U.PORTO

MESTRADO INTEGRADO EM PSICOLOGIA
PSICOLOGIA CLÍNICA E DA SAÚDE

Neuromyelitis Optica Spectrum Disorder: Contributions for a neuropsychological profile

Catarina Beatriz Pacheco Lopes

M

2021

Universidade do Porto
Faculdade de Psicologia e de Ciências da Educação

NEUROMYELITIS OPTICA SPECTRUM DISORDER: CONTRIBUTIONS FOR A NEUROPSYCHOLOGICAL PROFILE

Catarina Beatriz Pacheco Lopes

julho, 2021

Dissertação apresentada no Mestrado Integrado de Psicologia, Faculdade de Psicologia e de Ciências da Educação da Universidade do Porto, orientada pela Professora Doutora **Selene G. Vicente** (FPCEUP).

AVISOS LEGAIS

O conteúdo desta dissertação reflete as perspetivas, o trabalho e as interpretações do autor no momento da sua entrega. Esta dissertação pode conter incorreções, tanto conceptuais como metodológicas, que podem ter sido identificadas em momento posterior ao da sua entrega. Por conseguinte, qualquer utilização dos seus conteúdos deve ser exercida com cautela.

Ao entregar esta dissertação, o autor declara que a mesma é resultante do seu próprio trabalho, contém contributos originais e são reconhecidas todas as fontes utilizadas, encontrando-se tais fontes devidamente citadas no corpo do texto e identificadas na secção de referências. O autor declara, ainda, que não divulga na presente dissertação quaisquer conteúdos cuja reprodução esteja vedada por direitos de autor ou de propriedade industrial.

Resumo

Objetivo: O espetro da Neuromielite Ótica (NMO) é uma doença rara e a investigação relativa ao funcionamento cognitivo é escassa e não consensual. O objetivo principal é contribuir para a caracterização de um perfil neuropsicológico através da comparação de doentes com NMO, com doentes com Esclerose Múltipla (EM) e controlos saudáveis (CS) em medidas cognitivas, psicológicas e clínicas.

Método: Um total de 64 participantes participaram no estudo: 19 NMO, 27 EM e 18 CS. O protocolo neuropsicológico incluiu a versão portuguesa do Montreal Cognitive Assessment (MoCA), do Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) e da Fluência Verbal (Fonémica e Semântica). Adicionalmente, foram usadas a Hospital Anxiety and Depression Scale (HADS) e a Expanded Disability Status Scale (EDSS) para os grupos clínicos. Os dados dos NMO e EM foram recolhidos retrospetivamente. Os CS foram recrutados na comunidade.

Resultados: Os NMO apresentaram um desempenho cognitivo significativamente inferior ao dos CS, na velocidade de processamento de informação, concentração, processamento da linguagem e algumas funções executivas, nomeadamente a flexibilidade cognitiva, atenção sustentada e dividida. No entanto, não se verificaram diferenças entre os NMO e EM. Encontraram-se três preditores da disfunção cognitiva (critérios da BICAMS) na NMO e na EM – depressão, duração da doença e nível de incapacidade.

Conclusão: O perfil neuropsicológico da NMO encontrado neste estudo é concordante com dados descritos na literatura. Os preditores associados à disfunção cognitiva na NMO e na EM constituem um dado importante para investigação futura e para orientar a intervenção psicológica e cognitiva.

Palavras-chave: Neuromielite Ótica, Esclerose Múltipla, Cognição, Sintomatologia Psiquiátrica

Abstract

Objectives: Neuromyelitis Optica Spectrum Disorder (NMOSD) is a rare disease and a scarce number of studies regarding cognitive functioning is available in literature. Our main focus is to contribute to the characterization of the neuropsychological profile of NMOSD by comparing them with Multiple Sclerosis (MS) patients and Healthy Control (HC) in cognitive, psychological and clinical measures.

Method: A total of 64 participants were included in this study: 19 NMOSD, 27 MS, and 18 healthy controls (HC). The neuropsychological protocol included the Portuguese version of Montreal Cognitive Assessment (MoCA), the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) and Verbal Fluency (Phonemic and Semantic). We also used the Hospital Anxiety and Depression Scale (HADS) and the Expanded Disability Status Scale (EDSS) for clinical groups. NMOSD and MS cognitive data were mostly collected retrospectively. HC were volunteers recruited from the community.

Results: NMOSD patients had significant lower cognitive performance when compared to HC mainly in information processing speed, concentration, language processing and in some executive functions such as cognitive flexibility, sustained and divided attention. However, no significant differences were observed between NMOSD and MS patients. We found three predictors of cognitive impairment for NMOSD and MS – depression, disease duration and the level of disability.

Conclusion: The neuropsychological profile found in our study for NMOSD is consistent with the most consensual literature. Information regarding the predictors of cognitive impairment in both diseases and their different associations are important for future research and for guiding interventions more suitable for their psychological and cognitive needs.

Keywords: Neuromyielitis Optica, Multiple Sclerosis, Cognition, Psychiatric Symptoms

Introduction

Neuromyelitis Optica Spectrum Disorder (NMOSD) is a rare, idiopathic, immune-mediated inflammatory disease of the central nervous system (CNS), targeting mainly the spinal cord, optic nerves and brainstem (Narayan et al., 2018).

The prevalence of this condition varies through different populations worldwide, especially between races. For instance, the prevalence within white population is estimated to be 1/100,000, but among east Asians the prevalence rises to 3.5/100,000. Nonetheless, the higher prevalence of NMOSD occurs among black people with a ratio of 10/100,000 (Hor et al., 2020). It occurs mostly in women (about nine times higher prevalence than men) and may be partially explained by the higher susceptibility to autoimmune diseases due to hormonal reasons, however, further research is needed (Huda et al., 2019; Wingerchuk et al., 2007). The average age of onset is 40 years old, with a range from 3 to 80 years old (Weinshenker & Wingerchuk, 2017), with the majority of the cases being sporadic rather than familial, resulting in a more complex genetic condition (Matiello et al., 2010).

Clinical manifestations succeeding the recurrent inflammatory attacks include severe optic neuritis (ON) and longitudinally extensive transverse myelitis (TM), relapsing or monophasic, acute brainstem syndrome, acute diencephalic syndrome and cerebral syndrome with typical brain lesions (Czarnecka et al., 2020; Yabalak et al., 2020). The worst prognosis depends on the number of relapses within the first 2 years of the disease, the severity of the first attack, and having other comorbidities such as systemic lupus erythematosus or a related non-organ-specific autoimmune disorder or autoantibodies. Without an early diagnose and adequate treatment, it may lead to blindness, tetraplegia and death (Huda et al., 2019; Meng et al., 2016; Wingerchuk et al., 2007).

For a long period of time, NMOSD was misdiagnosed as a variant of Multiple Sclerosis (MS) because of their similar manifestations. However, since 2004, continuous research discovered specific biomarkers with high specification for NMOSD (> 90%), leading to the possibility of a distinct pathophysiological condition.

It begun with the discovery of a specific antibody serum (NMO-IgG) only present in patients diagnosed with atypical forms of MS but not in the classical MS patients (Lennon et al., 2004). With this finding, further research were set in motion to found the autoantigen bonded to the NMO-IgG – the Aquaporin-4 (AQP4), a water channel protein

present in many organs, but, in this disease, there was only immunoreactivity in the AQP4 present in CNS (in the astrocyte processes at the blood-brain barrier), kidney and gastric mucosa (Lennon et al., 2005). This autoantigen became the first biomarker for NMOSD.

The first diagnostic criteria was proposed by Wingerchuck and colleagues (1999) based on what had been reported, initially by Eugene Devic (19th century), and later by Asian clinicians as opticospinal MS – severe optic neuritis, myelitis and no other CNS disease. Regardless, a new criterion was proposed in 2006 by the same group due to new clinical manifestations, and laboratory, neuroimaging and immunopathologic findings, such as AQP4 immunoreactivity. This revision included the presence of aquaporin-4 seropositivity (AQP4-IgG+) as an important criteria, joining the previous requirements (Fujihara, 2019; Wingerchuk et al., 2006).

This new criterion was an improvement in discriminating MS from NMO, failing only in the introduction of the NMO as a spectrum, which occurred in 2007 once it was made clear that some patients showed atypical or incomplete clinical behavior, treatment and pathology or did not completely fulfill the previous diagnose criteria such as the seropositivity for AQP4 (Bennett, 2016). Moreover, the existence of seronegative AQP4 (AQP4-) patients was controversial since their diagnose could not rely on the biomarker known at the time, but only on their clinical manifestations (myelitis and spinal cord lesions) (Jarius et al., 2012).

When the focus turned to the differences between the clinical manifestation of AQP4+ and AQP4-, a new potential biomarker was found in a subset of the seronegative cases. Based on a previous study a group of researchers showed for the first time the actual presence of myelin oligodendrocyte glycoprotein (MOG) immune response in these patients, amplifying the spectrum to a more heterogenous condition (Haase & Schmidt, 2001; Mader et al., 2011).

The continuous research embracing the whole spectrum, led to a new revision of the diagnostic criteria for NMOSD by the International Panel for NMO Diagnosis (IPND). It happened in 2015 and embodied other clinical manifestations besides the classical ones: area postrema syndrome, acute brainstem syndrome, acute diencephalic syndrome, and symptomatic cerebral syndrome (Wingerchuk et al., 2015).

In addition to the physical symptoms previously mentioned, the damaging of brain areas in NMOSD may also originate cognitive impairments. Regardless, the studies conducted to objectively measure these deficits are scarce.

Recently, Czarnecka and colleagues (2020) carried out a systematic review of the literature which included 21 studies. They concluded that most of the research showed that approximately 29-67% of the NMOSD patients had cognitive impairments. However, some neuropsychological and neuroimaging studies included in this review revealed lower levels of impairment when compared to healthy controls and patients with MS (Kim et al., 2016). Despite the small number of studies and lack of agreement, most of them have reported deficits in attention, memory, processing speed, verbal fluency, verbal learning and some executive functions (cognitive flexibility, working memory and attention) (Czarnecka & Oset, 2020). These cognitive impairments may be related to reductions in white matter volume and integrity, even though there is no concrete data regarding this (Meng et al., 2016).

The heterogeneity of the results is partly attributed to methodological issues such as differences in the sample characteristics (e.g., size, sex, age, education, psychiatric disorders, ethnic background, antigen status), and in the neuropsychological assessment batteries used in each study. Depression also plays a central role, as a significant association was found between higher levels of depression and poor cognitive function, specifically in information processing speed, memory, and attention in NMOSD patients after acute relapses. Oppositely, anxiety manifestations appear to be worse in the earlier course of the disease due to the uncertainty caused by the condition (He et al., 2011; Meng et al., 2016; Miao et al., 2017).

Despite being two immune-mediated diseases, NMOSD contrasts from MS in some aspects. Compared to MS (age of onset around 29 years), NMOSD has a later onset. However, in the first 5 years of the disease, 50% of NMOSD patients with frequent and severe relapses become blind in one or both eyes, since they do not recover completely from it, following a course of cumulative disability (Wingerchuk et al., 2007). Nonetheless, one similarity between the two conditions is the higher prevalence in females, since in MS the ratio is 3.5-1, and this prevalence has been continuously increasing (Ahlgren et al., 2011).

The differences between the two conditions extend to the pathomecanisms of the inflammatory process, course, and progression of the disease. The primary cause of lesions in NMOSD is astrocyte impairments and the incapacitation is a result of the severe acute attacks, with rare cases of secondary progression, whereas the primary cause of lesions in MS is the demyelination and the permanent disability is a consequence of the secondary

progressive phase of the disease (Blanc et al., 2008; De Seze et al., 2016; Misu et al., 2007; Wingerchuk et al., 2007).

Only two studies aimed to compare the cognitive performances between NMOSD and MS have been carried, but the results are not consensual. Blanc and colleagues (2008) did not find differences between NMOSD and MS. However, more recently, Kim and colleagues (2016) showed different patterns of impairment between them: MS has greater deficits in verbal learning and memory domains whereas NMOSD has greater deficits in attention and information processing speed.

The NMOSD condition remains associated with a lot of open questions due to its complexity and also for being a relatively new area of interest, especially in the study of the cognitive domain. Even though not all studies in the field report cognitive impairments, the fact that some of them point out specific deficits, reveals the need for more research to clarify and create consensual information for diagnose and posterior intervention.

Bearing this in mind, the present study aims to contribute for a characterization of the neuropsychological profile of NMOSD, since, to date, there are only 6 studies comparing NMOSD patients with other demyelinating diseases (MS patients) and healthy controls. Moreover, this comparison will contemplate psychiatric and clinical variables such as anxiety, depression, duration of the disease and level of disability between the two diseases. The comparisons will be made by using a brief neuropsychological battery for MS to verify if there is any differences between the two demyelinating conditions.

1. Method

1.1 Participants

A total of 64 participants were included in this study: 19 NMOSD, 27 MS, and 18 healthy controls (HC). One HC was removed from the analyses. The mean age of the participants was 48.62 years (*SD* = 16.24), they had approximatly 10 years of education (*M* = 9.52, *SD* = 5.11) and the majority of the sample was composed by females (90.5%) taking into account that the groups were matched by sex given the characteristics of the NMOSD patients.

NMOSD and MS patients were mostly retrospectively selected from a specialized clinic unit for demyelinating diseases at the University Hospital do Porto (Centro

Hospitalar Universitário São João do Porto, CHUSJ). The NMOSD patients had their baseline for neurological and neuropsychological assessment during 2019, and MS patients between 2017 and 2019. The Ethical approval for the retrospective analysis of the patient´s clinical information was obtained from the Ethics Committee of the CHUSJ (CHUSJ, nº 09/2021). The study was conducted in agreement with the Helsinki Declaration. Written informed consent was obtained for all HC participants.

Patients were included in the study if they had: (1) criteria for MNOSD or MS confirmed by a neurologist. They were diagnosed as NMOSD according to the Wingerchucks' criteria (2015) and as MS according to 2017 Revised - McDonalds' criteria (Thompson et al., 2018); (2) available information regarding the MoCA, BICAMS subtests, Verbal Fluency (phonemic and semantic), HADS and EDSS; (3) 18 years old or more; (4) absence of major psychiatric illness, or other diseases that could explain the cognitive impairment or could interfere with cognitive performance; (5) having a score of 7 or lower in the Expanded Disability Status Scale (EDSS) since a higher severity score could compromise the realization of the neuropsychological assessment; and (6) the MS patients were matched by age, sex, and education with the NMOSD patients.

The presence of anxiety and depressive symptoms was not an exclusion criterion, given its linked to these neuropathological conditions. However, in general, the magnitude of these symptoms was similar across groups, see Table 1.

The NMOSD group (n = 19) was composed by 17 female patients (90%), with a mean age around 50 years old (M = 50.32, SD = 16.82) and approximately 9 years of education (M = 8.79, SD = 5.4, see Table 1). The number of acute relapses varied from 1 to 4 (M = 2, SD = 1.18) and the most frequent first clinical manifestation was optic neuritis (n = 11) followed by extensive transverse myelitis (n = 7). One patient had acute brainstem syndrome, even though some of them had other clinical manifestations along the progression of the condition. Another patient also had Lupus (immune-mediated disease). Regarding the NMOSD phenotype, 7 patients were seropositive for AQP4 (AQP4+), 7 were seronegative for AQP4 and MOG (AQP4-), and 4 patients were seronegative for AQP4, but seropositive for MOG (MOG). One patient's phenotype was unknown to the time of the evaluation due to some uncertainty regarding the laboratory findings. At the time of testing, their therapeutic for the symptoms control included immunosuppressors and immunomodulators such as Rituximab and Azathioprine.

Table 1.

Demographic and neuropsychological characteristics of Neuromyelitis Optica Spectrum Disorder (NMOSD), Multiple Sclerosis (MS) and Healthy Controls (HC) participants.

	NMOSD (n = 19)		MS (n = 27)		HC (n = 17)		*p*
	M *(SD)*	Range	M *(SD)*	Range	M *(SD)*	Range	
Sex (% male:female)	11:90	-----	7:93	-----	11:88	-----	.916
Age (years)	50.32 (16.82)	19-73	47.30 (16.09)	19-69	48.82 (16.61)	19-76	.923
Education (years)	8.79 (5.4)	4-17	9.78 (5.12)	4-17	9.94 (4.97)	4-17	.513
HADS							
Depression	6.86 (4.26)	1-16	5.89 (3.00)	1-11	3.94 (2.90)	0-10	.056
Anxiety	8.71 (4.68)	1-16	9.89 (3.14)	6-17	8.18 (4.83)	1-15	.479
EDSS	2.57 (1.36)	1-5	2.02 (1.48)	0-6	-----	-----	.270
Disease Duration (years)	5.22 (4.17)	1-14	12.68 (8.83)	1-29	-----	-----	**.001**
Number of relapses	2 (1.18)	1-4	-----	-----	-----	------	-----

Note. HADS, Hospital Anxiety and Depression Scale; HADS-D maximum score is 21; HADS-A maximum score is 21; EDSS, Expanded Disability Status Scale; EDSS maximum score is 10. All statistical analyses were considered significant at $p < .05$.

The MS group (n = 27) was composed by 25 female patients (93%), with a mean age around 47 years old (M = 47.30, SD = 16.09), and approximately 10 years of education (M = 9.78, SD = 5.12) as seen in Table 1.

HC (n = 19) were recruited in the community, and they were matched with the NMOSD and ME patients for age, sex and education (see Table 1). Fifteen were female (88%) with a mean age of, approximately, 49 years old (M = 48.82, SD = 16.61) and 10 years of education (M = 9.94, SD = 4.97). All of them were autonomous and had no known history of brain injury, neurological/psychiatric conditions, substance abuse or other conditions that could affect cognition.

All participants were European Portuguese native speakers. The three groups did not differ in the variables age, sex and level of education as illustrated in Table 1. The same pattern occurs for anxiety ($F(2, 48) = .75$, $p = .479$, $\eta 2 = .03$) and depression ($F(2, 48) = 3.06$, $p = .056$, $\eta 2 = .12$). Regarding the NMOSD and MS patients they did not differ in functional domains of the daily living activities measured by EDSS ($F(1, 35) = 1.26$, $p = .270$, $\eta 2 = .04$), but differed in the duration of the disease (number of years; $F(1, 39) = 10.83$, $p = .001$, $\eta 2 = .22$), since the MS patients have the disease for a longer period of time (M = 12.68 years, SD = 8.83) than the NMOSD (M = 5.22 years, SD = 4.17).

1.2 Materials

All participants were assessed with the same neuropsychological protocol: Global Cognition (MoCA), The Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS), Verbal Fluency (language processing and executive functions), Anxiety and Depression (HADS). The NMOSD and MS patients were also evaluated with the EDSS, a method of quantifying disability according to eight function systems. The sociodemographic and clinical data were collected through a clinical interview or obtained from patient records.

Montreal Cognitive Assessment (MoCA)

The Montreal Cognitive Assessment (MoCA) is a brief, screening test, that measures global cognition (Nasreddine et al., 2005; Portuguese version by Freitas et al., 2011). It consists in tasks that evaluate executive functions, visuospatial abilities, short-term memory, language, attention, concentration, working memory and temporal and spatial orientation. The total score is 30.

Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS)

The Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) is a reduced version of a more extended neuropsychological battery for MS, the Minimal Assessment of Cognitive Function in MS (MACFIMS; Benedict et al., 2006). The BICAMS is composed by the 3 MACFIMS tests with the higher psychometric properties of reliability and specification towards cognitive deterioration in MS patients. It takes less application time, even though it still evaluates the integrity or impairment of the most consensual cognitive domains that can deteriorate throughout the course of this demyelinating disease (Benedict et al., 2012; Oreja-Guevara et al., 2019). The BICAMS is translated and validated for Portuguese (Sousa et al., 2018).

More specifically, the first test is the *California Verbal Learning Test-II* (CVLT-II), a verbal learning and memory test, which consists of a list of 16 words. The words are read by the examiner within 5 trials, and the respondent task is to reproduce as many words as possible. The total score is the number of words evoked in the 5 trials with a maximum of 80 words evoked.

Another test is the *Brief Visuospatial Memory Test Revised* (BVMT-R) and it is designed to measure the visuospatial learning and memory by showing the individuals a matrix of six simple designs for 10 seconds and asking them to reproduce by memory what they remembered from those designs. This test has 3 trials, and the total score is based on the total score of each trial considering two criteria (1) location accuracy and (2) accuracy of each design. The maximum score is 36 points. The other test is the oral version of the *Symbol Digit Modalities Test* (SDMT), also present in others neuropsychological batteries for MS due to the ability to detect cognitive impairment over time (Nocentini et al., 2006). It examines the processing speed, the attention (divided and sustained) and concentration by showing the individuals a key-chart with two rows – one with meaningless symbols, and the second one with numbers (1-9). Each symbol has its corresponding number. The task consists of showing the participant several symbol rows and asking them to say the correspondent number for each one. The goal is to say as many numbers as possible according to the key-chart during 90s. The test score is the number of correct responses.

Verbal Fluency Test, phonemic and semantic

The Verbal Fluency Test (phonemic and semantic) is an easy and brief tool to evaluate processing speed, language and some executive functions components such as the cognitive flexibility (Cavaco et al., 2013; Vicente et al., 2021).

In the semantic component, it is asked to individual to generate as many names of animal species as they can within 1 minute. The score is made by counting the correctly named animals, without repetition nor variation in gender and number, and this specific task implies the search through conceptual or semantic memory (Baldo et al., 2006). In the other hand, the phonemic task consists in producing as many words as possible beginning with a specific letter (M, R, P, Portuguese validation by Cavaco et al., 2013) for 60 seconds each. The variations of gender and number of the same word are not accounted, whereas the repetition of the same word with the acknowledgement, from the individual, of the different meaning, as well as slang and other words from other languages generally used in Portugal are acceptable. The total score is the sum of the three letters, according to the conditions aforementioned. This task largely implies the lexical and phonologic memory (Baldo et al., 2006).

Hospital Anxiety and Depression Scale (HADS)

The Hospital Anxiety and Depression Scale (HADS) is a self-reported multiple-choice questionnaire with 14 questions, 7 regarding depression and 7 regarding anxiety (Portuguese version by Pais-Ribeiro et al., 2007). It is considered to be a reliable screening instrument for clinical significant anxiety and depression (Zigmond & Snalth, 1983). The maximum score for each subscale is 21. Normative data and cut-offs for the degree of severity for Portuguese are available (Pais-Ribeiro et al, 2007).

Expanded Disability Status Scale (EDSS)

The EDSS is a method of quantifying disability and monitoring their changes over the time and it was originally created for multiple sclerosis (Kurtzke, 1983).

The examination is made by a neurologist and the result range goes from 0 (Normal neurological exam, no disability in any Functional System) to 10 (Death due to MS). The results are based on sub-results of eight functional systems – pyramidal; cerebellar; brainstem; sensory; bowel and bladder function; visual function; cerebral functions; and other. Through 0-2.5 there is absence or mild disability, 3-5.5 there is moderate to significant disability in some functions and walking, although they are able to walk without help (e.g., from a cane). With a score higher than 6, the person needs help walking by using a cane or a wheelchair (7.5). From 8 to 10, the person is restricted to a wheelchair or to a bed, and, ultimately, dies from the disease.

1.3 Procedure

The neuropsychological protocol administration took approximately 20 minutes for each participant (HC, and for the NMOSD and MS patients which data was not collected retrospectively) in a session conducted in a single day. The order of administration of the protocol was: MoCA, BICAMS (in the order recommended: CVLT-II, BVMT-R, SDMT), Verbal Fluency (phonemic and semantic), and HADS. The EDSS was evaluated during the neurological routine appointment.

Data collection took place between February and May 2021 in the North and Center regions of Portugal (Braga, Porto and Aveiro). Each participant was tested individually, in a quiet room in two settings: (1) hospital and (2) home.

1.4 Statistical analyses

Descriptive statistics were used for sample characterization.

Comparisons between the three groups, NMOSD, MS and HC, in cognitive measures were explored with multivariate analysis of variance, MANOVAs followed by post hoc analysis attending Tukey's significance to access the effects between the groups. The values of skewness and kurtosis were always between -3 – 3, and -7 – 7, respectively (skewness, range = 0,46 - .89; kurtosis, range = .56 – 1.09), ensuring the normal distribution of the data (Kline, 2016; Marôco, 2010, 2018).

Comparisons between the three groups regarding the BVMT-R were explored with the Welch's ANOVA, once the assumption of homogeneity of variances was violated.

In terms of the NMOSD and MS patients, a multiple linear regression (enter method) was performed to examine the extent to which sociodemographic variables (age and education), disease duration, and psychiatric symptoms (depression and anxiety) influence the presence of cognitive impairment given by BICAMS criteria. Finally, correlations between the predictors found in the previous analysis and the neuropsychological performance were made using the pearson's r and spearman's r. All statistical analyses were considered significant at p <.05. Analyses were done using IBM SPSS® software (version 27).

2. Results

2.1 Comparisons between the three groups, NMOSD, MS and HC on cognitive tests

The scores obtained in the cognitive tests by the NMOSD and MS patients as well as by the HC can be seen in Table 2. The multivariate analysis of variance, MANOVA, showed a significant effect of the variable Group (NMOSD, MS and HC) in cognitive performance regarding the tests included in the model (Pillais' Trace = .32, F(10,108) = 2.09, p = .031, η2 = .16). A series of univariate ANOVAs were conducted to verify which cognitive measures significantly differed between groups. We found that the Group had a significant effect in the performance in MoCA (F(2,57) = 4.22, p = .020, η2 = .13), SDMT (F(2,57) = 3.61, p = .033, η2 = .11) and phonemic verbal fluency (F(2,57) = 7.19, p = .002,

η2 = .20). Aiming to see the comparisons specifically of these three tests across the three groups, a post-Hoc analysis was performed. The Tukeys' Test showed that there were significant differences in the performance on MoCA between NMOSD and HC (p = .018), with NMOSD patients having significantly lower results (M = 20.67, SD = 6.62) when compared to HC (M = 25.29, SD = 1.65*)* but there were no differences between NMOSD patients and MS patients (p = .107) and between HC and MS patients (p = .539) in this test. The same results were found regarding SDMT, since there were also significant differences between NMOSD and HC (p = .029), with NMOSD patients having lower scores (M = 34.89, SD = 23.34) when compared to HC (M = 51.47, DP = 10.00), but no differences were found when comparing them to MS patients (p = .629), and when comparing MS patients and HC (p = .132). Lastly, in the phonemic verbal fluency, both NMOSD and MS patients scored significantly lower (M = 22.74, SD = 14.14; M = 27.11, SD = 9.39, respectively) than HC (M = 36.37, SD = 9.00; p < .001 and p = .027, respectively), but there was no difference between NMOSD patients and MS patients (p = .335).

Table 2

Scores in MoCA, BICAMS (CVLT, BVMT-R and SDMT), and Verbal Fluency (Phonemic and Semantic) for NMOSD and MS patients as well as HC.

	NMOSD (n=19)	MS (n=27)	HC (n=17)	*p*	Post Hoc comparisons
	M *(SD)* Range	M *(SD)* Range	M *(SD)* Range		
Cognitive tests					
MoCA	20.67 (6.62) 9-30	23.69 (4.54) 10-30	25.29 (1.65) 22-28	**.020**	HC > NMOSD; MS = NMOSD HC = MS
BICAMS					
CVLT	47.47 (12.05) 21-69	50.37 (12.29) 24-72	48.47 (11.00) 30-71	.650	----------
BVMT-R	17.16 (12.69) 0-34	17.52 (10.01) 1-32	22.59 (5.46) 14-34	.060	----------
SDMT	34.89 (23.34) 0-68	40.07 (17.35) 9-72	51.47 (10.00) 39-72	**.033**	HC > NMOSD; MS = NMOSD HC = MS
Verbal Fluency					
Phonemic	22.74 (14.14) 4-49	27.11 (9.39) 13-49	36.37 (9.00) 22-56	**.002**	HC > NMOSD; MS = NMOSD HC > MS
Semantic	13.58 (5.35) 3-22	15.15 (5.15) 7-24	17.38 (3.52) 10-25	.092	---------

Note. MoCA, Montreal Cognitive Assessment; BICAMS, Brief International Cognitive Assessment for Multiple Sclerosis; CVLT, California Verbal Learning Test-II; BVMT-R, Brief Visuospatial Memory Test Revised; SDMT, Symbol Digit Modalities Test; HADS, Hospital Anxiety and Depression Scale; NMOSD, Neuromyelitis Optica Spectrum Disorder, MS, Multiple Sclerosis; HC, Healthy Control. All statistical analyses were considered significant at p <.05.

For the BVMT-R test a Welchs' ANOVA was performed. The results showed no significant differences in the BVMT-R performance between the three groups ($F(2,37) = 3.05$, $p = .060$, $\eta 2 = .05$).

2.2 Relationship between cognitive performance and clinical variables in NMOSD and MS patients

For the clinical groups (NMOSD and MS), a multiple regression analysis was conducted to explore the influence of sociodemographic (age and level of education) and clinical variables (duration of the disease, EDSS, depression and anxiety cores) on the cognitive performance based on BICAMS criteria for absence or presence of cognitive impairment (one or more tests with a percentile ≤ 5 means the presence of cognitive impairment). The results showed that the model was statistically significant and explained 43% the cognitive performance variance ($R^2 = .43$; $F(6,26) = 4.25$; $p = .006$). The strongest predictor was depression ($\beta = -.646$, $t(26) = -3.09$, $p = .006$), followed by the duration of the disease ($\beta = -.456$, $t(26) = -2.55$, $p = .019$) and EDSS ($\beta = -.386$, $t(26) = -2.20$, $p = .040$). Neither the anxiety, age and education were significant predictors ($p = .463$, $p = .109$ and $p = .364$, respectively).

Furthermore, focusing in each clinical group separately, for MS patients a significant association between the duration of the disease and the scores obtained in some of the cognitive tests was found: BVMT-R ($r(22) = -.79$, $p < .001$), SDMT ($r(22) = -.84$, $p < .001$) and Phonemic ($r(22) = -.46$, $p = .030$) and Semantic Verbal Fluency ($r(22) = -.71$, $p < .001$). The duration of the disease also influences the level of depression ($r(15) = .57$, $p = .027$) since the longer they had it, the higher the prevalence of the depressive symptoms. Regarding the EDSS, there was not a significant association with cognitive performance in any test.

On the other hand, the NMOSD patients showed significant and stronger relationships between higher levels of depression and cognitive impairment according to BICAMS criteria ($r(14) = -.69$, $p = .006$). In specific, these associations are more visible in BVMT-R ($r(14) = -.54$, $p = .045$) and SMDT ($r(14) = -.54$, $p = .047$). Even though there was no statistical differences in EDSS performance between NMOSD and MS patients, for NMOSD we found significant correlations between the EDSS and the CVLT ($r(14) = -.55$,

p = .044) and SDMT (r(14) = -.53, p = .050). Regarding the duration of the disease, there were no significant relationship with the cognitive variables.

3. Discussion

In this study we explore the neuropsychological profile in the NMOSD patients by comparing them with MS patients and HC. Despite the lack of knowledge regarding the impact of NMOSD on cognition, our results are congruent with most of the previous studies pointing out the absence of differences between the two clinical groups and significantly lower performance in NMOSD when compared to HC.

Accordingly, 58% of the NMOSD patients and 44% of the MS patients had a global cognitive impairment measured by MoCA. However, statistical differences were not found between these two conditions, and the NMOSD performed significantly poorer than HC.

Can we talk about a pattern of specific deficits that can differentiate NMOSD from HC? The BICAMS and the Verbal Fluency tests (Phonemic and Semantic) were used in this study to explore these issues.

When compared to HC, NMOSD showed significantly lower results regarding some cognitive domains. The difficulties occur specifically in the information processing speed, concentration and executive functions such as sustained and divided attention (SDMT), cognitive flexibility and language processing (Phonemic Verbal Fluency). Although these results are frequently reported in literature (Blanc et al., 2012; Saji et al., 2013; Vanotti et al., 2012; Wang et al., 2015), the present study did not find significant deficits regarding verbal (CVLT-II) and visual (BVMT-R) short-term memory, as found in other studies (Blanc et al., 2012; Cho et al., 2018; He et al., 2011; Wang et al., 2015).

However, an important aspect must be considered regarding visual memory. Visual dysfunctions not only can affect the results in tests that imply visual functions (Blanc et al,. 2008), but also the loss or reduction of fine motor skills can impact the performance in tests like BVMT-R which requires drawing. Three of the NMOSD patients had poorer performance in this test because of motor or visual incapacity, making it difficult to assume the presence or absence of deficits in visual memory.

The overall cognitive deficits reported are congruent with neuroimaging data that describes subcortical atrophy, initially reported for Wilson's disease, but gaining

continuous relevance for inflammatory conditions as a result of the implication of the decrease in white matter in the majority of NMOSD patients (Cummings, 1986). This has been associated with the decrease in information processing speed, impairments in executive functions, attention, and memory (Blanc et al., 2012; Vanotti et al., 2012).

Do NMOSD and MS patients have similar neuropsychological profiles?

The answer to this question is not a consensual one in literature. In our study no differences were observed in cognitive performance between NMOSD and MS patients. On one hand, this findings are coherent with the results found in three previous researches (Blanc et al., 2008; Moore et al., 2016; Vanotti et al., 2012) conducted with Caucasian population where the prevalence of NMOSD is lower, reflected in the number of participants ranging between 14 to 42 participants in each group. They reported that cognitive impairment between both conditions were similar, turning out to be difficult to delineate a line between their neuropsychological performance. On the other hand, Kim and colleagues (2016), in a study with Asian population found differences in the neuropsychological profile: MS patients had greater impairment in verbal learning and memory function, whereas higher deficits in attention and information processing speed were strongly associated with NMOSD patients. These differences can be explained by the fact that this last study was conducted with a significantly larger number of participants in each group (n = 85 *per* group).

Additionally, we were interested in exploring which clinical (duration of the disease, EDSS, depression and anxiety) or sociodemographic variables (age and level of education) could predict the cognitive impairment based in BICAMS criteria (one or more tests with a percentile ≤ 5 means the presence of cognitive impairment). The strongest predictors were depression, duration of disease and level of disability (EDSS), respectively.

Furthermore, correlation analysis between these predictors and cognitive impairment based on BICAMS criteria were conducted.

There was a significant relationship between the duration of the disease and the BICAMS cognitive measures, specifically in BVMT-R and SDMT in MS patients. This may be explained by the fact that they had significantly longer disease duration (M = 12.68, SD = 8.83) compared to NMOSD (M = 5.22, SD = 4.17). This is probably related with the fact that the majority of MS patients, even the ones with relapsing-remitting phenotype, evolve into a progressive course over the time, leading to a chronic progressive neurodegeneration. This progressive course is rarely seen in NMOSD patients, due to

differences in several aspects of the disease such as pathogenetic mechanisms (Kawachi & Lassmann, 2017) which can explain that the duration of the disease only impacts the cognitive impairment in MS. However, further research is needed to explore this association.

Regarding NMOSD, significant and negative correlation between the level of disability and cognitive performance may happen as a result of the severity of this condition. Blanc and colleagues (2008) reported that NMOSD has worse severity than MS attending to the EDSS results. However, our study did not find significant differences between the two conditions. This level of disability is shown to be strongly associated with deficits in verbal memory despite the fact that there were no significant differences between NMOSD and HC in our study. This may lead us to the thought that there is a tendency for this deficit with the increasing of neurological incapacities as found in other studies (Blanc et al., 2012; He et al., 2011; Saji et al., 2013; Wang et al., 2015).

Not only the level of disability impacts NMOSD, but also depression can impair cognitive performance, as previously reported by Moore and colleagues (2016) since they also found that EDSS and depression were significantly associated with poorer cognitive performance. Especially, the domain that seems to have greater performance prejudice is information processing speed, as a consequence of both impact of level of disability and psychiquiatric symptoms such as depression. This finding is coherent with what has been reported in literature since significant associations have been found between high levels of depression and deficits in the information processing speed (He et al., 2011) and between higher levels of disability and information processing speed impairments (Blanc et al., 2008) .

Since depression seems to be the most important predictor of cognitive impairment, and although there were no significant differences between groups, a clear tendency for higher levels of depression was observed for NMOSD when compared to HC.

These high levels can be the cause of deficits in cognition, but in this particular disease can also be another consequence of the deficiency in the AQP4 protein. An experimental study was conducted to explore the specific link between the high levels of depression in NMOSD and this specific protein, and found that deficiency in this biomarker results in a hippocampal neurogenesis decrease, which could contribute to the pathogenesis of depression, but further research is needed (Skucas et al., 2011).

Even though we did not evaluate this particular aspect, previous studies focused their attention on the impact of the depression and the disease itself in the quality of life.

They concluded that there is a significant negative effect on patients' lives, even if it's severity is only mild (Ayzenberg et al., 2021).

Our study may contribute for a more consensual caracterization of NMOSD neuropsychological profile. However, some limitations need to be pointed out. To this moment there is no specific battery for NMOSD so we had to use a neuropsychological battery created for another demyelinating disease (MS). The one choosen, BICAMS, was a reduced version of MACFIMS, so the interpretation of the results have to take this limitation into account. Related to this is the fact that BICAMS has a test that needs fine motor skills and visual functions (BVMT-R), which may potentially be impaired in this disorder, which can explain the poorer results more accurately than a possible cognitive impair. Lastly, our study has a small sample due to low prevalence of this rare disease, becoming a possible obstacle for more robust statistical inferences.

The lack of consensual information in this cientific field is due to scarcity of research, methodological differences (e.g., heterogeneity of the number and criteria of the participants selection; neuropsychological measures; control groups) and the low prevalence of the disease worldwide.

4. Conclusion

Our study provided a neuropsychological profile caracterization congruent with what has been reported in several studies regarding NMOSD.

The already known fact that NMOSD patients have a global cognitive impairment when compared to HC was found in our study, and a more exploratory analysis of the specific impaired domains revealed its presence in information processing speed, concentration, language processing and in some executive functions such as cognitive flexibility, sustained and divided attention.

Despite the fact that there was no significant difference between the NMOSD and the MS patients in cognitive performance, new data about the predictors for cognitive impairment have been found. Other than this, it was also seen that there were differences in the strongest predictors for each clinical condition, depression and level of disability for NMOSD, and depression and duration of disease for MS. These findings may encourage future research and have clinical implications for early intervention attending either disease duration, level of disability and depression.

The prevalence of the cognitive impairment in the majority of our NMOSD patients, associated with psychological comorbilities, also emphasyzes the need for appropriate mental and neuropsyhcological services, specifically, regarding interventions to help improving their managing skills for depressive symptoms and cognitive stimulation for the neuropsychological impairments.

References

Ahlgren, C., Odén, A., & Lycke, J. (2011). High nationwide prevalence of multiple sclerosis in Sweden. *Multiple Sclerosis Journal*, *17*(8), 901–908. https://doi.org/10.1177/1352458511403794

Ayzenberg, I., Richter, D., Henke, E., Asseyer, S., Paul, F., Trebst, C., Hümmert, M. W., Havla, J., Kümpfel, T., Ringelstein, M., Aktas, O., Wildemann, B., Jarius, S., Häußler, V., Stellmann, J. P., Senel, M., Klotz, L., Pellkofer, H. L., Weber, M. S., … Kleiter, I. (2021). Pain, Depression, and Quality of Life in Neuromyelitis Optica Spectrum Disorder: A Cross-Sectional Study of 166 AQP4 Antibody-Seropositive Patients. *Neurology(R) Neuroimmunology & Neuroinflammation*, *8*(3). https://doi.org/10.1212/NXI.0000000000000985

Baldo, J. V, Schwartz, S., Wilkins, D., & Dronkers, N. F. (2006). *Role of frontal versus temporal cortex in verbal fluency as revealed by voxel-based lesion symptom mapping*. 896–900.

Benedict, R. H. B., Amato, M. P., Boringa, J., Brochet, B., Foley, F., Fredrikson, S., Hamalainen, P., Hartung, H., Krupp, L., Penner, I., Reder, A. T., & Langdon, D. (2012). Brief International Cognitive Assessment for MS (BICAMS): international standards for validation. *BMC Neurology*, *12*. https://doi.org/10.1186/1471-2377-12-55

Bennett, J. L. (2016). Finding NMO: The evolving diagnostic criteria of neuromyelitis optica. *Journal of Neuro-Ophthalmology*, *36*(3), 238–245. https://doi.org/10.1097/WNO.0000000000000396

Blanc, Frédéric; Zéphir, Hélène; Lebrun, Christine; Labauge, Pierre; Castelnovo, Giovanni; Fleury, Marie; Sellal, Francois; Tranchant, Christine; Dujardin, Kathy; Vermersch, Patrick; Seze, J. (2015). *Cognitive Functions in Neuromyelitis Optica*. *65*(1), 84–88.

Blanc, F., Noblet, V., Jung, B., Rousseau, F., Renard, F., Bourre, B., Longato, N., Cremel, N., Di Bitonto, L., Kleitz, C., Collongues, N., Foucher, J., Kremer, S., Armspach, J. P., & de Seze, J. (2012). White matter atrophy and cognitive dysfunctions in neuromyelitis optica. *PLoS ONE*, *7*(4). https://doi.org/10.1371/journal.pone.0033878

Cavaco, S., Gonçalves, A., Pinto, C., Almeida, E., Gomes, F., Moreira, I., Fernandes, J., & Teixeira-Pinto, A. (2013). Semantic fluency and phonemic fluency: Regression-based

norms for the portuguese population. *Archives of Clinical Neuropsychology*, *28*(3), 262–271. https://doi.org/10.1093/arclin/act001

Cho, E. Bin, Han, C. E., Seo, S. W., Chin, J., Shin, J. H., Cho, H. J., Seok, J. M., Kim, S. T., Kim, B. J., Na, D. L., Lee, K. H., Seong, J. K., & Min, J. H. (2018). White matter network disruption and cognitive dysfunction in neuromyelitis optica spectrum disorder. *Frontiers in Neurology*, *9*(December), 1–10. https://doi.org/10.3389/fneur.2018.01104

Cummings, J. L. (1986). Review Article Subcortical Dementia. *British Journal Of Psychiatry*, 682–697.

Czarnecka, D., & Oset, M. (2020). *Cognitive impairment in NMOSD — More questions than answers*. *June*, 1–12. https://doi.org/10.1002/brb3.1842

De Seze, J., Kremer, L., & Collongues, N. (2016). Neuromyelitis optica spectrum disorder (NMOSD): A new concept. *Revue Neurologique*, *172*(4–5), 256–262. https://doi.org/10.1016/j.neurol.2016.03.003

First, J. O., & Letter, P. (2016). *Myelin injury without astrocytopathy in neuroin fl ammatory disorders with MOG antibodies*. *0*(0), 1–4.

Fujihara, K. (2019). Neuromyelitis optica spectrum disorders: Still evolving and broadening. *Current Opinion in Neurology*, *32*(3), 385–394. https://doi.org/10.1097/WCO.0000000000000694

Haase, C. G., & Schmidt, S. (2001). Detection of brain-specific autoantibodies to myelin oligodendrocyte glycoprotein, S100β and myelin basic protein in patients with Devic's neuromyelitis optica. *Neuroscience Letters*, *307*(2), 131–133. https://doi.org/10.1016/S0304-3940(01)01949-8

He, D., Chen, X., Zhao, D., & Zhou, H. (2011). Cognitive function, depression, fatigue, and activities of daily living in patients with neuromyelitis optica after acute relapse. *International Journal of Neuroscience*, *121*(12), 677–683. https://doi.org/10.3109/00207454.2011.608456

Hor, J. Y., Asgari, N., Nakashima, I., Broadley, S. A., Leite, M. I., Kissani, N., Jacob, A., Marignier, R., Weinshenker, B. G., Paul, F., Pittock, S. J., Palace, J., Wingerchuk, D. M., Behne, J. M., Yeaman, M. R., & Fujihara, K. (2020). Epidemiology of Neuromyelitis Optica Spectrum Disorder and Its Prevalence and Incidence Worldwide. *Frontiers in Neurology*, *11*. https://doi.org/10.3389/fneur.2020.00501

Huda, A. S., Whittam, A. D., Bhojak, B. M., Chamberlain, C. J., Noonan, D. C., F, E. A. J., Huda, S., Whittam, D., & Bhojak, M. (2019). *Neuromyelitis optica spectrum*

disorders. *19*(2), 169–176.

Jarius, S., Ruprecht, K., Wildemann, B., Kuempfel, T., Ringelstein, M., Geis, C., Kleiter, I., Kleinschnitz, C., Berthele, A., Brettschneider, J., Hellwig, K., Hemmer, B., Linker, R. A., Lauda, F., Mayer, C. A., Tumani, H., Melms, A., Trebst, C., Stangel, M., … Paul, F. (2012). Contrasting disease patterns in seropositive and seronegative neuromyelitis optica: A multicentre study of 175 patients. *Journal of Neuroinflammation*, *9*, 1–17. https://doi.org/10.1186/1742-2094-9-14

JF, K. (1983). Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology.*, *Nov;33*(11), 1444-52.

Kawachi, I., & Lassmann, H. (2017). *Neurodegeneration in multiple sclerosis and neuromyelitis optica*. 137–145. https://doi.org/10.1136/jnnp-2016-313300

Kim, S. H., Kwak, K., Hyun, J. W., Jeong, I. H., Jo, H. J., Joung, A., Kim, J. H., Lee, S. H., Yun, S., Joo, J., Lee, J. M., & Kim, H. J. (2016). Widespread cortical thinning in patients with neuromyelitis optica spectrum disorder. *European Journal of Neurology*, *23*(7), 1165–1173. https://doi.org/10.1111/ene.13011

Kim, S., Kwak, K., Jeong, I. H., Hyun, J., Jo, H., Joung, A., Yu, E., Kim, J., Lee, S. H., Yun, S., Joo, J., Lee, D., Lee, J., & Kim, H. J. (2016). *Cognitive impairment differs between neuromyelitis optica spectrum disorder and multiple sclerosis*. 1–9. https://doi.org/10.1177/1352458516636246

Lennon, P. V. A., Wingerchuk, D. M., Kryzer, T. J., Pittock, S. J., Lucchinetti, C. F., Fujihara, K., Nakashima, I., & Weinshenker, B. G. (2004). A serum autoantibody marker of neuromyelitis optica: Distinction from multiple sclerosis. *Lancet*, *364*(9451), 2106–2112. https://doi.org/10.1016/S0140-6736(04)17551-X

Lennon, V. A., Kryzer, T. J., Pittock, S. J., Verkman, A. S., & Hinson, S. R. (2005). IgG marker of optic-spinal multiple sclerosis binds to the aquaporin-4 water channel. *Journal of Experimental Medicine*, *202*(4), 473–477. https://doi.org/10.1084/jem.20050304

Mader, S., Gredler, V., Schanda, K., Rostasy, K., Dujmovic, I., Pfaller, K., Lutterotti, A., Jarius, S., Di Pauli, F., Kuenz, B., Ehling, R., Hegen, H., Deisenhammer, F., Aboul-Enein, F., Storch, M. K., Koson, P., Drulovic, J., Kristoferitsch, W., Berger, T., & Reindl, M. (2011). Complement activating antibodies to myelin oligodendrocyte glycoprotein in neuromyelitis optica and related disorders. *Journal of Neuroinflammation*, *8*(1), 184. https://doi.org/10.1186/1742-2094-8-184

Matiello, M., Kim, H. J., Kim, W., Brum, D. G., Barreira, A. A., Kingsbury, D. J., Plant,

G. T., Adoni, T., & Weinshenker, B. G. (2010). Familial neuromyelitis optica. *Neurology*, *75*(4), 310–315. https://doi.org/10.1212/WNL.0b013e3181ea9f15

Meng, H., Xu, J., Pan, C., Cheng, J., & Hu, Y. (2016). Cognitive dysfunction in adult patients with neuromyelitis optica : a systematic review and meta-analysis. *Journal of Neurology*. https://doi.org/10.1007/s00415-016-8345-3

Miao, X., Shi, Z., Chen, H., Zhou, H., & Yang, R. (2017). The impact of pain, anxiety and depression on sleep quality in chinese patients with neuromyelitis optica spectrum disorders. *Neurology Asia*, *22*(3), 235–241.

Misu, T., Fujihara, K., Kakita, A., Konno, H., Nakamura, M., Watanabe, S., Takahashi, T., Nakashima, I., Takahashi, H., & Itoyama, Y. (2007). Loss of aquaporin 4 in lesions of neuromyelitis optica: Distinction from multiple sclerosis. *Brain*, *130*(5), 1224–1234. https://doi.org/10.1093/brain/awm047

Moore, P., Methley, A., Pollard, C., Mutch, K., Hamid, S., Elsone, L., & Jacob, A. (2016). Cognitive and psychiatric comorbidities in neuromyelitis optica. *Journal of the Neurological Sciences*, *360*, 4–9. https://doi.org/10.1016/j.jns.2015.11.031

Narayan, R., Simpson, A., Fritsche, K., Salama, S., Pardo, S., Mealy, M., Paul, F., & Levy, M. (2018). Review article MOG antibody disease : A review of MOG antibody seropositive neuromyelitis optica spectrum disorder. *Multiple Sclerosis and Related Disorders*, *25*(June), 66–72. https://doi.org/10.1016/j.msard.2018.07.025

Nocentini, U., Pasqualetti, P., Bonavita, S., Buccafusca, M., De Caro, M. F., Farina, D., Girlanda, P., Le Pira, F., Lugaresi, A., Quattrone, A., Reggio, A., Salemi, G., Savettieri, G., Tedeschi, G., Trojano, M., Valentino, P., & Caltagirone, C. (2006). Cognitive dysfunction in patients with relapsing-remitting multiple sclerosis. *Multiple Sclerosis*, *12*(1), 77–87. https://doi.org/10.1191/135248506ms1227oa

Oreja-Guevara, C., Blanco, T. A., Ruiz, L. B., Pérez, M. Á. H., Meca-Lallana, V., & Ramió-Torrentà, L. (2019). Cognitive dysfunctions and assessments in multiple sclerosis. *Frontiers in Neurology*, *10*(JUN), 1–9. https://doi.org/10.3389/fneur.2019.00581

Saji, E., Arakawa, M., Yanagawa, K., Toyoshima, Y., Yokoseki, A., Okamoto, K., Otsuki, M., Akazawa, K., Kakita, A., Takahashi, H., Nishizawa, M., & Kawachi, I. (2013). Cognitive impairment and cortical degeneration in neuromyelitis optica. *Annals of Neurology*, *73*(1), 65–76. https://doi.org/10.1002/ana.23721

Skucas, V. A., Mathews, I. B., Yang, J., Cheng, Q., Treister, A., Duffy, A. M., Verkman, A. S., Hempstead, B. L., Wood, M. A., Binder, D. K., & Scharfman, H. E. (2011).

Impairment of select forms of spatial memory and neurotrophin-dependent synaptic plasticity by deletion of glial aquaporin-4. *Journal of Neuroscience*, *31*(17), 6392–6397. https://doi.org/10.1523/JNEUROSCI.6249-10.2011

Sousa, C., Rigueiro-Neves, M., Miranda, T., Alegria, P., Vale, J., Passos, A. M., Langdon, D., & Sá, M. J. (2018). Validation of the brief international cognitive assessment for multiple sclerosis (BICAMS) in the Portuguese population with multiple sclerosis 11 Medical and Health Sciences 1109 Neurosciences. *BMC Neurology*, *18*(1), 1–7. https://doi.org/10.1186/s12883-018-1175-4

Thompson, A. J., Banwell, B. L., Barkhof, F., Carroll, W. M., Coetzee, T., Comi, G., Correale, J., Fazekas, F., Filippi, M., Freedman, M. S., Fujihara, K., Galetta, S. L., Hartung, H. P., Kappos, L., Lublin, F. D., Marrie, R. A., Miller, A. E., Miller, D. H., Montalban, X., … Cohen, J. A. (2018). Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *The Lancet Neurology*, *17*(2), 162–173. https://doi.org/10.1016/S1474-4422(17)30470-2

Vanotti, S., Cores, E. V., Eizaguirre, B., & Melamud, L. (2012). *Cognitive performance of neuromyelitis optica patients : comparison with multiple sclerosis*. *November*, 357–361. https://doi.org/10.1590/0004-282X20130038

Vicente, S. G., Benito-Sánchez, I., Barbosa, F., Gaspar, N., Dores, A. R., Rivera, D., & Arango-Lasprilla, J. C. (2020). Normative data for Verbal Fluency and Object Naming Tests in a sample of European Portuguese adult population. *Applied Neuropsychology:Adult*, *0*(0), 1–12. https://doi.org/10.1080/23279095.2020.1868472

Wang, Q., Zhang, N., Qin, W., Li, Y., Fu, Y., Li, T., Shao, J., Yang, L., Shi, F. D., & Yu, C. (2015). Gray matter volume reduction is associated with cognitive impairment in neuromyelitis optica. *American Journal of Neuroradiology*, *36*(10), 1822–1829. https://doi.org/10.3174/ajnr.A4403

Waters, P. J., McKeon, A., Leite, M. I., Rajasekharan, S., Lennon, V. A., Villalobos, A., Palace, J., Mandrekar, J. N., Vincent, A., Bar-Or, A., & Pittock, S. J. (2012). Serologic diagnosis of NMO: A multicenter comparison of aquaporin-4-IgG assays. *Neurology*, *78*(9), 665–671. https://doi.org/10.1212/WNL.0b013e318248dec1

Weinshenker, B. G., & Wingerchuk, D. M. (2017). Neuromyelitis Spectrum Disorders. *Mayo Clinic Proceedings*, *92*(4), 663–679. https://doi.org/10.1016/j.mayocp.2016.12.014

Wingerchuk, D. M., Lennon, V. A., Pittock, S. J., Lucchinetti, C. F., & Weinshenker, B. G. (2006). Revised diagnostic criteria for neuromyelitis optica. *Neurology*, *66*(10), 1485–

1489. https://doi.org/10.1212/01.wnl.0000216139.44259.74

Wingerchuk, Dean M., Banwell, B., Bennett, J. L., Cabre, P., Carroll, W., Chitnis, T., De Seze, J., Fujihara, K., Greenberg, B., Jacob, A., Jarius, S., Lana-Peixoto, M., Levy, M., Simon, J. H., Tenembaum, S., Traboulsee, A. L., Waters, P., Wellik, K. E., & Weinshenker, B. G. (2015). International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. *Neurology*, *85*(2), 177–189. https://doi.org/10.1212/WNL.0000000000001729

Wingerchuk, Dean M, Lennon, V. A., Lucchinetti, C. F., Pittock, S. J., & Weinshenker, B. G. (2007). *The spectrum of neuromyelitis optica*. *6*(September).

Yabalak, A., Altunreden, B. & Akman Demir, G. (2020). *Cognitive Impairment in Neuromyelitis Optica*. 1–6.

Zigmond, A. S., & Snalth, R. P. (1983). The Hospital Anxiety and Depression Scale. Acta psychiatr. scand. [revista en Internet] 2014 [acceso 28 de noviembre de 2019]; 64(5): 361-370. *Acta Psychiatrica Scandinavica*, *67*(6), 361–370. https://www.ncbi.nlm.nih.gov/pubmed/6880820