on the MSNQ. However, interim analysis were required to examine a possible interaction (multicollinearity) between all correlated predictors.

Additionally, a within-subjects multiple linear regression was performed in order to examine the nature of this relationship. A significant regression equation was found; F (2, 73) = 99.21, p< .05 with an R2 of .73, indicating a good model. This suggests that both the PRMQ (B=.59, p<.001) and the AFI (B= .01, p=0.5) are good predictors of MSNQ scores in MS population, being the PRMQ highly significant. Collinearity diagnostic suggested that there was no multicollinearity between the variables with VIF<10, this indicates that no correction was required. Therefore, it is concluded that each independent predictor makes separate contribution in the statistical relationship with a 73% of variance of the MSNQ explained by both the PRMQ and the AFI. However, the 27% of variability remaining was unexplained, which could be due to the influence other factors or confounding variables; such as age, gender, or further cognitive features.

Discussion

It is uncertain how different prevalent cognitive domain deficits affect global cognitive dysfunction in MS. Moreover, the nature of this relationship remains unexplored. As predicted, this study showed a strong positive relationship between the PRMQ, the AFI and the MSNQ. These findings support the usefulness and effectiveness of the PRMQ and the AFI to measure and asses self-report cognitive function in MS. However, the statistical analyses showed that both variables made an individual contribution to the predicted outcome, being perceived memory impairment the MSNQ main predictor with greater variability explained. This indicates a higher correlation, hence, a stronger relationship between the PRMQ and the MSNQ. Hence, despite the hypothesis that the AFI would be closely associated to the MSNQ compared to the PRMQ according to previous research, the raised null hypothesis was rejected based on these findings. In addition, these results suggest drawing attention to memory deficit, in contrast to previous research, which hints IPS as the main cognitive deficit domain in MS. This also suggests further examination.

Previous evidence suggested that IPS underlies all cognitive deficits in MS, therefore, despite the fact all variables showed a positive relationship amongst, it was expected that perceived IPS was strongly associated with MS global cognitive deficit on the MSNQ. Nonetheless, the results indicated that self-report of cognitive difficulties in prospective and retrospective memory, as well as information processing speed or attention, made independent contributions to self-report of perceived global cognitive difficulties on the MSNQ. This suggests that different cognitive deficit functions may operate independently rather than interacting, which provides a deeper insight in their mechanisms, but also questions previous research and gives rise to new or less commonly examined approaches. For example, whether intervention target should change perspective and treat each cognitive function individually.

On the other hand, similarly to previous research, these findings reaffirmed the MSNQ accuracy and usefulness for evaluating different domains of cognitive function impairment in MS population, being the MSNQ a feasible and suitable measurement of global MS cognition, as well as for perceived MS cognition. Furthermore, the strong significance among variables supports that both IPS and memory underlie two of the main cognitive impairments in MS based on the MSNQ.

These findings are not exempt of limitations. Many researchers agreed that more cognitive impaired participants tend to underestimate their cognitive deficits. However, the consensus in the literature that cognitive deficits are overestimated or underestimated by individuals remain contradictory and discrepant. Although self-report measures and, more concretely, on-line or computerised self-report measures, have many advantages (e.g., confidentiality, ability to recruit large samples and different groups), these also have validity and reliability weaknesses. This is due to their lack of control over confounders, such as respondents' fitness and physical ability to complete surveys and questionnaires — which might be, in turn, related to the type of MS [Table 2].which may result in, for example, a second party completing them on behalf, exaggeration or under-report of severity of symptoms, and participants' mental or psychological state. For example, it is known that depression may influence or affect cognitive ability. If a person with MS suffers from depression, this might mediate, be the directly related to, or responsible for cognitive function decline perception rather than disease itself. Thus, the self-report constructs or measures employed in the study could not evaluate the respondents' answers accuracy or reliability due to a lack of control over these factors. This might have lead to a biased description of their cognitive ability perception. In other words, the sample might not be an exactly or accurately illustrative of the real MS population. Moreover, the influence of further factors like individual and demographic characteristics

Table 2. Descriptive Statistics of Demographic Data (Valid N= 76).

	Descriptive Statistics				
	N	Mean		Std. Deviation	Variance
What is your type of MS?	114	2.61	0.08	0.84	0.7
What is your gender?	115	1.75	0.04	0.48	0.23
How old are you?	115	3.52	0.06	0.7	0.5
What is your nationality?	115	197.08	6.24	66.94	4481.28
What is your country of residence?	113	197.75	6.43	68.34	4670.38
Which ethnic group best describes you? - Selected Choice	114	1.04	0.04	0.47	0.22
What is your current marital status?	114	2.05	0.16	1.67	2.78
Which of the following categories best describes your current employment	114	4.54	0.27	2.84	8.06

The table shows that the majority of participants were white young adult females (age range35-49) with either PPMS or PPMS when coded as it follows:

Type of MS: 1-CIS, 2-RRMS, 3-PPMS, 4-PSMS.

Gender: 1-Male, 2-Female, 3-Other.

Age: 1 (18-24), 2 (25-34), 3 (35-49), 4 (50-64), 5 (65+).

Ethnicity: 1-White/White British, 2-Black/Black British, 3-Asian/Asian British, 4- Hispanic, 5-Mixed, 6-Other.

Employment: 1-Employed Part Time, 2-Employed Full Time, 3-Self Employed, 4-Student, 5-Not employed looking for work, 6-Not employed not looking for work, 7-Retired, 8-Disabled, not able to work.

such as age, education, gender, marital status or occupation [Table 2] may also play an essential role on self-report, enabling further research on the current implications of these elements.

Furthermore, generally, people with higher socio-economic status and education might have more technological accessibility as well more facility to navigate the internet, thus, to complete questionnaires. Social gender roles may also be regarded as a factor of consideration. At a household level, for example, this might condition individual availability to take part in these studies.

On the other hand, a small sample size, resulting from the exclusion of missing cases, i.e. uncompleted questionnaires (missing values or blank responses) might have also had a relevant impact. Missing values might be explained by the duration of the study; although brief questionnaires were employed, the survey comprised multiple batteries which may elongate the completion time of this, affecting respondents' task performance. Previous factors like, for example, physical ability, might have equally and simultaneously influenced such performance.

Finally, it is also worth to mention that, with the exception of the MSNQ, the constructs employed for this study have not been currently tested and validated for the specific assessment of MS cognitive difficulties, which may also weaken the reliability of the findings. Notwithstanding, this opens a window for further investigation. The set of these additional variables and how they affect self-report of cognition in MS population requires further examination, thus, future replication and larger sample sizes. Future research could target the identification of effective tools or the improving existing ones, developing controls for confounders, and testing different constructs or measures on specific cognitive domains. Further future direction address the implications age, gender or type of MS.

Conclusion

Overall, the study found that perceived cognitive deficits affect global cognitive impairment in people with MS despite the individual and demographical features or other factors that may have an influence on cognitive decline in MS population. Different neuropsychological difficulties or cognitive deficit domains, such as memory (prospective and retrospective) deficits and IPS decline, independently affect global and perceived cognitive impairment of people with MS. These findings are relevant for understanding and interpreting the particular and combined mechanisms underlying cognitive impairment in MS, but may also be beneficial to link up with and support neuroimaging studies. Finally, this may help develop and improve assessment instruments to help identify cognitive difficulties. Additionally, this would aid health professionals present health information and raise feasible and effective daily life and treatment adaptations to help improve people with MS' quality of life from both a clinical practice perspective and a patient-level experience.

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