



# Cognitive impairment in neuromyelitis optica spectrum disorders: A comparison of the Wechsler Adult Intelligence Scale-III and the Wechsler Memory Scale Revised with the Rao Brief Repeatable Neuropsychological Battery



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## ABSTRACT

**Background:** Approximately 55% of patients with neuromyelitis optica spectrum disorder (NMOSD) show cognitive impairment as evaluated using the Rao Brief Repeatable Neuropsychological Battery (BRBN), but this frequency appears to be higher than the frequency of specific brain lesions in NMOSD.

**Objective:** We studied whether cognitive impairment could be observed in NMOSD patients with no or minor non-specific brain lesions.

**Methods:** We evaluated cognitive function in 12 NMOSD and 14 MS patients using the Wechsler Adult Intelligence Scale-III (WAIS-III), the Wechsler Memory Scale-Revised (WMS-R), and the BRBN. We judged as cognitively impaired patients whose scores were below the average by 2 standard deviations or greater in 2 or more cognitive domains.

**Results:** Cognitive impairment was observed in 5 MS patients (35.7%) and in the only NMOSD patient (8.3%) with symptomatic brain lesions, but not in the other NMOSD patients who had no or minor non-specific brain lesions. Meanwhile, 5 NMOSD (41.7%) and 4 MS (28.6%) patients who had normal cognition according to the WAIS-III and WMS-R were assessed as cognitively impaired by the BRBN (which is not standardized for age).

**Conclusions:** Cognitive function in NMOSD patients with no or mild non-specific brain lesions was preserved according to the WAIS-III and WMS-R.

## 1. Introduction

Cognitive impairment has been identified in patients with neuromyelitis optica spectrum disorder (NMOSD), ranging from 54% to 57% in frequency when evaluated with the Rao Brief Repeatable Neuropsychological Battery (BRBN) [1–4]. However, the pathological basis and MRI substrates of cognitive impairment in NMOSD remain unclear [5,6]. Interestingly, the frequency of this disorder appears to be higher than that of the specific brain lesions detected by conventional MRI [1–4]. Therefore, cognitive impairment has been indicated in NMOSD patients both with and without specific brain lesions. To explore the MRI substrates of cognitive impairment in NMOSD, it is necessary to determine whether cognitive impairment could exist in patients without specific brain lesions.

However, the previously reported frequencies of cognitive impairment in NMOSD may not be accurate because the batteries previously used for cognitive assessment were the BRBN and the Minimal Assessment of Cognitive Function in MS (MACFIMS), which are not standardized and are influenced by variables such as age, level of education (younger people with a higher educational level may demonstrate better performance) and, to a lesser extent, gender (women may perform better than men) [7–10].

In fact, Wechsler concluded that intelligence declines with age [11]. Therefore, corrections for these age-related declines have been incorporated into the calculation of IQ scores since the publication of the Wechsler-Bellevue Intelligence Scale to assist clinicians in distinguishing between normal age-related cognitive decline and impairment due to neurological or psychiatric disorders. Failure to account for age-

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related changes can lead to the misdiagnosis of cognitive impairment or dementia in the normal elderly [12]. We previously reported that it is possible to overestimate cognitive impairment in relatively old MS patients using the BRBN when comparing these results with those of the Wechsler Adult Intelligence Scale-III (WAIS-III) and the Wechsler Memory Scale-Revised (WMS-R), which are standardized and not influenced by age [13]. As the age of NMOSD onset is approximately 10 years older (approximately 40 years old) than that in MS, we should re-examine cognitive function in NMOSD patients with test batteries that are standardized for age.

In the present study, we investigated whether cognitive impairment could be observed in NMOSD patients with no or minor non-specific brain lesions. For comprehensive cognitive assessments, we used the WAIS-III and the WMS-R (which require several hours over 2 days or more), as well as the BRBN (requires 30 min), in NMOSD. As we suspected that overestimation might occur in middle-aged and older NMOSD patients, we primarily studied NMOSD patients over the age of 40 years.

## 2. Methods

### 2.1. Patients

A total of 12 NMOSD and 14 MS patients were recruited prospectively from those seen at the Department of Neurology at Tohoku University and the Department of Neurology at Tohoku Medical and Pharmaceutical University, Sendai, Japan between October 2012 and January 2015. NMOSD was diagnosed according to the 2006 Wingerchuk criteria [14], and MS was diagnosed according to the 2010 McDonald criteria [15]. Patients were tested for the presence of anti-aquaporin-4 (AQP4) antibody using an in-house recombinant immunofluorescence assay based on human AQP4-transfected HEK293 cells. The enrollment criteria were as follows: 1) current age between 20 and 75 years, 2) relapse-free for at least 3 months, 3) over 9 years of education, 4) Expanded Disability Status Scale (EDSS) score of 7.0 or lower, and 5) adequate vision to complete the tests. The exclusion criteria were 1) comorbid neurological diseases other than NMOSD or MS, and 2) a history of psychiatric illness, except for stable depressive symptoms. The study protocol was approved by the ethics committee of each participating site, and all patients gave written informed consent to participate in the study.

### 2.2. Neuropsychological assessment

All patients underwent brief cognitive screening (the Japanese version of the BRBN) and comprehensive cognitive assessments (WAIS-III and WMS-R), as previously described [13]. In this study, we used the mean and standard deviation (SD) of the BRBN scores of a total of 163 healthy Japanese controls from one of our previous studies. The mean age of the healthy controls was 39.2 years (SD. 11.9) in the previous study [9]. The WAIS-III is used to assess general intellectual ability, and the WMS-R is used to evaluate verbal and visual memory functions. Patients who scored below the average by 2 SDs or more in 2 or more cognitive domains in the combination of the WAIS-III and the WMS-R were considered to have significant cognitive impairment in this study.

### 2.3. Statistical analyses

We used the Student's *t*-test to compare the demographics and clinical characteristics between groups. JMP version 13.0 (SAS Institute Inc., Cary, NC, USA) was used for all analyses.

**Table 1**

Comparison of the background of participants between MS and NMO (mean  $\pm$  SD).

	MS (n = 14)	NMO (N = 12)	p value (Prob >  t )
Age	39.79 $\pm$ 6.53	53.67 $\pm$ 13.42	0.0022
Education	13.43 $\pm$ 1.45	13.08 $\pm$ 2.47	NS
EDSS	2.75 $\pm$ 1.76	3.63 $\pm$ 1.65	NS
Duration	11.29 $\pm$ 6.94	9.92 $\pm$ 7.89	NS
Disease-modifying treatment (%)	IFN $\beta$ (50%)	PSL [2] (100%)	
	fingolimod (29%) PSL [1] (14%) natalizumab (7%)	azathioprine (17%) tacrolimus (8%) methotrexate (8%)	
	PSL [1]: 5.0 mg	PSL [2]: 5 $\pm$ 2.9 mg	

## 3. Results

### 3.1. Patient profiles in NMOSD and MS

Patients with NMOSD were significantly older than those with MS. No differences in educational level, EDSS, and disease duration were observed between NMOSD and MS patients (Table 1). All patients with NMOSD and MS were receiving disease-modifying treatments at the time of examination. All NMOSD patients were positive for the anti-AQP4 antibody. Of the 12 NMOSD patients, 3 had chronic brain lesions without enhancement; 2 had non-specific chronic white matter lesions and one had a symptomatic (somnolence, amnesia, aphasia in acute phase) chronic lesion that involved bilateral cerebral deep white matter, the corpus callosum, and the pons.

### 3.2. Comparison of neuropsychological tests in NMOSD and MS

Based on the results of WAIS-III and WMS-R, cognitive impairment was observed in 35.7% of MS patients as previously described [13]. By contrast, cognitive impairment based on the results of the WAIS-III and the WMS-R was observed in an NMOSD patient with symptomatic brain lesions (NMO4) but not in the other NMOSD patients (Fig. 1).

NMOSD (41.7%) and 4 MS (28.6%) patients who were judged as cognitively intact by the WAIS-III and the WMS-R scored below the average by 2 SDs or more in at least 2 cognitive tests of the BRBN compared with the healthy control data. The discrepancy in the results between the BRBN and the combination of the WAIS-III and the WMS-R was most prominent in the NMOSD patients (Patients NMO8-12) over 55 years old (Fig. 1).

## 4. Discussion

In this study, NMOSD patients with no or mild non-specific brain lesions were cognitively intact according to the WAIS-III and the WMS-R, but they were occasionally judged as cognitively impaired by the BRBN. In particular, in NMOSD patients over 55 years old, the BRBN misevaluated multiple cognitive functions. These findings were more frequently observed in patients with NMOSD than in compared those with MS, possibly due to their older age.

In addition, as suggested in our previous study, the BRBN overestimated cognitive dysfunction in middle-aged patients, such as attention, information processing, and working memory in an NMOSD patient (Patient NMO3).

The BRBN is useful for the cognitive screening of patients in daily medical care, but it is not suited to the evaluation of older patients. As previously reported in a Caucasian MS population, additional standardized tests are necessary for the adequate assessment of cognitive deficits, which vary in individual patients [16].

By contrast, the results of the WAIS-III suggested that cognitive impairment in NMOSD is relatively mild and observed in particular

NMO patients	1	2	3	4	5	6	7	8	9	10	11	12
Age	28	41	41	50	51	53	54	55	56	71	72	72
Sex	F	F	F	F	F	F	F	F	F	F	F	F
Education	15	12	12	16	15	14	15	12	12	16	9	9
EDSS	1	4	5	3.5	5	4	2	1	2.5	5	6	4.5
Duration	2	19	9	12	20	6	1	6	6	3	9	26
Brain lesion	-	-	-	+++	+	-	-	-	-	-	++	-
VIQ	100	100	102	101	91	106	109	109	96	113	98	88
PIQ	87	88	88	71	98	108	101	106	91	109	72	92
FIQ	94	95	96	87	93	108	106	108	93	112	85	89
VC	111	104	99	116	90	102	104	104	90	114	99	92
PO	77	108	89	72	99	103	103	103	83	108	70	87
WM	79	90	107	69	94	103	105	100	103	102	92	83
PS	84	60	86	69	102	107	102	100	121	100	102	97
Verbal memory	114	114	86	80	90	105	109	96	101	116	107	110
Visual memory	99	113	106	62	108	114	119	106	99	125	96	112
General memory	111	115	91	71	95	109	114	99	100	121	104	112
Attention	84	101	97	87	109	123	113	98	107	107	86	103
Delayed recall	107	94	99	<50	91	107	111	95	96	115	107	107
SRT-LTS	35	57	39	24	50	53	55	23	20	49	43	26
SRT-CLTR	22	43	28	24	24	22	49	21	13	19	40	17
SRT-D	5	12	8	5	8	7	10	7	5	7	8	6
SPART	19	22	19	11	15	20	22	24	16	13	19	17
SPART-D	6	10	10	4	5	6	10	8	4	3	6	4
SDMT	47	49	37	33	58	45	53	46	54	31	28	43
PASAT 3sec	54	53	31	26	41	55	47	49	37	37	37	26
PASAT 2 sec	35	40	32	29	39	37	35	31	21	26	26	19
WLG	28	26	31	17	30	27	31	25	29	24	21	14

**Fig. 1.** Patient profiles and the results of the neuropsychological assessments of 12 NMOSD patients are shown. All patients completed the Wechsler Adult Intelligence Scale (WAIS)-III, the Wechsler Memory Scale-Revised (WMS-R), and the Japanese version of the Rao Brief Repeatable Neuropsychological Battery (BRBN). The WAIS-III assessed 7 cognitive domains: verbal IQ (VIQ), performance IQ (PIQ), full-scale IQ (FIQ), verbal comprehension (VC), perceptual organization (PO), working memory (WM), and processing speed (PS). The WMS-R assessed 5 cognitive domains: verbal memory, visual memory, general memory, attention, and delayed recall. The standardized scores of each domain are shown. At the bottom of each panel, the results of the BRBN are shown. Verbal learning and memory were assessed using the Selective Reminding Test–Long Term Storage (SRT-LTS), the Selective Reminding Test–Consistent Long-Term Retrieval (SRT-CLTR) and the Selective Reminding Test–Delayed (SRT-D). Visuospatial memory and learning were assessed using the Spatial Recall Test (SPART) and the Spatial Recall Test–Delayed (SPART-D). Attention, information processing and working memory were assessed using the Paced Auditory Serial Addition Tests (PASAT) and the Symbol Digit Modalities Test (SDMT). Verbal fluency was assessed via word list generation (WLG). The raw scores of each test battery are shown. In the BRBN study, the mean and SD of the scores of healthy controls from our previous study were used. Light gray indicates scores between 1 SD and 2 SD below the average of the healthy controls, and dark gray indicates scores > 2 SD below the average of the healthy controls.

Patients who scored below the average by 2 SDs or more in 2 or more cognitive domains in the combination of WAIS-III and WMS-R were considered to have significant cognitive impairment in this study. Cognitive impairment was observed in an NMOSD patient with symptomatic brain lesions (NMO4) but not in the other NMOSD patients. 5 NMOSD (41.7%) patients (Patients NMO 3, 9–12) who were judged as cognitively intact by WAIS-III and WMS-R scored below the average by 2 SDs or more in at least 2 cognitive tests on the Japanese version of the BRBN compared with the healthy control data. The discrepancy of the results between the BRBN and the combination of the WAIS-III and the WMS-R was most prominent in NMOSD patients over 55 years old (Patients NMO8 ~ 12). PASAT-2, Paced Auditory Serial Addition Test-2 s; PASAT-3, Paced Auditory Serial Addition Test-3 s.

domains, such as perceptual organization (PO), working memory (WM), and processing speed (PS), whereas cognitive impairment in MS is more severe and generally observed in multiple domains.

To date, cognitive impairment has been observed more frequently in NMOSD patients than in patients with brain abnormalities (Table 2) [1–5]. For example, Blanc and colleagues reported in 2012 that cognitive impairment was observed in 54% of patients with NMOSD when using the French version of the BRBN, whereas only 11% of the patients had MRI-detectable specific brain lesions. Liu and colleagues reported that cognitive impairment was observed in 48.2% of patients with NMOSD using mainly MACFIMS with some modifications, whereas 44.4% of the patients with NMOSD presented with nonspecific cerebral white matter abnormalities and 14.8% of them presented with MS-like lesions or typical NMOSD lesions. However, the BRBN and MACFIMS used in these reports were originally proposed to evaluate cognitive function in MS because they combined tests to evaluate the cognitive domains commonly affected by MS. Furthermore, the BRBN and MACFIMS have been validated in MS but not in NMOSD [17,18]. As the BRBN have not been standardized, BRBN test scores may be influenced by variables such as age, gender, and level of education. [7,8,19].

By contrast, Kim et al. applied a combination of several test batteries and recently reported that cognitive impairment was observed in 29% of NMOSD patients [6], which is lower than in other studies. They reported that, of 67 NMOSD patients with available brain MRI scans, 41 (61%) had chronic brain lesions without enhancement, although the proportion of the NMOSD-related brain lesions was not described. The authors suggested that the lower frequency of cognitive impairment in NMOSD patients in their cohort may have been caused by their relatively younger age and higher educational level relative to the patients involved in previous studies.

The actual frequency of cognitive impairment in NMOSD, especially in middle-aged or older patients, may be lower than the frequencies previously reported. Our study demonstrated that cognitive impairment in NMOSD patients with no or mild non-specific brain lesions could be overestimated by the BRBN, especially in older patients.

The present study is a single-center study with a small sample size, and its results could therefore be influenced by selection bias. Thus, the results should be confirmed by larger-scale analyses.

**Table 2**  
Reported cognitive assessments using several test batteries in patients with NMO/MS during remission phase.

Study	Participants	Age (mean ± SD)	Sex, F/M	Year of education (mean ± SD)	AQP4 Ab/NMO-IgG Positivity (%)	Cognitive test battery	Definition of cognitive impairment	Frequency of cognitive impairment	Brain MRI lesions in NMO/MS
(Blanc F, et al., 2008)	NMO/MS (n = 30)	43.5 ± 12.3	23/7	12.8 ± 2.8	17/30 (56.7%)	French BRBN*	At least one result that differed by > 2 SDs from that of healthy controls	NMO (56.7%)	6/30 (20%); unspecified periventricular T2-weighted hyperintensities (n = 2), numerous brain lesions corresponding to MS criteria (n = 3), and periaqueductal lesion (n = 1)
	Control (n = 30)	43.4 ± 12.1	23/7	13.3 ± 2.5				MS (36.7%)	
(Vanotti S, et al., 2013)	NMO/MS (n = 14)	36.86 ± 12.42	12/12	11.26 ± 3.29	ND	Spanish BRBN	Abnormal performance in at least two cognitive tests	NMO (57%)	6/14 (43%); Unspecific lesions (n = 4), Typical lesions AQP4 (n = 2)
	Control (n = 14)	37.93 ± 10.57	12/12	12.79 ± 3.55				MS (42.85%)	
(Saji, et al., 2013)	NMO/MS (n = 14)	47.5(40–60.3) <sup>a</sup>	14/0	10/13 <sup>b</sup>	13/13 (100%)	Japanese BRBN	Impaired performance on at least three cognitive tests	NMO/MS (57%)	2/13 (15%); corpus callosum lesions, 1/13 (8%); confluent lesions
	Control (n = 17)	36.0(30.5–42.5) <sup>a</sup>	12/5	17/17 <sup>b</sup>				MS (47%)	
(Blanc F, et al., 2012)	NMO/MS (n = 28)	45.3 ± 11.7	19/9	12.2 ± 2.9	12/28 (43%)	French BRBN	More than four subtests of the BRBN inferior to the 5th percentile	NMO (54%)	3/28 (11%); inflammatory lesions of the brain
	Control (n = 28)	42 ± 15.6	19/9	12.9 ± 3.4					
(Liu, et al., 2015)	NMO/MS (n = 54)	43.39 ± 10.38	48/6	10.57 ± 3.33	38/54 (70.4%)	MAGFI-MS	Scored at least 1.5SDs below the average of HCs in 2 or more cognitive domains	NMO (48.2%)	32/54 (59.3%); nonspecific WM abnormalities (n = 24), MS-like lesions (n = 4), typical NMO lesions (n = 4)
	Control (n = 27)	51.22 ± 7.44	22/5	11.61 ± 3.43					
(Kim, et al., 2016)	NMO/MS (n = 82)	36 ± 7	75/7	15 ± 2	71/82 (87%)	Multiple tests**	Scored lower than the fifth percentile compared with HCs in at least three domains	NMO (29%)	41/67 (61%); supratentorial lesions (n = 26), infratentorial lesions (n = 4), both supratentorial and intratentorial lesions (n = 11)
	Control (n = 58)	34 ± 8	32/26	15 ± 2				MS (50%)	
	Control (n = 45)	38 ± 7	39/6	15 ± 2					

ND not described.

<sup>a</sup> Median (interquartile range).

<sup>b</sup> No. of subjects with education for ≥ 12 y.

\* Plus tests such as cross tapping, go/no-go, and digit span.

\*\* Seoul Verbal Learning Test, Korean version of the Hopkins Verbal Learning Test–Revised, Rey Complex Figure Test, Controlled Oral Word Association Test, Symbol Digit Modalities Test, Paced Auditory Serial Addition Test, Digit Span test, Stroop Color and Word tests.

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