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Association of Visual Impairment in Neuromyelitis Optica Spectrum Disorder With Visual Network Reorganization

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IMPORTANCE Severe visual impairment is one of the major symptoms in neuromyelitis optica spectrum disorder (NMOSD), but functional network reorganization induced by the diminished sensory input has not been investigated thus far.

OBJECTIVE To examine adaptive visual network connectivity changes in NMOSD.

DESIGN, SETTING, AND PARTICIPANTS In this cross-sectional study, data were collected from May 1, 2013, through February 31, 2016, from 31 patients with aquaporin-4 antibody–positive NMOSD and 31 age- and sex-matched healthy control individuals at the Department of Neurology and NeuroCure Clinical Research Center at Charité–Universitätsmedizin Berlin, Berlin, Germany.

MAIN OUTCOMES AND MEASURES Visual function (high-contrast visual acuity and contrast sensitivity), optical coherence tomography (peripapillary retinal nerve fiber layer and ganglion cell layer thickness), and resting-state functional magnetic resonance imaging (functional connectivity of large-scale brain networks).

RESULTS Thirty-one patients with NMOSD (mean [SD] age, 48.2 [13.9] years; 28 women and 3 men) and 31 healthy controls (mean [SD] age, 47.2 [15.3] years; 28 women and 3 men) participated in the study. Patients had a selective and pronounced increase of functional connectivity in the primary and secondary visual networks. Increased primary visual network connectivity correlated with reduced high-contrast visual acuity ($r = -0.39$, $P = .006$), reduced low-contrast sensitivity ($r = -0.33$, $P = .03$), and more severe retinal damage measured by optical coherence tomography ($r = -0.4$, $P = .01$). Furthermore, visual functional connectivity was significantly higher in patients with a history of optic neuritis compared with patients without optic neuritis (mean [SD] regression coefficients, 50.0 [4.3] vs 34.6 [5.6]; $P = .04$).

CONCLUSIONS AND RELEVANCE Impaired visual function and retinal damage are associated with selective reorganization of the visual network in NMOSD. These findings advance the understanding of visual system dysfunction in NMOSD and, more generally, provide insight into pathophysiologic responses of the visual system to impaired visual input.

Editorial page 274

Related article page 287

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Severe visual dysfunction after attacks of optic neuritis (ON) is a typical clinical feature of neuromyelitis optica spectrum disorder (NMOSD).[1] Poor residual vision is a major contributor to a more rapid accumulation of neurologic disability in NMOSD compared with multiple sclerosis (MS), the main differential diagnosis.[2] Observations from several NMOSD cohorts underpin the significant visual disability that results from ON. For example, 60% of patients with relapsing NMOSD in a US study[3] were functionally blind in at least 1 eye after a mean disease duration of 7.7 years, whereas a study[4] from the United Kingdom and Japan reported bilateral permanent visual disability in 18% of patients after a median disease duration of 75 months.

Neuroimaging studies in patients with MS and ON have reported both structural changes in the retrogeniculate visual pathway, including the occipital cortex, suggesting anterograde transsynaptic degeneration,[5-7] and functional alterations of connectivity and plasticity in larger visual networks, indicating adaptive mechanisms in the visual system.[8-11] However, interpretation of structural and functional consequences of ON in MS is limited by the presence of demyelinating lesions in the optic radiation and typically relatively mild visual impairment. In contrast, NMOSD constitutes an ideal model for the investigation of functional changes after ON given the absence of optic radiation lesions in typical cases together with severe visual impairment.

Although functional reorganization after structural damage is now increasingly recognized as a relevant mechanism in neurologic disorders, it is important to disentangle whether changes in functional magnetic resonance imaging (MRI) activation or functional connectivity represent compensatory or detrimental processes.[12,13] For example, adaptive plasticity can successfully compensate for impaired function in patients with focal lesions (ie, increased activity or connectivity is associated with better motor or cognitive performance).[14,15] In contrast, increased activity or functional connectivity after structural damage can also be associated with impaired motor and cognitive functions, suggesting maladaptive plasticity.[16,17]

We therefore investigated visual network functional connectivity changes associated with severe visual impairment and structural retinal damage in a cohort of patients with aquaporin-4 (AQP4) antibody-seropositive NMOSD. Functional connectivity alterations were analyzed in association with visual function (high- and low-contrast visual acuity [VA]) and optical coherence tomography (OCT) measures (peripapillary retinal nerve fiber layer [pRNFL] and ganglion cell layer thickness). We hypothesized that the severity of visual impairment and of retinal thinning in patients with NMOSD and ON would be associated with functional connectivity alterations in visual networks.

Key Points

Question Is visual impairment in neuromyelitis optica spectrum disorder associated with adaptive functional network reorganization?

Findings In this cross-sectional study of 31 patients with aquaporin-4 antibody–positive neuromyelitis optica spectrum disorder, a selective and pronounced increase of visual network functional connectivity was observed. This increased connectivity was associated with impaired visual function and retinal damage and was more pronounced in patients with a history of optic neuritis.

Meaning Visual impairment and anterior visual system damage are associated with a selective reorganization of functional visual networks in neuromyelitis optica spectrum disorder.

Methods

Patients and Controls

Thirty-one patients with NMOSD who fulfilled the 2015 international consensus diagnostic criteria[18] were recruited from the outpatient clinics of the NeuroCure Clinical Research Center and the Department of Neurology, Charité–Universitätsmedizin Berlin, Berlin, Germany, between May 1, 2013, and February 31, 2016 (**Table**). Serum samples from all patients were tested for AQP4 and myelin-oligodendrocyte-glycoprotein (MOG) antibodies by an accredited clinical laboratory (Euroimmun). Inclusion criteria were white ethnicity and anti-AQP4 antibody seropositivity. Patients with MOG antibodies and relevant ophthalmologic comorbidities were excluded. Furthermore, OCT data from patients with a refractive error greater than ±6 diopters were excluded from analysis. Patients were treated with rituximab (n = 17), azathioprine (n = 6), mycophenolate mofetil (n = 2), teriflunomide (n = 1), or tocilizumab (n = 1) or received no treatment (n = 4). All patients were relapse free and without high-dose corticosteroid treatment at least 2 weeks before the MRI investigations. The control group comprised 31 healthy individuals from the institute's research database who had no history of neurologic or psychiatric diseases and were matched for age and sex (Table). All data are presented as mean (SD). The study was approved by the Charité–Universitätsmedizin Berlin Ethics Committee. All study participants gave written informed consent for research and publication.

Visual Function and OCT

Visual function testing was performed with a vision screener (Optec 6500, Stereo Optical Inc). High-contrast VA was measured using Early Treatment Diabetic Retinopathy Study charts at a simulated 20-foot distance and analyzed as the total number of correctly identified letters. Contrast sensitivity was measured using Functional Acuity Contrast Test charts at photopic (85 candela) conditions. The Functional Acuity Contrast Test was performed at 5 different spatial frequencies.[19] Contrast sensitivities were then combined as area under the curve over all spatial frequencies. All tests were performed monocularly and binocularly with habitual refractive error correction. Retinal layer measurements were acquired with a Heidelberg Spectralis spectral-domain OCT (Heidelberg Engineering) and are reported according to Advised Protocol for OCT Study Terminology and Elements recommendations.[20] The pRNFL thickness was determined using the device's standard protocol from a circular scan around the optic nerve head (scanning angle, 12°; automatic real-time tracking, 16-100 repetitions). Macular volume

Table. Demographic and Clinical Data of Patients With NMOSD

Variable	Finding
Age, mean (SD), y	48.2 (13.9)
Sex, M/F, No.	3/28
AQP4 antibody, No.	
Positive	31
Negative	0
Disease duration, mean (SD), y	6.9 (7.8)
EDSS score, median (range)	4.0 (0-6.5)
Optic neuritis	
Unilateral	10
Bilateral	11
None	10
Visual acuity, mean (SD)	
logMAR	0.29 (0.61)
Letters	38.2 (19.7)
FACT score, AUC, mean (SD)	1.30 (0.80)
pRNFL, mean (SD), µm	76.4 (23.3)
GCIP, mean (SD), µm	56.8 (13.7)

Abbreviations: AQP4, aquaporin-4; AUC, area under the curve; EDSS, Expanded Disability Status Scale; FACT, Functional Acuity Contrast Test; GCIP, ganglion cell and inner plexiform layer; NMOSD, neuromyelitis optica spectrum disorder; pRNFL, peripapillary retinal nerve fiber layer.

was acquired using a custom protocol that focused on the fovea (61 B-scans; scanning angle, 30° × 25°; high-speed mode [768 A-scans per B-scan]; automatic real-time tracking, 15 repetitions). Scans were checked for correct centering, sufficient signal strength, and segmentation based on the OSCAR-IB criteria.[21] One patient was excluded from analysis because of severe myopia. Intraretinal segmentation was automatically performed with the manufacturer's software (Heidelberg Eye Explorer, version 1.9.10.0 with Spectralis Viewing Module, version 6.0.9.0). All segmentation results were controlled by an experienced grader (F.C.O.) and corrected when necessary. The combined ganglion cell–inner plexiform layer (GCIPL) was extracted as volume within the standard 6-mm Early Treatment Diabetic Retinopathy Study ring around the fovea and converted to thickness measures.

MRI Data Acquisition

The MRI data were acquired at the Berlin Center for Advanced Neuroimaging at Charité–Universitätsmedizin Berlin (Magnetom Tim Trio 3-T scanner, Siemens) using the following sequences: (1) a high-resolution, 3-dimensional magnetization-prepared rapid gradient-echo sequence (voxel size, 1-mm isotropic) and (2) an echo-planar imaging sequence for the acquisition of resting-state data (repetition time, 2250 milliseconds; voxel size, 3.4-mm isotropic; 260 volumes; eyes closed).

Resting-State Functional Connectivity Analysis

Resting-state functional MRI data were analyzed with independent component analysis and dual regression using FSL software (FMRIB Software Library, http://www.fmrib.ox.ac.uk).[22,23] Preprocessing included discarding the first 4 volumes to obtain steady-state magnetization, slice-time correction, motion correction, spatial smoothing with a 6-mm full-width-at-half-maximum gaussian kernel, mean-based intensity normalization, and temporal high-pass filtering (cutoff at 100 seconds). Absolute head motion was below 1.5 mm for all 62 participants, and no significant differences were found between patients with NMOSD and healthy controls in absolute (0.37 [0.15] vs 0.35 [0.32] mm) and relative motion (0.13 [0.06] vs 0.12 [0.06] mm; $P = .45$). After preprocessing, resting-state networks common to all healthy controls were identified using a data-driven approach (ie, temporal concatenation independent component analysis as implemented in FSL MELODIC) and closely resembled the canonical networks previously reported.[24] The main analysis focused on the 2 components that captured the primary and secondary visual cortex networks (also referred to as the medial and lateral visual network) because of our aim to investigate functional connectivity changes associated with visual impairment in NMOSD (**Figure 1**).[24,25] The primary visual network comprises the calcarine sulcus and medial extrastriate regions (eg, lingual gyrus and cuneus) bilaterally, whereas the secondary visual network includes the occipital pole, the lateral occipital cortex, and the occipital part of the fusiform gyrus. In addition, we investigated group differences in a set of 6 other canonical large-scale networks that represented major functional systems (ie, the sensorimotor, auditory, left and right frontoparietal, salience, and default mode networks).[24,25]

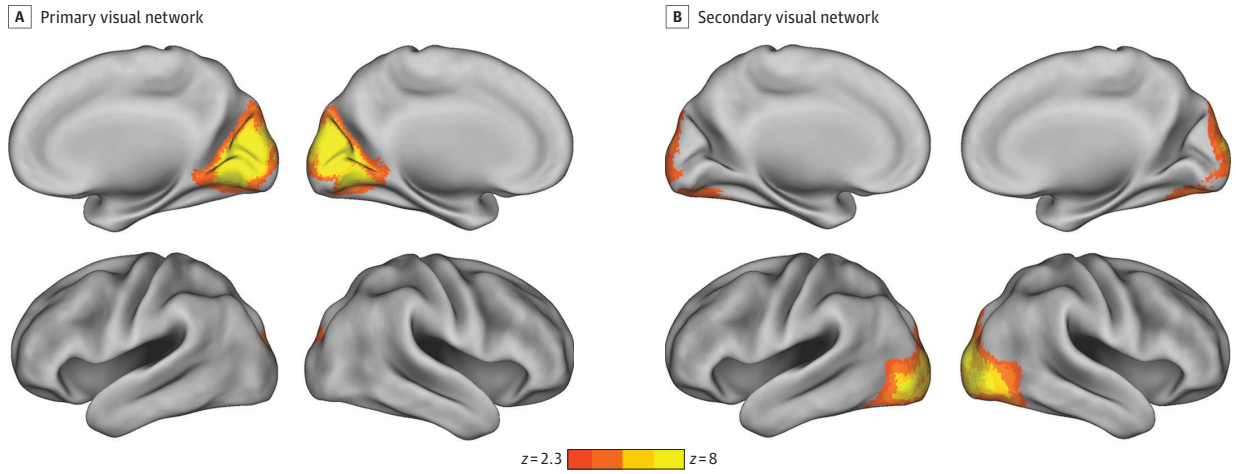
Statistical Analysis

Statistical analysis for functional connectivity group differences was conducted using dual regression and nonparametric permutation testing as implemented in the FSL tool Randomise (5000 permutations) using threshold-free cluster enhancement for correction of multiple comparisons ($P < .05$, family-wise error corrected). Functional connectivity regression coefficients were extracted from visual cortex regions with significant group differences. We used generalized estimating equation (GEE) models[26] as implemented in R Project 3.2.2 and geepack 1.2-0.1 to assess the correlation between functional connectivity changes and OCT or visual function in patients. Both eyes of each participant were included as separate cases; OCT or visual function measures were set as the response variable and functional connectivity as the independent variable. The GEE working correlation matrix was set to *exchangeable*, thereby accounting for within-participant intereye correlations. Demographic variables were compared between groups using independent-sample *t* tests (age) and the Fisher exact test (sex).

Results

Thirty-one patients with NMOSD (mean [SD] age, 48.2 [13.9] years; 28 women and 3 men) and 31 healthy controls (mean [SD] age, 47.2 [15.3] years; 28 women and 3 men) participated in the study. Patients had extensively increased functional connectivity within the primary visual network bilaterally compared with healthy controls (Figure 1A). These functional connectivity alterations were observed throughout the whole network, including the calcarine sulcus, the

Figure 1. Primary and Secondary Visual Networks



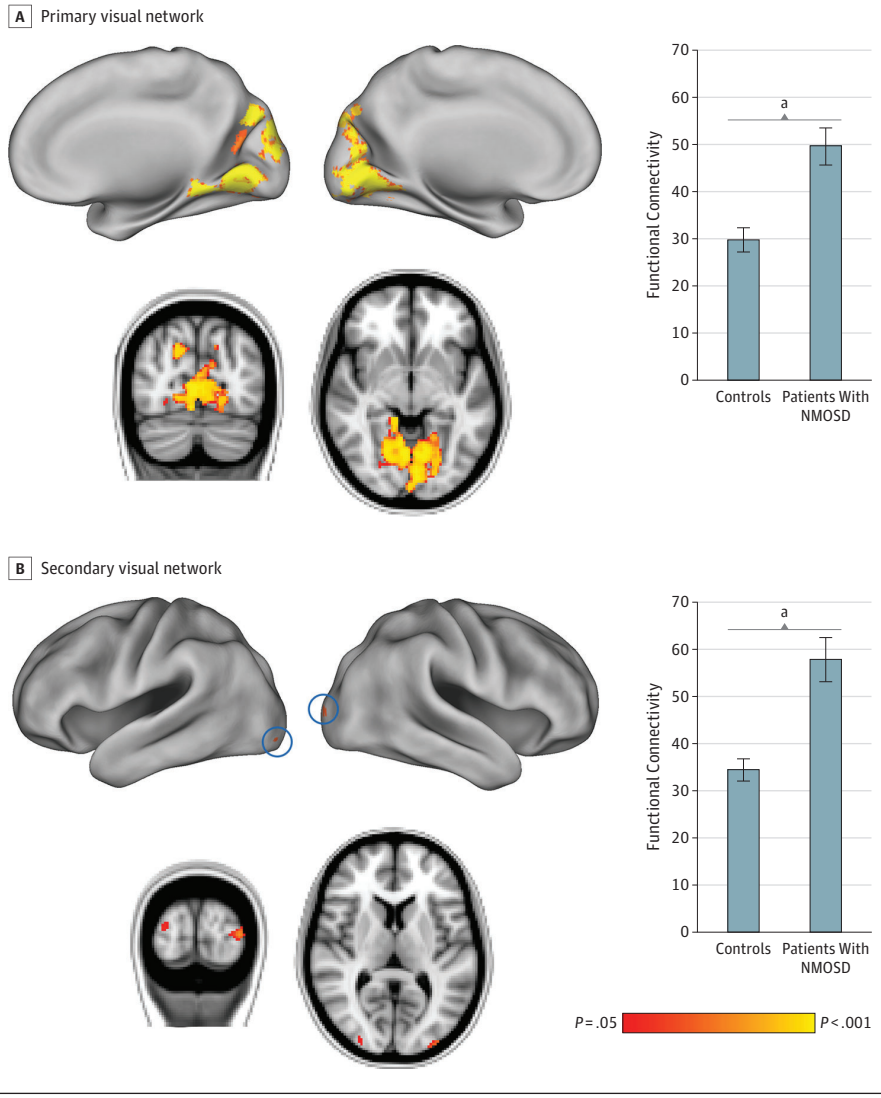
The primary (A) and secondary (B) visual networks were identified using independent component analysis.

lingual gyrus, and cuneus, but also extended to regions outside the primary visual network, including the lateral occipital cortex, the occipital fusiform gyrus, and the middle temporal gyrus. To further characterize these functional connectivity differences between patients and controls, regression coefficients from regions of interest with significantly different functional connectivity were extracted. This analysis found positive regression coefficients for both groups, albeit with higher functional connectivity in patients (Figure 1A). In contrast to the markedly increased functional connectivity within the primary visual network, functional connectivity within the secondary visual network was increased in patients compared with controls only in circumscribed regions of the occipital pole bilaterally (Figure 1B). Extracted regression coefficients similarly showed increased functional connectivity in patients compared with controls (**Figure 2**). For the remaining investigated networks (ie, the sensorimotor, auditory, left and right frontoparietal, salience, and default mode networks), no significant functional connectivity differences between patients and controls were observed.

Next, we assessed whether the functional connectivity alterations correlated with visual function, retinal integrity, and history of ON in patients. The GEE models revealed a significant negative correlation between high-contrast VA and functional connectivity of the primary (B, −0.320 [0.117]; $r = -0.39$; $P = .006$) and secondary (B, −0.324 [0.122]; $r = -0.41$; $P = .008$) visual networks (**Figure 3**); thus, lower high-contrast VA was associated with higher visual network functional connectivity. Similarly, low-contrast sensitivity was negatively correlated with primary visual network functional connectivity (B, −0.012 [0.005]; $r = -0.33$; $P = .03$) (Figure 3). Moreover, patients with previous ON had significantly higher primary visual network functional connectivity compared with patients without prior ON (regression coefficients, 50.0 [4.3] vs 34.6 [5.6]; $P = .04$) and compared with healthy controls (regression coefficients, 50.0 [4.3] vs 27.1 [2.3]; $P < .001$) (**Figure 4**), whereas there was no group difference between patients without prior ON and healthy controls (regression coefficients, 34.6 [5.6] vs 27.1 [2.3]; $P = .24$). No difference was found between patients with unilateral and bilateral ON (regression coefficients, 52.3 [6.4] vs 43.5 [6.3]; $P = .34$). Finally, primary visual network functional connectivity was negatively correlated with GCIPL thickness (B, −0.198 [0.077]; $r = -0.4$; $P = .01$) but not with pRNFL thickness (B, 0.07 [0.04]; $r = 0.3$; $P = .12$) in all patients (Figure 3). In line with a previous study,[27] high-contrast VA and GCIPL thickness were significantly correlated in patients (B, 1.32 [0.2]; $r = 0.69$; $P < .001$). In a combined GEE model of primary visual network functional connectivity, high-contrast VA, and GCIPL thickness, the correlation between functional connectivity and VA no longer remained significant when controlling for GCIPL thickness (B, −0.120 [0.109]; $P = .28$), likely related to the high correlation between VA and GCIPL. In contrast to the primary visual network, secondary visual network functional connectivity was not significantly correlated with low-contrast sensitivity (B, −0.008 [0.007]; $P = .27$), GCIPL thickness (B, −0.023 [0.067]; $r = -0.05$; $P = .73$), and pRNFL thickness (B, −0.006 [0.004]; $r = -0.17$; $P = .49$) and was not significantly different between patients with and without previous ON (regression coefficients, 54.5 [10.2] vs 58.5 [5.6]; $P = .74$).

Functional connectivity of both visual networks did not correlate significantly with the time since the last ON attack (primary visual network: B, 17.7 [11.5]; $r = 0.2$; $P = .12$; secondary visual network: B, 27.6 [15.4]; $r = 0.24$; $P = .07$). The Expanded Disability Status Scale score was not correlated with high-contrast VA (B, −1.32 [1.5]; $r = -0.13$; $P = .38$), low-contrast sensitivity (B, −0.035 [0.057]; $r = -0.09$; $P = .53$), or primary ($r = 0.17$, $P = .22$) and secondary ($r = 0.22$, $P = .12$) visual network functional connectivity. Furthermore, there was no difference in primary and secondary visual network functional connectivity among patients receiving rituximab, any of the other treatments, or no treatment.

Figure 2. Visual Network Connectivity in Neuromyelitis Optica Spectrum Disorder (NMOSD)



A, Patients with NMOSD had substantially increased functional connectivity within the entire primary visual network bilaterally (calcarine sulcus, lingual gyrus, and cuneus) and regions outside the primary visual network, including the lateral occipital cortex, occipital fusiform gyrus, and middle temporal gyrus ($P < .05$, familywise error corrected). Coronal and axial sections are shown in the lower panel and regression coefficients extracted from regions with significant group differences on the right. B, Secondary visual network functional connectivity was increased in the occipital pole bilaterally. Coronal and axial sections are shown in the lower panel and extracted regression coefficients on the right. Error bars indicate SD.

[a] $P < .05$.

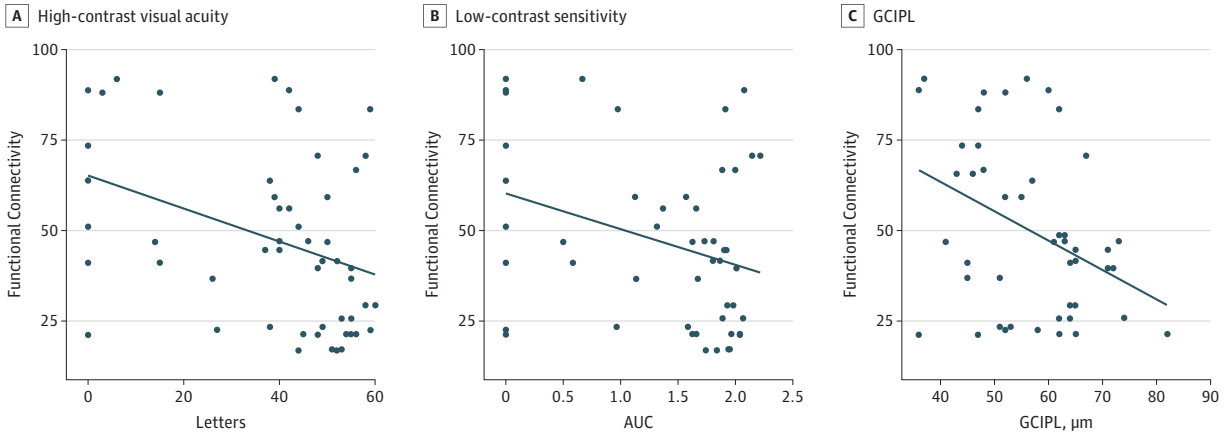
Discussion

Aquaporin-4 antibody-positive NMOSD is associated with a selective and pronounced increase of functional connectivity in visual cortical networks, whereas no other large-scale networks are affected. Patients with NMOSD with previous ON had significantly higher visual functional connectivity than did patients with NMOSD without ON. Of importance, increased visual functional connectivity was associated with more severe retinal damage and reduced VA.

Supratentorial brain MRI typically shows normal findings or only nonspecific lesions in most patients with NMOSD.[28] Nevertheless, NMOSD prevalence, clinical presentation, and frequency of MRI abnormalities depend on ethnicity and AQP4 antibody status.[29,30] For example, deep gray matter damage has been reported in Chinese[31] but not in Western patients[32] and, beyond that, is more frequent in patients with NMOSD with MOG antibodies than with AQP4 antibodies.[33] As a key point of this study, we therefore investigated a homogeneous study sample that included only white patients with AQP4 antibody-positive NMOSD.

Visual impairment is a major clinical symptom in NMOSD and responsible for severe disability and reduced quality of life.[34] Patients experience monophasic or recurrent attacks of ON frequently causing functional blindness.[3,4,35] Visual loss and associated retinal damage (ie, RNFL and ganglion cell layer thinning) are significantly more severe in NMOSD than in MS.[36,37] Advanced structural imaging analyses revealed mild thinning of the visual cortex and impaired microstructural integrity restricted to the optic radiation in patients with NMOSD when stringent correction for multiple comparisons was applied.[38,39] Microstructural alterations of the optic radiation correlated with retinal nerve fiber layer thinning, presumably indicating secondary visual pathway degeneration following ON.[38,40] We found that patients with AQP4 antibody-positive NMOSD exhibit extensively increased functional connectivity in the visual cortex. This increased con-

Figure 3. Correlation of Visual Network Connectivity With Visual Function and Retinal Damage

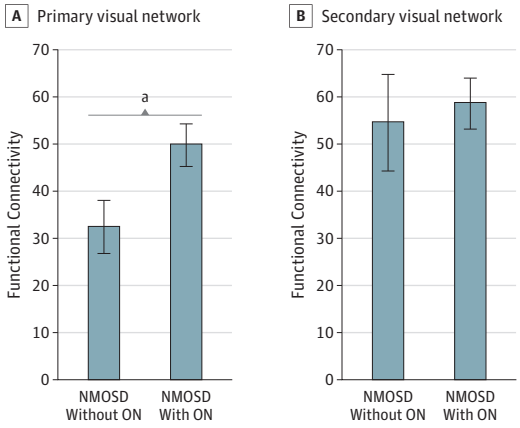


A and B, Correlation analyses using generalized estimating equation models revealed that impaired high-contrast visual acuity and impaired low-contrast sensitivity were associated with increased primary visual network connectivity regression coefficients. C, Reduced ganglion cell–inner plexiform layers (GCIPLs) of the retina (ie, retinal damage) were likewise associated with increased primary visual network connectivity. AUC indicates area under the curve.

nectivity was correlated with reduced visual activity and reduced GCIPL thickness, suggesting that the observed network changes are related to retinal damage and consecutively impoverished visual input. This hypothesis is supported by the observation that large parts of the primary visual network, which includes the primary visual cortex, were affected, in contrast to the mostly unaffected secondary visual network that covers higher visual areas. This relationship is further corroborated by the finding that patients with ON had significantly higher primary visual network functional connectivity compared with patients without ON and healthy controls, whereas patients without ON did not differ from controls.

Given the high correlation between VA and GCIPL thickness, visual network connectivity changes could be driven by reduced visual input and/or by retinal damage directly. Thus, increased functional connectivity could reflect an attempted compensatory or noncompensatory mechanism of network reorganization in response to GCIPL damage and impaired visual function. Indeed, it has been suggested that increased functional connectivity can compensate for structural damage at early disease stages in MS.[16] Alternatively, the correlation between increased visual cortex functional connectivity and impaired visual function could indicate a maladaptive process.[16,41] For example, increased functional connectivity of the hippocampus predicted worse memory performance in one study,[42] and increased thalamic connectivity correlated with more severe cognitive impairment in another study.[43] Likewise, Hawellek et al[44] observed that increased connectivity within the default mode network and the frontoparietal control network indicated more severe cognitive deficits. The authors considered 2 possible explanations for their findings: (1) a maladaptive plasticity that directly contributes to worsening deficits and (2) a loss of diversity in large-scale cortical dynamics caused by widespread MS-related white matter damage. In the latter hypothesis, diffuse structural damage would reduce functional network flexibility and force spontaneous connectivity fluctuations to adhere to a more rigid

Figure 4. Visual Network Connectivity in Patients With Neuromyelitis Optica Spectrum Disorder (NMOSD) With and Without a History of Optic Neuritis (ON)



A, In the primary visual network, patients with NMOSD and previous ON had significantly higher functional connectivity compared with patients with NMOSD without prior ON. B, In the secondary visual network, no connectivity differences were observed between patients with NMOSD with and without ON. Error bars indicate SD.

[a] $P < .05$.

prevalent activity pattern. In a similar vein, deprived visual input might cause a comparable loss of diversity in visual network connectivity patterns in NMOSD, resulting in an apparent functional connectivity increase. To further investigate and disentangle these hypotheses and to explore the exact association between impaired function and altered connectivity, longitudinal resting-state functional MRI studies are needed.[45]

Previous studies[10,11,46,47] that investigated the functional consequences of ON focused on patients with MS. However, results from these studies are naturally affected by demyelinating brain lesions that also affect the optic radiation and by

relatively preserved or recovered visual function. Most task-based functional MRI studies[46,47] in patients with MS have found diminished primary visual cortex responses to visual stimuli subsequent to ON. Using resting-state functional MRI, a previous study[10] reported small regions of increased and decreased functional connectivity in the extrastriate and peristriate visual cortex following ON in patients with MS with fully recovered VA. A large study[48] observed that reduced functional connectivity in MS is correlated with disability and T2 lesion load. However, similarly reduced functional connectivity within the primary visual cortex was found in patients with clinically isolated syndrome with acute ON and normal brain MRI findings.[11] Of interest, the opposite pattern (ie, extensively increased functional connectivity in the primary visual cortex) was observed in patients with Leber hereditary optic neuropathy.[49] This mitochondriopathy leads to bilateral visual loss between the ages of 15 and 35 years without structural brain damage or white matter lesions. Notably, patients with longer disease duration had higher visual functional connectivity. In NMOSD, 2 previous studies[50,51] investigated visual cortex functional connectivity but did not relate their findings to visual function, history of ON, or retinal integrity. Although one study[50] observed increased connectivity using the same methodologic approach as applied in the present investigation, another study[51] found decreased connectivity in higher visual cortex regions using a seed-based approach. Additional differences between these 2 studies that might contribute to the diverse findings include AQP4 antibody status and ethnicity of included patients. Taken together, however, the data from patients with NMOSD, MS, and Leber hereditary optic neuropathy suggest that increased visual network connectivity represents a pathophysiologic response pattern in long-standing, severe visual impairment without accompanying white matter lesions.

Limitations

A limitation of this study is its cross-sectional design, which, although showing a strong association between functional connectivity changes and impaired VA and retinal damage, does not allow the delineation of the underlying causal relationships.

Conclusions

This study found that ON-related retinal damage and visual impairment are associated with an extensive increase in functional connectivity within the primary visual network in patients with AQP4 antibody–positive NMOSD. Longitudinal studies are now needed to further disentangle the involved pathophysiologic mechanisms and identify possible implications for the treatment of visual impairment in NMOSD.

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Study concept and design: Finke, Paul.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Finke, Paul.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Finke, Zimmermann.
Obtained funding: Ruprecht, Brandt, Paul.
Administrative, technical, or material support: Finke, Pache, Bellmann-Strobl, Paul.
Study supervision: Finke, Ruprecht, Brandt, Paul.

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