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Rapid Visual Information Processing neuropsychological test for remote cognitive assessment in multiple sclerosis: A preliminary study

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ABSTRACT. L'obiettivo di questo lavoro preliminare è di valutare l'applicabilità del Rapid Visual Information Processing (RVIP) test in full-remote, insieme ai test DASS-21 per depressione ansia e stress, CFQ e MSNQ per i fallimenti cognitivi, al fine di misurare la velocità dell'elaborazione delle informazioni (Information Speed Processing - IPS) che risulta essere deficitaria nei pazienti con SM. I risultati suggeriscono come l'RVIP veicoli molte informazioni utili e che possa essere utilizzato in una valutazione dell'IPS in modalità full-remote. Infine, il modello di regressione logistica, costruito usando il True Positive Rate dell'RVIP, mostra una buona specificità di classificazione dei soggetti nei due gruppi. Sviluppi futuri dovranno considerare un campione più ampio e valutare preliminarmente le competenze digitali.

SUMMARY. Multiple sclerosis (MS) is a neurodegenerative disease that causes many neuro-cognitive deficits. The test batteries used for clinical evaluation are not always able to detect the slight variations since they do not always consider the subject's baseline but only the reference value computed on the population. Furthermore, the low frequency of assessment, also due to the sparse distribution of MS centres makes the test unable to detect slight fluctuations that could indicate the onset of new deficits. Remote neuropsychological evaluation performed with a high frequency, can provide useful information on the subject's baseline, going beyond the limits of population normative values, and become enough sensitive to measure significant variations on a single subject. In line with the European Union (EU) directives on telemedicine, this work aims to evaluate the usefulness of the remote Rapid Visual Information Processing (RVIP) test to assess the Information Speed Processing (IPS) which is impaired in 40% of MS patients. The other already validated tests used in this work were the Depression Anxiety Stress Short Scale (DASS-21) tests for depression, anxiety and stress, the Cognitive Failure Questionnaire (CFQ) and the Multiple Sclerosis Neuropsychological Questionnaire (MSNQ) both for cognitive failures. Data from 44 subjects (12 with MS and 32 healthy) were acquired. The results show that the True Positive Rate (TPR) of the RVIP is lower in the MS group compared to the Healthy Group. The logistic regression model can classify the subjects into two groups with good specificity. This quickly and non-invasive neuropsychological test performed in remotely, allow us to estimate of the most reliable true parameter of IPS and increase the signal-to-noise ratio performing repeated measures with a high frequency. The present work shows that a remote evaluation of some specific neuropsychological domains is possible and together with a traditional assessment, it can support the clinician in adjusting the therapy, reducing costs and the impact on the individual, and improving the outcome.

Keywords: *Cognitive Processing Speed, Telemedicine, Multiple sclerosis, Rapid Visual Information Processing*

INTRODUCTION

Multiple sclerosis (MS) is a neurodegenerative disease that leads to a progressive loss of myelin, affecting central nervous system (CNS) functions, including the cognitive domain (Lassmann, 2018). MS is more common in female people and on the North of the Earth. Actually, is not clear which is the most important risk factor associated with this distribution between solar radiation, environmental factors, pathogens or genetics (Compston & Coles, 2008). The diagnostic process is complex and includes several biomedical, neurological, radiological and biochemical tests. The course of the disease depends on the MS type. It can be remitting-relapsing or progressive, with several subgroups. The remitting-relapsing MS is characterized by periods with symptoms interspersed with periods without symptoms: this trend has a discrete ladder shape. The progressive MS type is generally slower but without any remission and with increasing severity of symptoms: this trend has a more linear shape without negative derivative (Brownlee, Hardy, Fazekas & Miller, 2017).

It is well known that in MS, cognitive impairment could be present 40-70% of total cases (Chiaravalloti & DeLuca, 2008) and for this, neuropsychological assessment is necessary to address the clinician to personalized cognitive, physical and pharmacological therapy (Rao, Leo, Bernardin & Unverzagt, 1991). Furthermore, cognitive impairment in MS people, which leads to a quality of life (QoL) deterioration, is presented with a high variance throughout the population. Principal cognitive functions impaired in people with MS are:

- long-term memory;
- sustained and selective attention;
- problem-solving;
- attention switching;
- information processing speed (IPS).

In addition, it is necessary to assess psychological conditions due to depressive or anxiety disorders onset (Macias & Ciampi, 2019). Many psychological and neurological batteries for cognitive assessment were used in the literature. Mini-Mental State Examination (MMSE) (Tombaugh & McIntyre, 1992) is useful but not sufficiently sensitive, due to the proof effect, because it is devised for elderly people. More common are the *Brief Repeatable Battery of Neuropsychological Test* (*BRB-NT*) (Rao et al., 1991), the *Minimal Assessment of Cognitive Function in MS* (*MACFIMS*) (Benedict et al., 2006) and the *Brief International Cognitive Assessment for Multiple Sclerosis* (*BICAMS*) (Langdon et al., 2012). All of them assess IPS, specifically using *Symbol Digit Modalities Test* (*SDMT*) (Smith, 1973), but its tests not use the response time (RT) with very high precision, useful to catch minimal difference performance between two or more sessions. In general, neuropsychological tests are validated on populations, and for this, they cannot take into account the baseline of the subject (Eckert, Keren, Roberts, Calhoun & Harris, 2010). Despite this, it is crucial to use the derivative of the performance trend acquired over time to detect the slightest difference from the previous session or the prior healthy state before the onset of MS (Schoenberg et al., 2011). The derivative could be useful to identify some prodromal symptoms of cognitive decline onset or worsening symptoms. Additionally, the bias in the data might be a consequence of the hospital environment (similar to the white coat hypertension effect). Finally, the MS centre also does not have a wider distribution throughout the region since it is expensive, difficult to get to the hospital, and difficult for patients to travel throughout the pathology wards, making evaluations even less regular. Through telemedicine, a neuropsychological assessment of important pathology-related aspects might assist the doctor in quickly changing the course of treatment for a better outcome (Ziemssen et al., 2015).

Related works

Neuropsychological assessment traditionally requires an in-person clinical expert to evaluate cognitive functions, but there are some advantages to using a computerized-remote assessment system.

In (Settle, Robinson, Kane, Maloni & Wallin, 2015), the authors used neuropsychological instruments in two modalities: live-in-office (LIO) and remote-in-office (RIO). To assess the IPS, they used *Symbol Digit Modalities Test* (*SDMT*) (Smith, 1982): in this task, the participants have to match the correct number corresponding to a symbol in a correct key looking at the legend. The time to perform this task is measured. The authors also used the *Automated Neuropsychological Assessment Metrics* (*ANAM-MS*) (Reeves, Winter, Bleiberg & Kane, 2007) to assess several cognitive functions: attention, reaction time, information processing speed, memory, and decision-making. Results show no significant difference in ANAM-MS and little difference in

SDMT between the two modalities (LIO and RIO). Moreover, they find that the SDMT score is highly predictive of ANAM-MS scores and this suggests SDMT could be used for a screening assessment. Moreover, based on the SDMT score, clinicians can choose to perform a more detailed assessment.

In (Barcellos et al., 2018), the authors used the *California Verbal Learning Test – second version* (*CVLT-II*) (Delis, Kramer, Kaplan & Ober, 1987), a part of *Brief International Cognitive Assessment for Multiple Sclerosis* battery (*BICAMS*) (Benedict et al., 2012). The CVLT-II assesses verbal memory: clinicians read a list of words five times and participant have to recall as many words as possible. They collect data from 180 people with MS and 90 without MS diagnosis (Healthy group). The difference in the score was statistically significant between the Healthy and MS group, both in-person and in remote modality assessment.

No differences were found in the two modalities between MS assessed in-person and remote.

In (Barcellos et al., 2021), the authors collected data from 100 people with MS, divided into two groups: 50 people to in-person assessment group and 50 people to remote assessment group. All subjects were assessed by CVLT-II and SDMT. The authors observe the strong correlation between the final score of two modalities (r = .85, $p<10^{-28}$ for SDMT and r = .71, $p<10^{-15}$ for CVLT-II). Moreover, shuffling the order of the two modalities does not affect the results.

In (Rogers et al., 2022), authors used SDMT, CVLT-II, *Brief Visuospatial Memory Test-Revised* (*BVMT-R*) (Benedict, 1997), where subjects have to draw figures previously seen, *Trail-Making Test* (*TMT*) (Reitan & Wolfson, 1992) for visual attention and task switching assessment, and *Multiple Sclerosis Neuropsychological Questionnaire* (*MSNQ*) (Benedict et al., 2003) for a self-screening on cognitive impairments. The research was conducted considering two groups both composed of 34 people, one with in-person and remote assessment and one only with remote assessment. The results show no significant differences between the two groups for CVLT-II and SDMT final scores.

In a recent review (Wojcik et al., 2019), the literature about computerized neuropsychological assessment devices (CNADs) in MS was analyzed. The results show how some computerized instrument to assess cognitive impairment in multiple sclerosis could be useful to clinicians due to psychometric qualities although several computerized tests for cognition does not yet demonstrate adequate reliability and validity. Nevertheless, computerized tests could be useful for identifying the prodromal symptoms capturing the very tiny difference in some parameters as RT that is impossible with traditional tests.

Our work

This preliminary work aims to perform a web-based assessment method for cognitive functions to evaluate the utility of a remote assessment of cognitive function in MS people, with a focus on IPS and its relation with some psychological aspects. Our hypothesis is based on the assumption confirmed by literature (Chiaravalloti & DeLuca, 2008; Rao et al., 1991) that MS people have the worst performance in IPS tasks. This work tries to evaluate this cognitive domain in remote modalities during the Covid-19 pandemic period. Due to Covid-19 Italian law, it was not possible to compare in-remote with in-person assessments and also was not possible to explain the usage of the platform used for that study. The *Rapid Visual Information Processing* (*RVIP*) test (Talland, 1966) was used to assess the speed of information processing and the number of correct, wrong or miss answers to an information flow based on specific rules. The RVIP test is already present in *Cambridge Neuropsychological Test Automated Battery* (CANTAB, 2016), a battery used in the evaluation of functions cognitive composed of several tests with automatic scoring. Our result shows how RVIP is a useful neuropsychological instrument to assess IPS in MS patients in a web-based context, and it conveys the same information as the Go/No-Go test (Donders, 1969) with more details on sustained attention and working memory. Moreover, the score of MSNQ (Migliore et al., 2021) was in line with the result of the *Cognitive Failure Questionnaire* (*CFQ*) (Broadbent, Cooper, Fitzgerald & Parkes, 1982). Although the weak sample and the different distribution of age in the two groups that not allow a generalization of results, the logit model showed the relation between the TPR (True Positive Rate) of the RVIP and the MS diagnosis.

METHOD

The IPS is a part of the cognitive domain of complex attention, referring to the storing and manipulation of information for a short time. The RVIP test evaluates the continuous performance on the detection or avoidance of

specific targets. Based on how many targets or non-target are correct detecting (HIT), wrong detecting (FA), missed (MISS) or correct rejecting (CR). RVIP complementary assesses impulsivity using False Positive Rate (*FPR*) index:

$$FPR = \frac{nFA}{nNonTarget}$$

where *nFA* is the total of the wrong answers to non-target sequences/stimulus, and *nNonTarget* is the total of the non-target sequences/stimulus presented.

Before starting, participants have to learn the target sequences. After a very short training, participants observe a stream of single digits (from 0 to 9) appear on the screen and they have to press a button (space bar) as soon as they identify the last digit of the target sequence, consisting of three digits. As shown in Table 1, the indexes used to assess the results are:

- HIT: correct answers to a target sequence over total target stimuli;
- False alarm (FA): wrong answer to a non-target sequence over the number of total non-target stimuli;
- MISS: not-answer to a target sequence over total target stimuli;
- Correct rejection (CR): correct rejected answers to a non-target sequences/stimulus.

This paradigm as a cognitive task was used as a measure of sustained attention began in the 1960s to estimate the effect of alcohol intake (Talland, 1966).

Rapid Visual Information Processing

The test used in the present work is a simplified version of the RVIP (Jones, Sahakian, Levy, Warburton & Gray, 1992). This version solves some ambiguities due to the possible succession of two consequential target sequences. The original target sequences proposed were the following: 2-4-6, 3-5-7, 4-6-8, 5-7-9.

This test was used to evaluate sustained attention in visual sensory modality, following the subcutaneous administration of nicotine to subjects with Alzheimer's dementia and is also present in the CANTAB battery. The main rule for this task is to detect the target sequence by pressing the button only when the last (third) digit appears: the first two digits can alert the participant to be ready for pressing the button. The version used in this work uses only two target sequences: 2-4-6, 3-5-7.

This avoids the improbable but possible cases of two target sequences appearing one after another. Instead, if two concatenated sequences should appear, the participant could not understand which triplet is the target and lose the last target sequence and for this reason, two target sequences were excluded. Each stimulus lasts 400 milliseconds (ms) followed by an interval between stimuli (ITI - inter-trial interval) of variable ms, between 300 and 600 ms, to prevent the subject from habituation to the distance between two stimuli. Thus, it can be possible to stimulate sustained attention and max-

Table 1 – Possibile answers

	Target	**Non-Target**
Answer	*HIT*	*FA*
Non-Answer	*MISS*	*CR*

Legenda. HIT = correct detecting; FA = wrong detecting; MISS = missed; CR = correct rejecting.

imise the probability of FA occurrences. Through the RVIP is possible to analyze many scores: in addition to the four parameters that can also be calculated in the Go /No-Go to verify if the sustained attention (Hit, Miss, False alarm, Correct rejection) it is possible to assess the speed information processing through the analysis of these parameters over time because is necessary to store the target sequences.

Self-assessment questionnaires

Data from questionnaires were collected. The questionnaires used were the following.

- *Depression Anxiety Stress Scales short version* (Lovibond & Lovibond, 1995): the DASS-21 is a tool, already validated on the Italian population (Bottesi et al., 2015), useful for discriminating against depressive from anxious symptoms, and whose principal component analysis showed that 1/3 of the items refer to a third factor that has been identified as a measure of stress (characterized by irritability, nervous tension, difficulty relaxing and agitation). The original article, using the extended version with 42 items, analyzed the psychometric properties and identified a strong correlation between the depression component and the *Beck Depression Inventory* (*BDI*; Beck, Steer & Brown, 1996) score. Moreover, it was shown the correlation between the anxiety component and the *Beck Anxiety Inventory* (*BAI*; Beck, Epstein, Brown & Steer, 1993) score, a very common tool used in clinical practice. The scale, in addition to measuring the three components (depression, anxiety and stress), can discriminate very well between depression and anxiety, maximizing the internal consistency between items of the same construct. The short version (Henry & Crawford, 2005), the DASS-21, was created to have a smaller instrument than the original 42-item version, keeping the psychometric components within adequate limits to be used in a clinical context. Therefore, DASS-21 has good construct validity, and factor analysis identified that although the items refer to a general factor of psychological discomfort, a part of the variance of each of them is explained by the three factors (Depression – Anxiety – Stress), and shown high reliability. Compared to the extended version of 42 items, the DASS-21 has the advantage of being able to be administered to people with poor attention sustained. The advantage of using DASS-21 compared to DASS-42 is to improve the discrimination power between a score due to psychological disorder instead of neurological damage.
- *Cognitive Failures Questionnaire*: the CFQ is a tool used in the self-assessment context of cognitive functions which, through 25 questions, investigates the errors of memory, perception or distractions that can occur in daily life. Operationally, it investigates errors by asking how often some common cognitive failures occur (e.g. "Do you fail to notice signposts on the road?"). This tool was used for the validation of the MSNQ, showing a high correlation between the two scores. Furthermore, it has been included in the present work since it has already been validated on the Italian population (Stratta, Rinaldi, Daneluzzo & Rossi, 2006), where the multi-factorial nature of the measured constructs was confirmed to measure: memory, concentration, inattention/distractibility, interpersonal intelligence, memory for names.

  The validation study of CFQ showed a high Cronbach's alpha, as well as no relationship between test score and age, while there was a slight but significant correlation between total test score and years of education. However, the validation study has a group of university students as a sample, and if this eliminates disturbing factors of a too-heterogeneous sample with many variables, it does not guarantee an extension of the results to the whole Italian population, which is noted by the authors themselves who recommend carrying out more accurate analyzes on more numerous and heterogeneous samples. Despite this, they assume that years of education could be interpreted as an operational measure of intelligence and therefore the results could be a "reflection of the cognitive variables related to intellectual performance".
- *Multiple Sclerosis Neuropsychological Questionnaire* (*Patient and Informant* sections): the *Multiple Sclerosis Neuropsychological Questionnaire* (*MSNQ*) is a short questionnaire composed of 30 self-administered questions: 15 are for the person with MS (patient, MSNQ-P) and 15 are for the informant (MSNQ-I, i.e. a person who knows the patient and his daily routine), designed precisely to be administered quickly by non-specialist staff. The participants have to rate each question on a Likert scale, from "Problem not encountered" (0) to "Occurs very frequently" (4). A higher score indicates more cognitive deficits. It was built based on an analysis of the scientific literature on the existing tools and on the clinical experience of the authors to capture all the

variations in cognitive functions that occur in people with MS. The items referring to depressive symptoms were excluded, although the initial intention was to combine some items referring to depressive disorders (such as those of the BDI) with questions on cognitive failures. Originally, self-administered questionnaires were found to predict *Expanded Disability Status Scale* (*EDSS*) (Kurtzke, 1983) scores sufficiently, but for assessment of cognition, they may not be reliable because memory impairment is strongly associated with depressive symptoms. People with dementia tend to overestimate their cognitive abilities, and for this, an association of information collected by the patient together with the information from the informant could increase the predictivity of the results. From an analysis of the collected data on MSNQ (O'Brien et al., 2007), it was possible to observe that MSNQ-P is very useful for estimating depressive symptoms while MSNQ-I is useful for effectively estimating cognitive functioning in daily activity as a screening measure, due to difficulty in self-estimate cognitive impairments. Finally, the dissociation between the responses of the patient and those of the informant may be an indication of dementia, with implications of anosognosia and reduced self-awareness. This instrument is recently validated on the Italian population (Migliore et al., 2021).

Data acquisition and descriptive statistics

Data collection was done using the Psytoolkit platform (Stoet, 2010, 2017), and analyzed using Phyton programming language (Van Rossum & Drake Jr, 1995) and Jamovi software (Jamovi Project, 2021). In Figure 1 and in Figure 2 are shown some screenshots of the website built for the data acquisition.

Data from 44 subjects were collected, 12 and 32 from the MS and Healthy group, respectively, during the period between November and December 2020, during the second lockdown in Italy, through the support of associations and online communities due to the difficulty to recruit people within a hospital or clinical centre, both for Healthy and MS groups. In particular, through the Association "Sclerosi Multipla Albero di Kos" it was possible to recruit patients among their subscribers for the MS group, and the Healthy group it was published online a public notice specifying the exclusion criteria. Also due to Italian law, it was not possible to perform study design with one group in presence and one remote to make the comparison. The inclusion criteria were to have had an MS diagnosis and for Healthy groups was not to have had an MS diagnosis. Moreover, the exclusion criteria for both groups were related to not having had other diagnoses of psychiatric and/or neurological diseases or previous neurological damage. Figure 3 shows the age distribution of the sample dividend into gender groups.

In particular, the TPR was used as a metric of performance:

$$TPR = \frac{nHIT}{nTarget}$$

where *nHIT* is the total number of the correct answer (HIT) to a target sequence/stimulus, and *nTarget* is the total of the target sequence/stimulus.

RESULTS

Due to the low sample size, it was impossible to perform separate analyses based on different types of MS.

Cognitive performance

The results showed in Table 2 show a significant difference of *TPR RVIP* between the MS and Healthy group, where the first group had better performance. The *t*-test was used to verify if the difference was statistically significant (on the last line of Table 2) and the same result was achieved for the Go/No-Go test (TPR Go/No-Go, see Table 3). The *t*-test was used to verify if the difference was statistically significant as shown in Table 3 on the last line.

Despite this, RT does not differ between the two groups. The results in Table 4 of the questionnaires show a strong correlation between the total scores of the CFQ and the MSNQ-P, which confirms the construct validity of the two diagnostic tools.

Unfortunately, the number of MSNQ-I answers does not allow any statistical analysis. An interesting finding shown in Table 5 is a negative correlation between the TPR of the Go/No-Go test of the Healthy group and the score of the CFQ inattention subscale and this shows the high sensitivity for Go/No-Go to measure the inattention domain. The correlation between the TRP of Go/No-Go and the CFQ inattention score in the MS group was not statistically

Figure 1 – Screenshot of RVIP test

SECONDA PARTE

Vedrete comparire in rapida successione una serie di numeri singoli tra zero e nove (0-9). Prestando la massima attenzione, se dovesse comparire, in questo esatto ordine, la sequenza di numeri

2 – 4 – 6

oppure

3 – 5 – 7

va premuta la BARRA SPAZIATRICE al momento della comparsa dell'ultima cifra della sequenza (quindi alla comparsa del 6 o del 7)

Figure 2 – Screenshot of DASS-21

Item	Molto	Abbastanza	Occasionalmente	Raramente	Mai
Si distrae facilmente?	◯	◯	◯	◯	◯
Perde il filo del discorso mentre ascolta qualcuno che parla?	◯	◯	◯	◯	◯
È rallentato quando prova a risolvere problemi?	◯	◯	◯	◯	◯
Dimentica gli appuntamenti?	◯	◯	◯	◯	◯
Dimentica cosa ha letto?	◯	◯	◯	◯	◯
Ha difficoltà a descrivere programmi o varietà televisivi che ha recentemente visto?	◯	◯	◯	◯	◯
Le istruzioni le devono essere ripetute?	◯	◯	◯	◯	◯
Le devono essere ricordate le cose da fare?	◯	◯	◯	◯	◯
Dimentica gli appuntamenti che ha pianificato?	◯	◯	◯	◯	◯
Ha difficoltà a rispondere alle domande?	◯	◯	◯	◯	◯
Ha difficoltà a fare due cose nello stesso momento?	◯	◯	◯	◯	◯
Dimentica cosa una persona le sta dicendo?	◯	◯	◯	◯	◯
Ha difficoltà a controllare gli impulsi?	◯	◯	◯	◯	◯
Ride o piange per futili motivi?	◯	◯	◯	◯	◯
Parla eccessivamente o si focalizza molto su un suo interesse personale?	◯	◯	◯	◯	◯

Figure 3 – Age average by group divided by gender

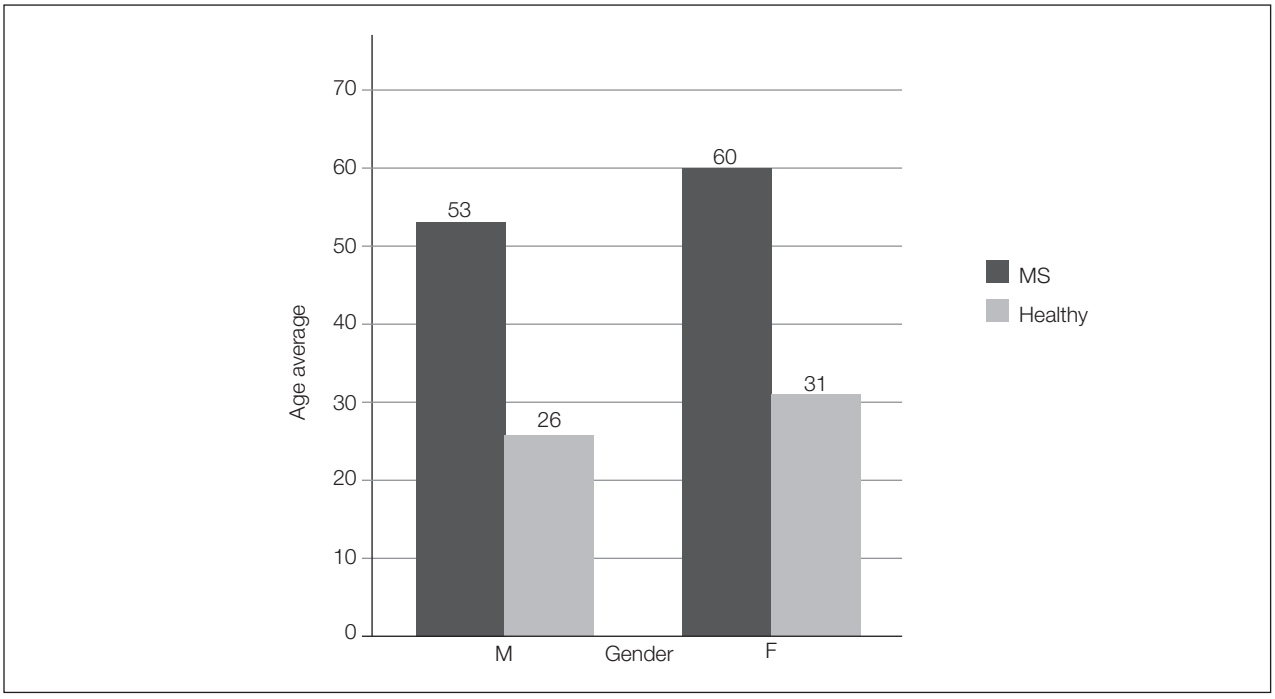


Table 2 – TPR RVIP over group

	MS group±*SD*	**Healthy group±*SD***
TPR RVIP	.36±.29	.67±.30
n	12	32
***t*-test**	***p*-value**	***df***
3.03	$p<.005$	42

Legenda. TPR = True Positive Rate; RVIP = *Rapid Visual Information Processing; df* = degree of freedom.

Table 3 – Go/No-Go RVIP over group

	MS group±*SD*	**Healthy group±*SD***
TPR Go/No-Go	.34±.25	.8±.21
n	12	32
***t*-test**	***p*-value**	***df***
6.218	*p*<.001	42

Legenda. df = degree of freedom.

Table 4 – Correlation coefficients between MSNQ-patients and CFQ

	MS group	**Healthy group**
Corr. (MSNQ-P – CFQ)	.86	.77
p-value	*p*<.001	*p*<.001

Legenda. MSNQ = *Multiple Sclerosis Neuropsychological Questionnaire;* CFQ = *Cognitive Failure Questionnaire.*

Table 5 – Correlation coefficients between TRP Go/No-Go and CFQ inattention

	Healthy group	***p*-value**
Corr. (TPR Go/No-Go – CFQ inatt.)	−.52	*p*<.005
Corr. RT avg HIT (RVIP – Go/No-Go)	.326	*p*<.05

Legenda. TPR = True Positive Rate; CFQ = *Cognitive Failure Questionnaire*; RT = response time; HIT = correct detecting; RVIP = *Rapid Visual Information Processing*.

significant, probably due to the low number of samples.

Furthermore, a positive correlation shown in Table 5 was observed between the results of the RT HIT mean between the Go/No-Go and the RVIP test, both in the MS and Healthy groups. This suggests that the use of the RVIP maintains the information acquired by the Go/No-Go and adds the information relating to the number of sequences detected which shows correct retention of the information in memory and a sufficient IPS. This result shows how Go/No-Go can be replaced by RVIP to avoid information redundancy by acquiring more detailed data.

Depression – Anxiety – Stress

Results on DASS-21 (Table 6 for mean and Table 7 for *t*-test results) show that scores do not show any statistically significant difference between the two groups (MS, Healthy). The result may support the hypothesis that IPS is lower in the MS group due to the disease (Hauser & Oksenberg, 2006).

Interaction between cognitive performance, depression and MSNQ(P-I) scores

As said before, self-perception of cognitive decline could be masked by cognitive decline itself and accepted as depression. Unless the low sample size, the result shows that MSNQ-P score is more correlated with depression compared to MSNQ-I score. The results are merely indicative (see Table 8) considering the high *p*-value probably due to the low sample size.

Table 6 – Average scores on DASS-21 dimensions

	Depression±*SD*	**Anxiety±*SD***	**Stress±*SD***
Healthy	14.9±10.5	9.06±7.38	20.3±9.87
MS	14.2±12.7	7.67±9.14	14.3±12.1

Table 7 – *t*-test on DASS-21 dimensions

***t*-test Depression**	***p*-value**	***df***
.161	*p*>.05	42
***t*-test Anxiety**	***p*-value**	***df***
.523	*p*>.05	42
***t*-test Stress**	***p*-value**	***df***
1.681	*p*>.05	42

Legenda. df = degree of freedom.

Table 8 – Correlation between MSNQ scores and Depression score

	Depression (DASS-21)	*p*-value
MSNQ-P score	.598	*p*>.05
MSNQ-I score	.362	*p*>.05

Legenda. MSNQ = *Multiple Sclerosis Neuropsychological Questionnaire.*

Conversely, a higher correlation between performance at cognitive tests (RT and HIT, FA, CR, MISS for Go/No-Go and RVIP) with MSNQ-I compared to MSNQ-P scores are expected, but no differences were found in this data.

Logistic regression

The logit model was built using as an independent variable the MS diagnosis (0 = Healthy Group, 1 = MS Group) and as a dependent variable the TPR RVIP. The result shows that the model can detect a Healthy person from MS person with a .844 specificity score and a .705 precision score, as shown in Table 10, Table 11 and the Area Under the Curve (AUC) of the model in Figure 4. Figure 5 it is shown the probability of an MS diagnosis given the empirical value (round black dot), and the theoretical curve (black line). Parameters shown in Table 9 and the general equation of the logit model are the following:

$$P(x) = \frac{1}{1 + e^{-(\beta_0 + \beta_1 x)}}$$

After training the model, the parameters estimate were shown in Table 9 (in this model Healthy group is the reference). As a consequence, the real equation after replacement of the β_0 and β_1 terms becomes:

$$P(x) = \frac{1}{1 + e^{-(0{,}6 - 3{,}03x)}}$$

CONCLUSION

This preliminary work shows how a web-based assessment of some cognitive domains is possible, which could be useful if carried out constantly and with a higher frequency. The combination of remote assessments with in-person assessments can help the clinician to understand the progression of the disease and adapt the therapy. Moreover, continuous data acquisition can be useful to link data of visible injuries acquired with medical imaging techniques with cognitive performance (Sperling et al., 2001). Furthermore, a remote evaluation can be useful to reduce any bias due to the clinical environment and reduce the stress due to travel in people with motor disabilities. Nevertheless, the domestic environment should be checked before the assessment to guarantee the absence of distracting stimuli, as well as internet connection stability and the quality of the

Table 9 – The estimated parameters of logit model

Predictor	Estimate	*p*-value
Intercept (β_0)	.6	.326
Beta (β_1)	−3.03	.009

Table 10 – Confusion matrix of logit model

Classification Table				
		Predict		
		Healthy	**MS**	
Observ	**Healthy**	27	5	84.4%
	MS	8	4	33.3%

Table 11 – Metrics of the logit model

Precision	Specificity	Sensitivity	AUC
.705	.844	.364	.795

Legenda. AUC = Area Under the Curve.

Figure 4 – AUC curve plot

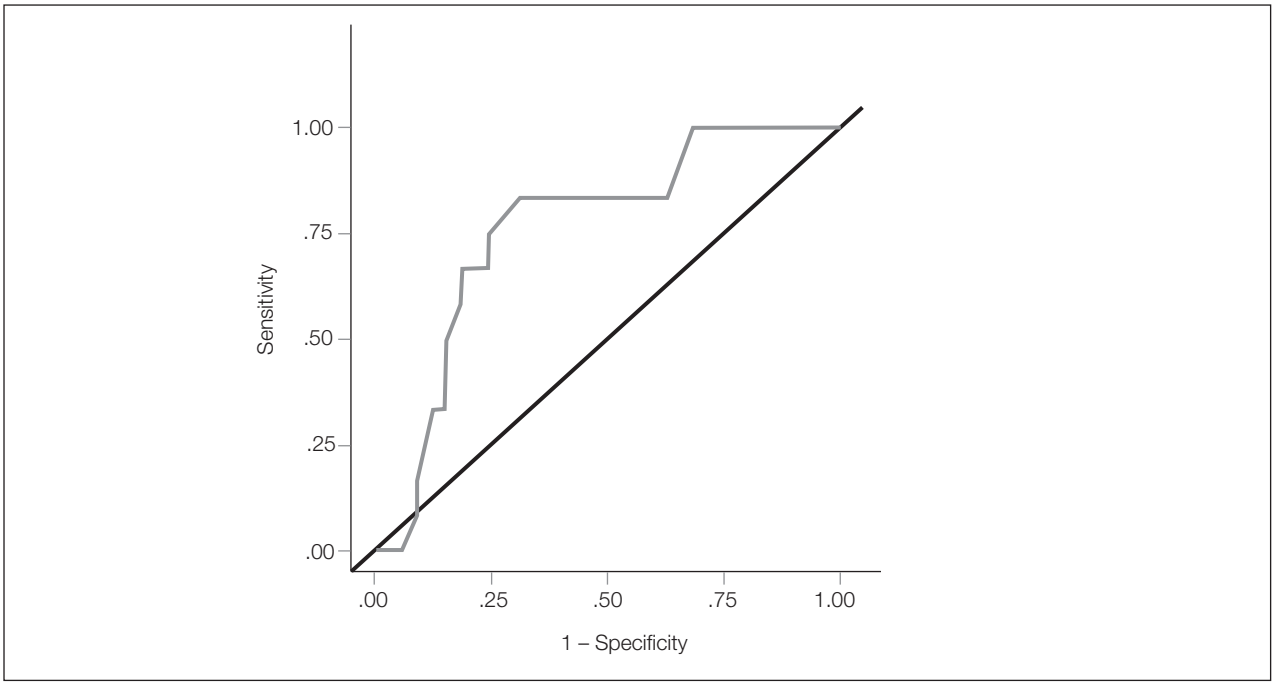
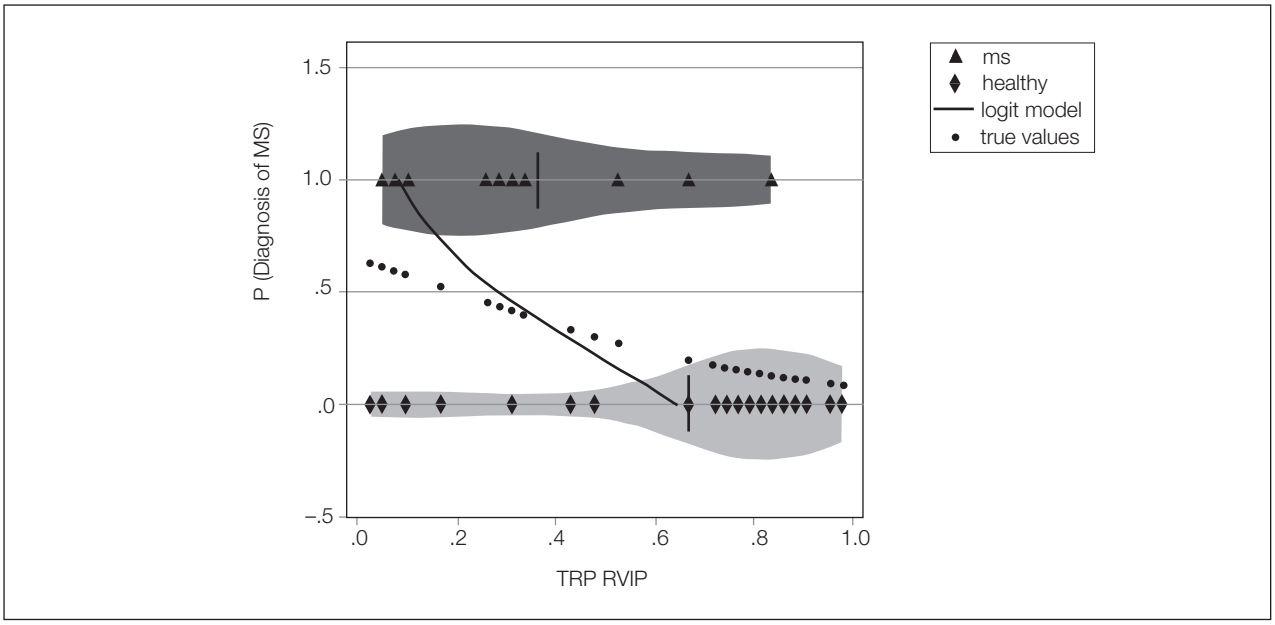


Figure 5 – Logit model on violin distribution



Legenda. Grey and light grey dots represent the empirical value of TRP RVIP with probability equal to 1 or 0; round black dots represent the probability of empirical value after computing the probability with Equation 4; the black line represents the model based on Equation 4.

device, as shown in (Rogers et al., 2022). The data shown are promising even if affected by the low sample size and the high age difference that can affect the result due to physiological cognitive deterioration (Eckert et al., 2010), as well as how the gender could influence the results (Roivainen, 2011). It could be interesting to build a mediation/moderation model to better understand the interaction between age, gender, cognitive performance and illness presence/absence. Another limitation of this work was the absence of a measurable difference between the in-person and remote assessment of the same group, due to Italian law on Covid-19. Furthermore, future studies will include the assessment of digital skills, also including questionnaires that investigate the propensity of patients to be part of telemedicine pathway (Toscano et al., 2022). Moreover, this type of assessment can be framed in telemonitoring interaction, integrating traditional health-care services (Gallo et al., 2022). This is needed to exclude some interactions and confounding factors between age, gender, digital skills and cognitive impairments due to MS. In addition, a future remote assessment will include an evaluation of the usability of the platform, to exclude some difficulties due to technical problems. Moreover, future research should acquire several measures on the same subject performing a within study to analyze the trend of performance in function of time going beyond of normative population and compute better the IPS parameters increasing the signal-to-noise ratio. Future studies should consider larger samples to validate these conclusions and, using a computer vision algorithm for image segmentation (Placidi, Cinque, Polsinelli, Splendiani & Tommasino, 2019), link the performance of cognitive measurement to the newest plaques and their morphological and topographical proprieties, to improve knowledge of cognitive functions and the cognitive correlates of MS. Moreover, it could be useful to reduce the invasive exams needs to understand the course of the disease. Finally, it could be useful to perform both between and within study design, to find personal variation patterns (over her/his baseline) on some specific cognitive domain. The within part of the research could be useful to estimate the self-perception of the cognitive impairments, with caregiver information.

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References

BARCELLOS, L.F., BELLESIS, K.H., SHEN, L., SHAO, X., CHINN, T., FRNDAK, S., DRAKE, A., BAKSHI, N., MARCUS, J., SCHAEFER, C. et al. (2018). Remote assessment of verbal memory in ms patients using the california verbal learning test. *Multiple Sclerosis Journal*, *24* (3), 354–357.

BARCELLOS, L.F., HORTON, M., SHAO, X., BELLESIS, K.H., CHINN, T., WAUBANT, E., BAKSHI, N., MARCUS, J., BENEDICT, R.H. & SCHAEFER, C. (2021). A validation study for remote testing of cognitive function in multiple sclerosis. *Multiple Sclerosis Journal*, *27* (5), 795–798.

BECK, A.T., EPSTEIN, N., BROWN, G. & STEER, R. (1993). Beck anxiety inventory. *Journal of Consulting and Clinical Psychology*.

BECK, A.T., STEER, R.A. & BROWN, G. (1996). Beck Depression Inventory – II. *Psychological assessment*.

BENEDICT, R.H. (1997). *Brief visuospatial memory test – revised*.

BENEDICT, R.H., AMATO, M.P., BORINGA, J., BROCHET, B., FOLEY, F., FREDRIKSON, S., HAMALAINEN, P., HARTUNG, H., KRUPP, L., PENNER, I. et al. (2012). Brief international cognitive assessment for ms (bicams): International standards for validation. *BMC Neurology*, *12* (1), 1–7.

BENEDICT, R.H., COOKFAIR, D., GAVETT, R., GUNTHER, M., MUNSCHAUER, F., GARG, N. & WEINSTOCK-GUTTMAN, B. (2006). Validity of the minimal assessment of cognitive function in multiple sclerosis (macfims). *Journal of the International Neuropsychological Society*, *12* (4), 549–558.

BENEDICT, R.H., MUNSCHAUER, F., LINN, R., MILLER, C., MURPHY, E., FOLEY, F. & JACOBS, L. (2003). Screening for multiple sclerosis cognitive impairment using a self- administered 15-item questionnaire. *Multiple Sclerosis Journal*, *9* (1), 95–101.

BOTTESI, G., GHISI, G., MARTA, CONFORTI, E., MELLI, G. & SICA, C. (2015). The Italian version of the Depression Anxiety Stress Scales – 21: Factor structure and psychometric properties on community and clinical samples. *Comprehensive Psychiatry*, *60*, 170–181.

BROADBENT, D.E., COOPER, P.F., FITZGERALD, P. & PARKES, K.R. (1982). The Cognitive Failures Questionnaire (CFQ) and its correlates. *British Journal of Clinical Psychology*, *21* (1), 1–16.

BROWNLEE, W.J., HARDY, T A., FAZEKAS, F. & MILLER, D.H. (2017). Diagnosis of multiple sclerosis: Progress and challenges. *The Lancet*, *389* (10076), 1336–1346.

CANTAB, C.C. (2016). *Cognitive assessment software*. Cambridge Cognition: Cambridge, UK.

CHIARAVALLOTI, N.D. & DeLUCA, J. (2008). Cognitive impairment in multiple sclerosis. *The Lancet Neurology*, *7* (12), 1139–1151.

COMPSTON, A. & COLES, A. (2008). Multiple sclerosis. *The Lancet*, (372), 1502–1517.

DELIS, D.C., KRAMER, J.H., KAPLAN, E. & OBER, B.A. (1987). California Verbal Learning Test. *Assessment*.

DONDERS, F.C. (1969). On the speed of mental processes. *Acta Psychologica*, *30*, 412–431.

ECKERT, M.A., KEREN, N.I., ROBERTS, D.R., CALHOUN, V.D. & HARRIS, K.C. (2010). Age-related changes in processing speed: Unique contributions of cerebellar and prefrontal cortex. *Frontiers in Human Neuroscience*, *10*.

GALLO, P., BATTAGLIA, M., AMATO, M., BERTOLOTTO, A., FILIPPI, M., GASPERINI, C., GHIRARDI, A., PATTI, F., SERASCHI, C., TEDESCHI, G., TOZZI, V., TROJANO, M., URSILLO, P., ABBRUZZESE, M., COSENTINO, M. & MARVULLI, M. (a cura di) (2022). *Agenas promuove PDTA per la sclerosi multipla: Indicazioni per la creazione delle reti di assistenza*. Agenzia Nazionale per i Servizi Sanitari Regionali.

HAUSER, S.L. & OKSENBERG, J.R. (2006). The neurobiology of multiple sclerosis: Genes, inflammation, and neurodegeneration. *Neuron*, *52* (1), 61–76.

HENRY, J.D. & CRAWFORD, J.R. (2005). The short-form version of the Depression Anxiety Stress Scales (DASS-21): Construct validity and normative data in a large non- clinical sample. *British Journal of Clinical Psychology*, *44* (2), 227–239.

JAMOVI PROJECT, T. (2021). *Jamovi (version 1.6)*. Computer Software.

JONES, G., SAHAKIAN, B., LEVY, R., WARBURTON, D.M. & GRAY, J. (1992). Effects of acute subcutaneous nicotine on attention, information processing and short-term memory in Alzheimer's disease. *Psychopharmacology*, *108* (4), 485–494.

KURTZKE, J.F. (1983). Rating neurologic impairment in multiple sclerosis: An Expanded Disability Status Scale (EDSS). *Neurology*, *33* (11), 1444–1444.

LANGDON, D., AMATO, M., BORINGA, J., BROCHET, B., FOLEY, F., FREDRIKSON, S., HÄMÄLÄINEN, P., HARTUNG, H., KRUPP, L., PENNER, I. et al. (2012). Recommendations for a brief international cognitive assessment for multiple sclerosis (bicams). *Multiple Sclerosis Journal*, *18* (6), 891–898.

LASSMANN, H. (2018). Multiple sclerosis pathology. *Cold Spring Harbor Perspectives in Medicine*, *8* (3), a028936.

LOVIBOND, P.F. & LOVIBOND, S.H. (1995). The structure of negative emotional states: Comparison of the Depression Anxiety Stress Scales (DASS) with the Beck Depression and Anxiety Inventories. *Behaviour Research and Therapy*, *33* (3), 335–343.

MACIAS ISLAS, M.A. & CIAMPI, E. (2019). Assessment and impact of cognitive impairment in multiple sclerosis: An overview. *Biomedicines*, *7* (1), 22.

MIGLIORE, S., LANDI, D., PROIETTI, F., D'AURIZIO, G., SQUITIERI, F., MATALUNI, G., NICOLETTI, C.G., CURCIO, G. & MARFIA, G.A. (2021). Validity of the Italian multiple sclerosis neuropsychological screening questionnaire. *Neurological Sciences*, *42* (11), 4583–4589.

O'BRIEN, A., GAUDINO-GOERING, E., SHAWARYN, M., KOMAROFF, E., MOORE, N.B., & DeLUCA, J. (2007). Relationship of the Multiple Sclerosis Neuropsychological Questionnaire (MSNQ) to functional, emotional, and neuropsychological outcomes. *Archives of Clinical Neuropsychology*, *22* (8), 933–948.

PLACIDI, G., CINQUE, L., POLSINELLI, M., SPLENDIANI, A. & TOMMASINO, E. (2019). Automatic framework for multiple sclerosis follow-up by magnetic resonance imaging for reducing contrast agents. *International Conference on Image Analysis and Processing*, 367–378.

RAO, S.M., LEO, G.J., BERNARDIN, L. & UNVERZAGT, F. (1991). Cognitive dysfunction in multiple sclerosis.: I. frequency, patterns, and prediction. *Neurology*, *41*(5), 685–691.

REEVES, D.L., WINTER, K.P., BLEIBERG, J. & KANE, R.L. (2007). Anam® genogram: Historical perspectives, description, and current endeavors. *Archives of Clinical Neuropsychology*, *22* (Suppl 1), S15–S37.

REITAN, R.M. & WOLFSON, D. (1992). *Neuropsychological evaluation of older children*. Neuropsychology Press.

ROGERS, F., BANE, E., DWYER, C.P., ALVAREZ-IGLESIAS, A., JOYCE, R.A. & HYNES, S.M. (2022). Remote administration of bicams measures and the trail-making test to assess cognitive impairment in multiple sclerosis. *Neuropsychological Rehabilitation*, 1–24.

ROIVAINEN, E. (2011). Gender differences in processing speed: A review of recent research. *Learning and Individual differences*, *21* (2), 145–149.

SCHOENBERG, M., LANGE, R., MARSH, P., SAKLOFSKE, D., KREUTZER, J., DELUCA, J. & CAPLAN, B. (2011). Premorbid intelligence. *Encyclopedia of Clinical Neuropsychology*, 2004–2010.

SETTLE, J.R., ROBINSON, S.A., KANE, R., MALONI, H.W. & WALLIN, M.T. (2015). Remote cognitive assessments for patients with multiple sclerosis: A feasibility study. *Multiple Sclerosis Journal*, *21* (8), 1072–1079.

SMITH, A. (1973). *Symbol Digit Modalities Test*. Los Angeles: Western Psychological Services.

SMITH, A. (1982). *Symbol Digit Modalities Test (SDMT). Manual (revised)*. Los Angeles: Western Psychological Services.

SPERLING, R.A., GUTTMANN, C.R., HOHOL, M.J., WARFIELD, S.K., JAKAB, M., PARENTE, M., DIAMOND, E. L., DAFFNER, K.R., OLEK, M.J., ORAV, E.J. et al. (2001). Regional magnetic resonance imaging lesion burden and cognitive function in multiple sclerosis: A longitudinal study. *Archives of Neurology*, *58* (1), 115–121.

STOET, G. (2010). Psytoolkit: A software package for programming psychological experiments using linux. *Behavior Research Methods*, *42* (4), 1096–1104.

STOET, G. (2017). Psytoolkit: A novel web-based method for running online questionnaires and reaction-time experiments. *Teaching of Psychology*, *44* (1), 24–31.

STRATTA, P., RINALDI, O., DANELUZZO, E. & ROSSI, A. (2006). The use of the Italian version of the Cognitive Failures Questionnaire (CFQ) in a sample of undergraduate students: A validation study. *Rivista di Psichiatria*, *41* (4), 260.

TALLAND, G.A. (1966). Effects of alcohol on performance in continuous attention tasks. *Psychosomatic Medicine*, *28* (4), 596–604.

TOMBAUGH, T.N. & McINTYRE, N.J. (1992). The mini-mental state examination: A comprehensive review. *Journal of the American Geriatrics Society*, *40* (9), 922–935.

TOSCANO, S., PATTI, F., CHISARI, C.G., ARENA, S., FINOCCHIARO, C., SCHILLACI, C.E. & ZAPPIA, M. (2022). Reliability of televisits for patients with mild relapsing–remitting multiple sclerosis in the covid-19 era. *Neurological Sciences*, *43* (4), 2253–2261.

VAN ROSSUM, G. & DRAKE Jr, F.L. (1995). *Python reference manual*. Amsterdam: Centrum voor Wiskunde en Informatica.

WOJCIK, C.M., BEIER, M., COSTELLO, K., DELUCA, J., FEINSTEIN, A., GOVEROVER, Y., GUDESBLATT, M., JAWORSKI III, M., KALB, R., KOSTICH, L. et al. (2019). Computerized neuropsychological assessment devices in multiple sclerosis: A systematic review. *Multiple Sclerosis Journal*, *25* (14), 1848–1869.

ZIEMSSEN, T., DE STEFANO, N., SORMANI, M.P., VAN WIJMEERSCH, B., WIENDL, H. & KIESEIER, B.C. (2015). Optimizing therapy early in multiple sclerosis: An evidence-based view. *Multiple sclerosis and related disorders*, *4* (5), 460–469.