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Original article

Visual system damage and network maladaptation are associated with cognitive performance in neuromyelitis optica spectrum disorders.

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ABSTRACT

Background Neuromyelitis Optica Spectrum Disorders (NMOSD) is an autoimmune disease leading to disability from optic neuritis, myelitis and more rarely brain stem attacks and encephalitis. Patients with NMOSD also exhibit cognitive deficits, the cause of which remains unclear. Recent evidence highlights sensory-cognitive parallel processing converging on the primary visual cortex. The objective of this study was to investigate the effect of the primary visual network disruption from damage caused by optic neuritis on cognition in NMOSD.

Methods Twenty-nine aquaporin-4 antibody seropositive patients with NMOSD and 22 healthy controls (HC) completed the brief repeatable battery of neuropsychological tests (BRB-N) and underwent 3 Tesla MRI. Primary visual network functional connectivity (FC) at resting state was analyzed and correlated with performance on BRB-N. These correlations were compared between the groups.

Results Patients performed significantly worse than HC on the BRB-N Index score ($t = 2.366$, $p = 0.02$). Among HC, visual network FC decreased significantly as cognitive performance on the BRB-N Index score increased (rho(17) = -0.507, $p = 0.02$). Among patients, this association was absent (rho(23) = 0.197, $p = 0.18$), and the difference in correlation direction and strength to HC was significant ($z = -2.175$, $p = 0.01$). Visual network FC was able to explain 19% of the variance in cognitive performance in HC, but none in patients.

Conclusions A physiological association of the primary visual network FC and cognitive performance appears absent in patients with NMOSD, suggesting a partial explanation for cognitive deficits. Our findings extend neuroscientific concepts on sensory-cognitive parallel processing neural networks to a clearly defined pathological state, and may be relevant for other diseases with visual system damage.

1. Introduction

Neuromyelitis Optica Spectrum Disorder (NMOSD) is an autoimmune disease of the central nervous system, in the majority of cases associated with pathogenic antibodies against the astrocyte water channel, aquaporin-4 (Metz et al., 2016). Clinically, patients with NMOSD present with relapsing myelitis and optic neuritis (ON), and more seldom also with brainstem and cerebral attacks (Wingerchuk et al., 2015; Jarius et al., 2012). Unlike multiple sclerosis (MS), where the occurrence of progressive neurodegeneration is clearly

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established, patients with NMOSD rarely experience a progressive disease course and exhibit clinical disability resulting primarily from attacks (Wingerchuk et al., 2007; Pache et al., 2016). For instance, ON regularly leads to profound vision loss and poor recovery regardless of treatment (Schmidt et al., 2017).

Despite this disability-from-attack relationship in NMOSD, patients further present with thus far unexplained symptoms like depression (Chavarro et al., 2016), fatigue (Seok et al., 2017) and cognitive deficits (Dai et al., 2016; Oertel et al., 2019; Eizaguirre et al., 2017), which are highly relevant for health-related quality of life (Dai et al., 2016; Eaneff et al., 2017). Cognitive deficits among patients with NMOSD are consistently reported in the literature, although studies disagree on their type and frequency. While some authors report impaired performance specific to tests of attention, concentration and processing speed (Oertel et al., 2019; Eizaguirre et al., 2017), others suggest deficits in multiple cognitive domains, including learning, memory, executive function and impulse inhibition (Dai et al., 2016; He et al., 2011; Blanc et al., 2008). Likewise, the etiology of cognitive dysfunction is unclear with some studies reporting a potential association of cognitive performance with subcortical (Kim et al., 2017) or cortical (Saji et al., 2013) gray matter atrophy, whereas others reporting no such association (Kim et al., 2016).

The objective of this study was to investigate the association of the functional connectivity (FC) of the primary visual network and cognitive deficits in NMOSD. This was motivated by our recent finding in an overlapping cohort from the same natural history study at our center that FC of the visual resting state network was significantly increased in NMOSD, and that this increase was dependent on afferent visual system damage caused by ON (Finke et al., 2018; Papadopoulou et al., 2019).

In this regard anterograde afferent neurodegeneration subsequent to ON can transmit damage via the thalamic lateral geniculate nucleus to the visual cortex (Finke et al., 2018; Papadopoulou et al., 2019; Tur et al., 2016). Structure and function of the afferent visual pathway not only influences vision but is also associated with higher order cognitive processes as cognitive neuroscience studies suggest a coupling of visual processing and attentional processing circuits converging on the primary visual cortex (Kastner and Pinsk, 2004; Olshausen et al., 1993; Shipp, 2004). In the healthy individual intrinsic functional connectivity of the primary visual cortex at rest exhibits synchronous activation of the visual cortex (calcarine sulcus and closely related lingual gyrus and cuneus; Finke et al., 2018) in the absence of visual stimuli, which may represent maintenance of the system during rest and its capacity for efficient function during activation. (Van den Heuvel and Hulshoff Pol, 2010; Beckmann et al., 2005)

We thus hypothesized that sustained visual deficits in patients with NMOSD would be associated with higher order cognitive processes reliant on overlapping anatomical areas. To investigate this, we first compared cognitive performance of aquaporin-4-antibody positive patients with NMOSD with that of healthy controls (HC). We then investigated the impact of resting state FC of the primary visual network on cognition between patients and HC.

2. Methods and materials

2.1. Patients and controls

Patients were enrolled from 2013 to 2016 as part of an ongoing natural history study of NMOSD conducted at the NeuroCure Clinical Research Center at the Charité - Universitätsmedizin Berlin, Germany. Potential participants were included in this study if: (a) they had a diagnosis of NMOSD according to the 2015 International Panel for NMO Diagnosis criteria (Wingerchuk et al., 2007); (b) had an aquaporin-4 antibody seropositive test; and (c) German was their primary language. Participants older than 60 years of age were excluded to eliminate the interaction of aging and disease processes on both MRI parameters and cognitive performance. There were no further prerequisites to undergo the cognitive battery. However, we included only patients who had complete battery of cognitive test, and therefore a few patients were excluded from participation based on desire to stop testing after start or inability to complete the cognitive tests. Out of 61 NMOSD patients, who consented to participate in the natural history study, 29 satisfied the inclusion/exclusion criteria and completed the cognitive testing. Twenty-two HC with comparable level of education, and matched on age and gender distribution to the patient group were selected from the institute's research database. (Table 1) This study was approved by the local ethics committee (EA1/131/09), and all participants provided written informed consent. Testing was performed on the same day. Visual network FC of 24 patients and 22 HC included in this study has been reported previously (Finke et al., 2018).

Table 1
Demographic and clinical characteristics of patients.

	NMOSD	Healthy controls	P value
N	29	22	
Age (years)	47.9 ± 13.8	41.7 ± 13.5	0.118
Gender (Female,%)	93	82	0.215
Level of education[a]	3/16/10	1/6/15	0.058
EDSS[b]	4.0 (0–7.0)	–	
Disease duration (years)	7.68 ± 6.16	–	
Relapse rate	4(1–16)	–	
Time since last relapse (months)	22.8 ± 20.7	–	
History of optic neuritis (%)	62	–	
Visual Acuity (logMAR)	0.088 ± 0.342	0.084 ± 0.284	0.967
Treatment (*N*)		–	
Rituximab	18		
Azathioprine	4		
Other	5		
No treatment	2		

[a] Grade School/Middle School/High School.
[b] EDSS: Expanded Disability Severity Score. Data are either provided in median (min-max) or mean ± standard deviation.

2.2. Cognition

We administered the German version of Rao's Brief Repeatable Battery of Neuropsychological tests (BRB-N) (Rao, 1991; Scherer et al., 2004). The BRB-N is a widely utilized cognitive battery of tests selected statistically for relevance to patients with a common neuroimmunological disease (namely, multiple sclerosis) from a comprehensive neuropsychological assessment. (Rao, 1991) Moreover, this battery has been shown to be of relevance to patients with NMOSD (Eizaguirre et al., 2017; Blanc et al., 2008; Saji et al., 2013) and our clinicians were experienced in its administration. The current version of the BRB-N was translated and validated in a large cohort from the same geographical area as our center (27, Supplement A). The BRB-N consists of five tests probing four cognitive domains, which includes a global cognitive performance *BRB-N Index* score. The individual domains include the following: *Learning and Short-term Memory* assessing verbal and visuo-spatial encoding and immediate recall; *Long-term Memory*, assessing verbal and visuo-spatial retrieval after encoding has taken place and a distraction task has been performed; *Attention and Concentration*, evaluating sustained attention and information processing; and *Executive Function*, evaluating semantic fluency. The Selective Reminding Test long-term storage (SRT-LTS) score, the Selective Reminding Test consistent long-term storage (SRT-CLTS) score and the Spatial Recall Test (SPART) make up the *Learning and Short-term Memory* domain. The Selective Reminding Test delayed recall (SRT-DR) score and the Spatial Recall Test delayed recall (SPART-DR) score make up the *Long-term Memory* domain. The 2-second Paced Auditory Serial Addition Test (PASAT), the 3-second PASAT and the Symbol Digit Modalities Test (SDMT) comprise the *Attention and Concentration* domain. The *Executive Function* domain consists of the categories verbal fluency Word List Generation (WLG) test score. Details of the relevant

Table 2
Comparison of cognitive performance Z scores between patients with NMOSD and healthy controls.

Cognitive domain	NMOSD (N = 29)	Controls (N = 22)	Test statistic	Effect size	P value*
BRB-N† Index score	**0.339 (1.219)**	**1.061 (0.959)**	***t*(49) = 2.289**	***d* = 0.658**	***P* = 0.026**
Learning and short-term memory	0.522 (1.242)	0.968 (1.018)	*t*(49) = 1.373	*d* = 0.393	*P* = 0.176
Long-term memory	0.545 (1.036)	0.786 (0.639)	*t*(49) = 0.962	*d* = 0.280	*P* = 0.341
Attention & concentration	−0.402 (1.314)	0.413 (0.936)	*t*(49) = 2.470	*d* = *0.714*	*P* = *0.017*
Executive function	0.232 (1.369)	0.814 (1.192)	*t*(49) = 1.589	*d* = 0.453	*P* = 0.118

† BRB-N: Brief Repeatable Battery of Neuropsychological tests (Rao, 1991); Z score results for BRB Index in bold.
* one-sided.

tests have been previously thoroughly described. (Boringa et al., 2001) The optional 2-second PASAT scores were excluded from all composite score calculations because a large number patients were unable to complete this task as a result of it being too stressful.

Z-scores of individual tests were averaged in each domain, adjusted for age, gender and education to the local population, and scaled as described by Scherer et al. (Scherer et al., 2004) to retain only non-overlapping variance. Utilizing the adjusted for age, gender and education z-scores in all analyses allows comparison of the groups considering imperfect matching on those demographic confounders. Moreover, as the focus of this analysis was to compare the performance of the groups on cognition and how cognitive performance was related to FC of the primary visual cortex, we utilized Fisher's z score to compare the strengths of the correlations between these variables. This statistical method was selected because it is less influenced by the sample size as would be the alternative, a multiple regression analysis.

2.3. Resting state functional connectivity of visual network

High-resolution T1-weighted magnetization-prepared rapid gradient echo (MPRAGE) cerebral scans (TR = 1900 ms, TE = 2.55 ms, flip angle 9°, FOV 240 × 240; TI = 900 ms, resolution = 1 × 1 × 1 mm^3) were acquired on a 3 Tesla Siemens MAGNETOM Tim Trio scanner (Siemens, Erlangen, Germany). Echo planar imaging sequences were acquired in the same MRI session, obtaining resting state data with the following metrics: 260 vol, acquisition time 10 min; eyes closed. Preprocessing of resting state fMRI data included discarding of the first four volumes to obtain steady-state magnetization, slice-time correction, motion correction, spatial smoothing with a 6 mm full-width-at-half-maximum (FWHM) Gaussian kernel, mean-based intensity normalization and temporal high-pass filtering (cut-off at 100 s). Resting-state networks common to all HC were identified using independent component analysis with FSL MELODIC (Beckmann et al., 2005). This was followed by dual regression analysis and nonparametric permutation testing with FSL randomise (5000 permutations; threshold-free cluster enhancement for correction of multiple comparisons; $p < 0.05$, family-wise error corrected), as described previously (Finke et al., 2018). FC regression coefficients were extracted from primary visual network regions with significant group differences.

2.4. Visual acuity

Visual acuity (VA) of our patient group was tested monocularly under habitually corrected conditions with the Functional Vision Analyzer Optec 6500 P system (Stereo Optical Co., Chicago, Illinois) at a simulated distance of 20 feet. High-contrast VA was tested using Early Treatment Diabetic Retinopathy Study (ETDRS) charts (Kaiser, 2009).

2.5. Statistical analyses

Statistical analyses were performed with SPSS Version 24 (IBM, Armonk, NY, USA). We compared continuous variables between the patient and control groups with t-tests and categorical variables with χ^2 tests. Primary outcome was BRB-N Index score, and all cognitive domain analyses should be considered exploratory in nature. Cognitive score group comparisons between patients with NMOSD and HC were one-sided, testing if patients with NMOSD performed worse than HC. All other tests were two-sided. Correlations of normally distributed variables were performed with Pearson's correlation coefficient, while those of non-Gaussian distribution (logMAR, FC), with the non-parametric Spearman's rho. We used Fischer's z test to estimate the significance of effect of group on correlations of interest per Wuensch (Wuensch, 2007). Statistical significance was represented by a $p < 0.05$. Due to the explorative design of the study correction for multiple comparisons was not carried out.

3. Results

3.1. Cognitive performance

On average, patients performed numerically worse than HC on all cognitive domains, but this difference only reached statistical significance for the BRB-N Index domain ($p = 0.026$) and the Attention and Concentration domain ($p = 0.018$; Table 2). Effect sizes evaluated with Cohen's d for differences on both cognitive domains ($d = 0.66$, $d = 0.71$, respectively) suggest a moderate difference between the groups. BRB-N Index score captures performance across all cognitive domains and is a measure of global cognition, while the Attention and Concentration targets auditory and visual attention. Only one patient was cognitively impaired, defined as scoring 2 standard deviations below the population healthy control mean on the BRB-N Index as recommended by the German BRB-N validation study (Scherer et al., 2004). This patient performed below average on all cognitive domains and presented with clinically impaired Attention and Concentration and Executive function, but not Short- or Long-term Memory. No other patients exhibited impaired performance on the Executive function, Short- or Long-term Memory domains. However, one other patient exhibited impaired performance on the Attention and Concentration domain – the overall BRB-N Index score of this patient was not impaired as a result of above average performance on the other cognitive tests.

Cognitive performance of BRB-N Index or any of the subdomains was independent of visual acuity (not shown), suggesting that the general ability to perform cognitive testing with vision-dependent tasks was not reduced in patients.

3.2. Functional connectivity of the primary visual network and cognitive performance

As previously reported from data of the same observational study, FC of the primary visual network was higher in NMOSD patients than in HC (Finke et al., 2018). This was also the case for the overlapping cohort from the same natural history study at our center investigated in this study (FC in patients 44.6 ± 21.0, in controls 29.6 ± 14.8, t(38) = 2.529, $p = 0.016$). We hypothesized that this increase was maladaptive and potentially associated with cognitive dysfunction in NMOSD. Indeed, within the HC group, FC of the primary visual network and BRB-N index scores were negatively correlated, i.e. visual network FC decreased as BRB-N Index scores improved ($r = -0.507$; $p = 0.019$;

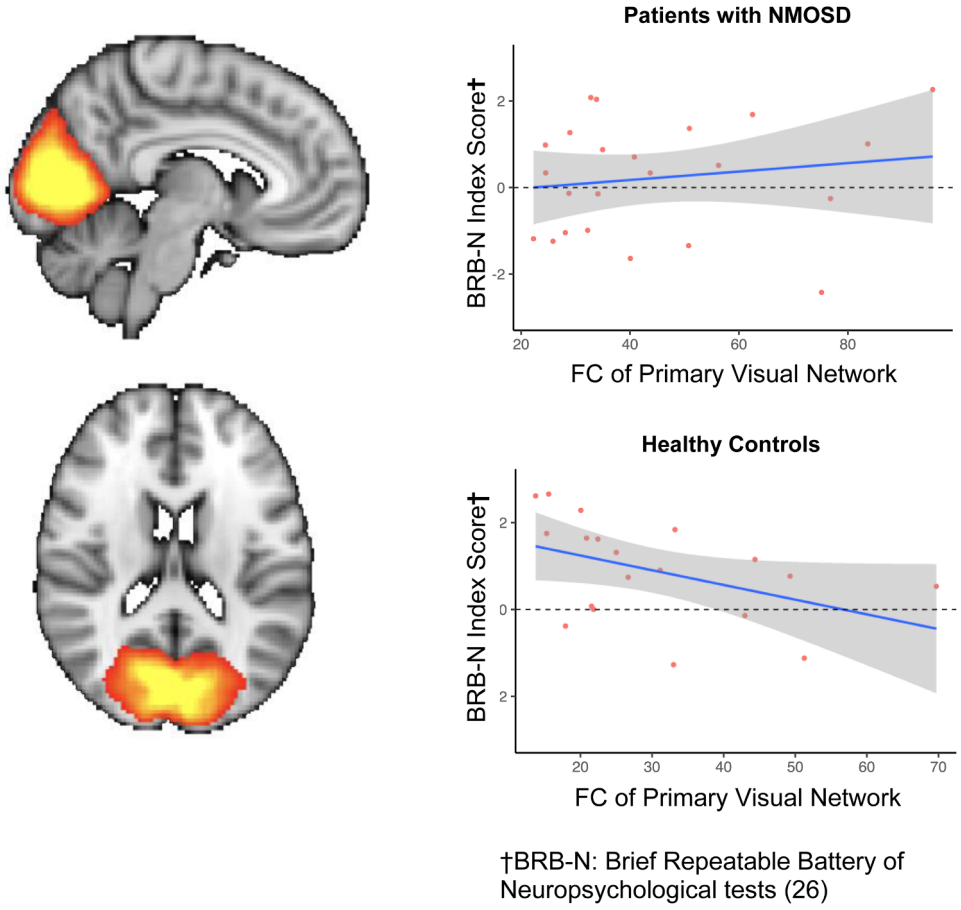

Fig. 1. . Primary visual network functional connectivity (FC) and cognitive performance in NMOSD patients and healthy controls.

Table 3
Correlation of cognitive performance and visual network functional connectivity.

Correlation coefficients	BRB-N† Index score	Short-term memory	Long-term memory	Attention and concentration	Executive function
Controls	**−0.507**	−0.574	−0.265	−0.355	−0.350
p value	**0.019**	0.008	0.152	0.081	0.084
N	**17**	17	17	17	17
Patients	**0.197**	0.123	0.113	0.202	0.364
p value	**0.184**	0.289	0.304	0.178	0.044
N	**23**	23	23	23	23
Fisher's z	**−2.175**	−2.229	−1.106	−1.653	−2.144
p value	**0.014**	0.013	0.134	0.049	0.016

† BRB-N: Brief Repeatable Battery of Neuropsychological tests(26). Results for BRB Index in bold.

Fig. 1; Table 3). A similar moderate negative association was observed between visual network FC and Short-term Memory ($r = -0.574$; $p = 0.008$), while there was a trend in the associations between FC and the Attention and Concentration ($r = -0.355$; $p = 0.081$), and FC and Executive Function ($r = -0.350$, $p = 0.084$, Table 3).

Among patients, however, the strength of the associations between primary visual network FC and cognitive performance (i.e. the BRB-N Index score and cognitive domain sub-scores; Table 3) was attenuated. Moreover, the direction of all correlations between primary visual network FC and cognitive performance domains was positive among patients, i.e. as visual network FC decreased cognitive performance worsened, but was negative among HC. (Table 3 and Figure 1) The major focus of our analysis, the strength and direction of the associations between visual network FC and cognition, as illustrated with the Fisher's z scores, differed significantly between patients and HC for all cognitive domains except long-term memory (i.e. visual network FC and BRB-N Fisher's z score $= -2.175$, $p = 0.014$; Table 3.)

In a lineal regression model, visual network FC could not explain the variance in cognitive performance among patients ($R^2 = 2\%$, $p = 0.478$), while among HC, FC of the visual network explained 19% of the variance of cognitive performance measured with BRB-N Index ($R^2 = 19.3\%$, $p = 0.060$).

4. Discussion

Here, we report the impact of the neural correlates of vision loss, the most frequent initial presentation of patients with NMOSD, on cognitive performance. We found a significant difference in the relationship of visual network FC with cognitive performance between patients and HC: among HC, better performance on all cognitive domains was associated with decreased FC of the primary visual cortex; while in patients, better performance on all cognitive domains was associated with increased FC of the primary visual cortex. Our results may provide a partial explanation for the loss of efficiency of neural networks utilized in cognitive performance among patients with aquaporin-4 positive NMOSD.

On average patients with NMOSD exhibit specific cognitive deficits but do not have cognitive impairment. We report that patients from our center, although scoring lower than healthy individuals on all cognitive domains, exhibited significant deficits only on tests of attention and concentration. This is consistent with previous reports on cognition among NMOSD patients (Dai et al., 2016; Oertel et al., 2019; Eizaguirre et al., 2017; He et al., 2011; Blanc et al., 2008; Kim et al., 2017). Moreover, some authors also report deficits on tests of verbal learning and memory (He et al., 2011), but not visuo-spatial learning

and memory. Although our patients performed within the lower end of healthy individuals' range on the SDMT, PASAT and WLG, their performance was not formally impaired on any cognitive domain or test according to a clinical criterion of less than 2 standard deviations below the healthy average representative of the population. The discrepancy of which cognitive functions and the extent to which they are affected among patients with NMOSD may reflect the heterogeneity of cohorts, geographic or ethnic confounders; as well as differences in test administration and raw scores interpretation.

Sustained network alterations in the visual system secondary to afferent optic nerve damage, as observed in this cohort of patients with NMOSD, are associated with cognitive performance, especially when relying on overlapping neural networks. This suggests that FC changes within the primary visual network are maladaptive and impact not only vision, but also some aspects of cognitive function. These findings are consistent with overwhelming evidence from vision neuroscience connecting sensory and cognitive processing converging on the primary visual cortex and thalamus (Kastner and Pinsk, 2004; Olshausen et al., 1993; Shipp, 2004) and translate the concepts of bottom up and top down sensory-cognitive modulation to a pathological state.

Our findings are consistent with studies on the plasticity and efficiency of functional networks in the healthy brain: as cognitive performance increased, FC decreased within our healthy cohort – denoting a more efficient neural network. This significant association of cognitive performance and FC of the primary visual network observed among HC was not preserved in patients. Instead, an inverse association was observed within the patient cohort: as cognitive performance increased, FC within the primary visual network also increased, thus attenuating its efficiency.

Studies in healthy individuals (Kastner et al., 1999) show that synchronization of neural activity between the thalamus and the visual cortex during auditory and visual attention tasks occur in two loops converging on the primary visual cortex. One processing stream is initiated with sensory information input to the retina via the thalamic lateral geniculate nucleus to the visual cortex. A parallel attention-processing loop occurs via the superior colliculus to the visual cortex, the thalamic pulvinar and higher cortical areas (Kastner et al., 1999; Simola et al., 2009). Kastner and colleagues (Kastner et al., 1999) showed that healthy participants focusing their attention to a specific visual field in the absence of visual stimuli had an increase of fMRI BOLD signal 30–40% from baseline in the V1, V2 and V4. In addition, Simola and colleagues (Simola et al., 2009) extracted areas of activation in the visual cortex during visual tasks performed by healthy subjects. The same subjects performed voluntary attention tasks in which the same areas exhibited a significantly enhanced fMRI BOLD signal. The interaction of these bottom-up and top-down processing streams is also supported by evidence from resting-state FC studies in healthy human participants. Spadone et al. (Spadone et al., 2015) reported cross-modulation of resting-state BOLD fluctuations of partially overlapping visual network and dorsal attention network. Active attentive state, consistent with our findings in HC, decreased the connectivity of the visual network while enhancing connectivity of the dorsal attention network and overlapping areas. Our findings contribute to the extensive research on vision neuroscience by showing that dysfunction in the visual processing neural network secondary to pathological changes modulates the function of the overlapping attention processing network.

A contribution of vision loss to cognitive dysfunction has been previously reported from simulations and in other diseases. In one large study comprising 420 patients with different eye diseases, patients performed worse on cognitive tests than controls (Harrabi et al., 2015). However, participants were older than 65 years, and thus non-linear age-related effects or contribution of undiagnosed mild cognitive impairment could not be ruled out. In another randomized-control study healthy individuals with VA of 6/6 (20/20) wore cataract simulation goggles with filters of varying degrees of opacity (Wood et al., 2009). In the experimental conditions, VA and cognitive performance, specifically probing attention, were significantly worse than in the control condition (no filter goggles). Such interaction and modulation of sensory and higher-order cognitive processes typically fall under the umbrella of bottom-up or top-down theories of information processing (Pylyshyn, 1999; Itti and Borji, 2015). However, this dichotomy of information processing models may be blurred as the integration of sensory input and cognitive control share overlapping neural networks (Kastner and Pinsk, 2004; Olshausen et al., 1993; Shipp, 2004; Van den Heuvel and Hulshoff Pol, 2010; Kastner et al., 1999; Simola et al., 2009).

An important confounder when testing an association between cognitive and visual performance stems from the fact that many cognitive tests rely on vision to assess cognitive function. It is possible that cognitively demanding tasks in the setting of visual deficits require more effort and thus place a greater demand on neural processing. To avoid such confounding, neuropsychology experts recommend visual function prescreening prior to neuropsychological assessment of patients with multiple sclerosis (Benedict et al., 2002), another neuroinflammatory disease affecting the optic nerve. In our study, the association of purely auditory tests with visual function was comparable to the association with vision-based tests as previously reported in patients with multiple sclerosis (Wieder et al., 2013).

Results from our study should be considered with a few limitations. Because of the low prevalence of NMOSD and our strict inclusion criteria, our sample size was small. Our results cannot be extrapolated to patients who are not aquaporin-4 antibody seropositive, e.g. myelin oligodendrocyte glycoprotein (MOG) antibody seropositive or aquaporin-4/MOG antibody double seronegative patients. In addition, due to the small sample size a methodological decision was made not to correct our results for multiple comparisons, which may result in overestimating the observed group differences. However, considering the exploratory design of this study this was an acceptable methodological limitation.

Another important limitation of our study was not closely matching HC to patients on education as well as our HC being of slightly younger age on average, albeit not statistically significant. Education and age are well-recognized confounders of cognition. Therefore, we chose to utilize the z scores per Scherer et al. (Scherer et al., 2004) as those scores are adjusted for age, gender and education from the local Berlin, Germany population and allow for the comparison across individuals with different demographics. Further, education in Germany is structured differently from education in other countries, therefore perusing the adjusted z scores allows for comparison across subjects and studies.

Another important limitation of our study was the lack of visual function data among HC. Therefore, we could not assess whether the association of the functional impairment of vision was specific to the patient group. Nevertheless, we show that the underlying structural and functional neural correlates of visual function were associated with cognitive performance and were significantly different between patients and HC. More importantly, the significant inverse association of cognitive performance and FC of the primary visual network observed among HC was not preserved in patients.

In addition, further confounders of the association of primary visual network with cognition, such as the thalamus and the dorsal attention network would be important to investigate.

In summary, our study illustrates that cognitive deficits in NMOSD can be partially explained by FC maladaptation of the primary visual network. Our study provides clear evidence that overlapping neural networks are relevant in NMOSD, and can potentially influence

cognitive performance. Further, our results present NMOSD as an adequate disease model to study the association of sensory and attentional cross-modulatory neural processes. Future research should address resting-state FC of the attention network and its association with cognitive performance and visual deficits within similar cohorts and primary disorders of vision.

CRediT authorship contribution statement

Velina S. Chavarro: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Validation, Visualization, Writing - original draft, Writing - review & editing. **Judith Bellmann-Strobl:** Data curation, Investigation, Project administration, Validation, Visualization, Writing - review & editing. **Hanna G. Zimmermann:** Investigation, Validation, Visualization, Writing - review & editing. **Michael Scheel:** Investigation, Validation, Visualization, Writing - review & editing. **Claudia Chien:** Investigation, Validation, Visualization, Writing - review & editing. **Frederike C. Oertel:** Investigation, Validation, Visualization, Writing - review & editing. **Martin Weygandt:** Investigation, Validation, Visualization, Writing - review & editing. **Klemens Ruprecht:** Investigation, Validation, Visualization, Writing - review & editing. **Friedemann Paul:** Conceptualization, Funding acquisition, Investigation, Resources, Supervision, Validation, Visualization, Writing - review & editing. **Carsten Finke:** Formal analysis, Investigation, Resources, Validation, Visualization, Writing - review & editing. **Alexander U. Brandt:** Conceptualization, Data curation, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing.

Declaration of Competing Interests

None

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Disclosures

HZ received research grants from Novartis, unrelated to this study. AUB is cofounder and shareholder of technology startups Motognosis GmbH and Nocturne GmbH. He is named as inventor on several patent applications describing serum biomarkers for multiple sclerosis, perceptive visual computing for motor function assessment and retinal image analysis.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2020.102406.

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