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Changes in brain functional connectivity and clinical correlations in neuromyelitis optica spectrum disorder: a longitudinal resting-state fMRI study

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Abstract

Objectives Neuromyelitis Optica Spectrum Disorder (NMOSD) affects the optic nerves and spinal cord, but its longitudinal effects on brain function remain unclear. This study aims to examine changes in brain functional connectivity over time in NMOSD patients and assess their correlation with clinical outcomes, and explore whether shifts in connectivity, especially within the default-mode hub Brodmann area 23 (BA23), are indicative of changes in clinical status.

Methods Clinical assessments and resting-state fMRI data were analysed from 31 non-relapsing NMOSD patients at baseline and during one-year follow-up, and from 20 age- and gender-matched healthy controls (HCs) at baseline. We identified resting-state networks (RSNs) using independent component analysis (ICA). Functional connectivity (FC) was analyzed both within RSNs and between region-of-interest seeds and whole-brain voxels. Comparisons between groups (HCs vs. Baseline, HCs vs. Follow-up) and within the patient group (Baseline vs. Follow-up), as well as correlations with clinical evaluations, were conducted.

Results Significant FC changes were observed in NMOSD patients. At baseline, NMOSD patients exhibited significantly reduced FC in the lateral visual, sensorimotor, executive control, and left dorsal visual networks; however, these abnormalities showed partial recovery over time. Meanwhile, further decreases were noted in the medial visual and right dorsal visual networks at follow-up. Conversely, a significant increase in FC within the default mode network, particularly in the BA23 region, correlated with improvements in EDSS scores ($r = 0.53$, $p < 0.01$). Declines in connectivity between the BA23 region and both the lingual and fusiform gyri were associated with worsening Expanded Disability Status Scale (EDSS) scores ($r = -0.38$, $p < 0.05$) and reduced visual acuity ($r = -0.45$, $p < 0.05$).

Conclusion NMOSD patients exhibit both compensatory and progressive changes in brain functional connectivity over time. Alterations in the BA23 region are closely associated with clinical outcomes, highlighting its potential as a functional biomarker.

Highlights

1. Dynamic alterations in brain functional connectivity were observed in NMOSD patients during follow-up, reflecting both recovery and deterioration.

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2. Increased connectivity within the default mode network, especially in the BA23 region, suggests compensatory neural adaptations.

3. Reduced connectivity between BA23 and visual processing regions (fusiform and lingual gyri) was linked to declines in visual acuity and neurological function.

Keywords Neuromyelitis optica, fMRI, Independent component analysis, Functional connectivity, Disease process

Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is a chronic relapsing autoimmune disorder characterized by severe episodes of optic neuritis and longitudinally extensive transverse myelitis, which can result in significant visual impairment and neurological disability [1]. Beyond these primary symptoms, NMOSD can also impact the brainstem, potentially leading to severe cases of intractable nausea and respiratory failure [2]. Given these severe outcomes, early and accurate diagnosis followed by effective immunosuppressive therapy is essential to manage the disease and mitigate long-term disability [2].

Advancements in fMRI techniques have illuminated significant alterations in brain functional connectivity associated with NMOSD. Studies have shown substantial reductions in functional connectivity within the visual and sensorimotor networks, correlating directly with symptoms of visual impairment and motor dysfunction [3]. Additionally, other studies have reported increased connectivity within the default mode network (DMN) and the dorsal attention network, alongside decreased connectivity in the visual and cerebellar networks [4, 5]. Moreover, studies have shown that the Brodmann area 23 (BA23), as an important component of the DMN, exhibits abnormal functional connectivity changes that are closely linked to cognitive impairment in NMOSD patients. For instance, Yang et al., using resting-state fMRI found that reduced functional connectivity within the default mode network—including BA23—was significantly correlated with cognitive dysfunction [6]. These findings suggest that alterations in BA23 functional connectivity may serve as an important neurobiological marker for assessing the clinical severity and cognitive impairment in NMOSD. These findings suggest a reorganization of neural circuits in response to the disease's progression, indicating potential biomarkers for monitoring disease progression and assessing clinical function impacts [7].

Recent findings further suggest that the increased connectivity in networks such as the DMN might be compensatory, related to maintaining cognitive function amidst the disease's progression [7]. Conversely, decreases in connectivity in other brain areas have been correlated with poorer cognitive outcomes, highlighting the broad impact of NMOSD on brain function and the potential for these metrics to guide therapeutic strategies [4, 6, 7]. The sensory and motor network abnormalities, as revealed by rs-fMRI, show that loss of function within disease-target networks may elicit cross-modal plasticity across sensory networks, potentially preserving clinical function. This adaptation signifies the brain's resilience to pathological impacts [8]. Moreover, computational tools have been employed to enhance diagnostic accuracy and clinical decision-making, differentiating NMOSD from similar disorders like multiple sclerosis, using a multimodal data fusion approach [9].

However, despite the insights provided by numerous studies, the majority of existing research on brain function in NMOSD has been cross-sectional. This limits our understanding of how brain connectivity changes evolve with disease progression. Thus, our study aims to longitudinally assess changes in functional connectivity and their correlation with clinical outcomes such as Expanded Disability Status Scale (EDSS) scores and visual acuity in NMOSD patients, in order to advance our understanding of the dynamic neural mechanisms underlying NMOSD and inform the development of functional biomarkers.

Materials and methods

Participants

The ethical review board of our institution approved the research protocol, and informed consent was obtained in writing from all participants. To examine the longitudinal alterations in brain function in NMOSD patients, we performed an a priori power analysis using G*Power, specifying a medium effect size (Cohen's $d = 0.5$), a two-tailed significance level of $\alpha = 0.05$, and statistical power $(1-\beta) = 0.80$. This analysis indicated that a minimum of 34 participants is required to detect the hypothesized effects. Thus, the study initially included 35 individuals diagnosed with NMOSD and 20 healthy controls (HCs), matched by age and gender. Inclusion criteria required participants to be between 18 and 70 years of age and right-handed. Participants with NMOSD were diagnosed according to the revised guidelines by Wingerchuk et al. [10]. Only individuals seropositive for NMO-IgG (AQP4 antibodies) were included. In addition, the diagnosis required the presence of at least one core clinical

characteristic (such as optic neuritis or acute myelitis). The AQP4 antibody testing was performed at the Neurology Department using a cell-based assay through quantitative flow cytometry. Exclusion criteria included contraindications for MRI, any significant head trauma or neuropsychiatric disorders in the past, other autoimmune diseases (such as systemic lupus erythematosus), or poor image quality. We recorded the duration of patient's illness and the number of relapses from the initial onset to the baseline assessment at the time of patient enrollment. Besides, for each patient visual acuity was measured using Tumbling E charts [11], and the severity of the disease was assessed with the Expanded Disability Status Scale (EDSS) scores [12]. Visual acuity was measured under standardized conditions using the logarithm of the minimum angle of resolution (LogMAR) scale. Data were collected from NMOSD patients at both baseline and the 1-year follow-up, resulting in two sets of data. During the follow-up period, four patients experienced relapses and received clinical treatment, and were therefore excluded. Ultimately, 31 patients completed both the baseline and follow-up assessments and were included in the final analysis. Thus, the 31 enrolled participants were in remission phase during this study, and none received relevant medications such as corticosteroids or immunosuppressants. The control group, however, had data collected only at baseline.

Data acquisition

MR images were acquired using a Siemens MAGNETOM Trio 3.0 Tesla system. To reduce motion, participants' heads were stabilized with soft foam padding, and earplugs were used to lessen scanner noise. Instructions were given to the participants to keep their eyes closed, remain still, avoid specific thought processes, and stay attentive during the scan sessions. Resting-state functional MRI utilized a 2D Echo Planar Imaging method, with the settings as follows: TR/TE = 2000/30 ms; FOV = 220 × 220 mm; acquisition matrix = 64 × 64; FA = 90°; slice thickness = 4 mm; 32 interleaved transverse slices were used to cover the entire brain; a total of 180 images were captured per session. Furthermore, sagittal 3D T1-weighted images were generated using a brain volumetric sequence with the parameters: TR = 1600 ms; TE = 2.1 ms; TI = 1000 ms; FA = 9°; FOV = 176 × 224 mm; matrix size = 176 × 224; and a slice thickness of 1 mm. All MR images were visually inspected for artifacts during the data collection phase. In cases where artifacts were identified, the affected sequences were immediately rescanned, ensuring the collection of high-quality MR images for all subjects, in line with the rigorous quality control standards of the study.

fMRI data preprocessing

The FMRIB Software Library version 6.0.3 (FSL; http://www.fmrib.ox.ac.uk/fsl/) was employed for preprocessing the MRI data. The preprocessing routine for individual datasets included several steps: motion correction was conducted using MCFLIRT [13], non-brain tissue was removed using BET [14], spatial smoothing was applied using a Gaussian kernel with a full-width at half-maximum (FWHM) of 5 mm, and high-pass temporal filtering was performed. For image registration, FLIRT [15] facilitated the alignment of functional scans to high-resolution anatomical scans, and subsequent refinement in the alignment to standard space was achieved through FNIRT nonlinear registration [13, 16].

Independent component analysis (ICA) and component selection

Group ICA was used to deconstruct all the data into independent components using Melodic plug-in of FSL. The mixed dataset included data from HCs, baseline and follow-up data of NMOSD patients. From this dataset, a total of 20 independent components (ICs) [17] was set for group ICA ($p < 0.05$, TFCE corrected). Dual regression was performed to extract subject-specific time courses and spatial maps for each IC. We based our analysis on the 8 resting-state networks (RSNs) identified by Beckmann et al. [18]. The selection of the group ICA components was determined by a combination of image correlation and visual observation. We first calculated the spatial correlation between the ICs derived from our group analysis and the 8 RSNs identified by Beckmann et al. For this purpose, we employed the built-in fslcc command from FSL to measure the spatial correlations, ensuring a standardized approach to analyzing the connectivity within the RSNs. Subsequently, we performed a comparative visual check on the components with higher correlations to ensure accurate matching with the specified RSNs.

Changes in intra-RSN functional connectivity

To investigate the functional connectivity (FC) alternation within each RSN, the z-maps of the RSNs were compared using two-sample t tests between the NMOSD patients and HC groups (Baseline vs HC, Follow-up vs HC, $p < 0.05$, TFCE corrected). Paired-sample t-tests were used to examine changes in functional connectivity within networks in NMOSD patients at baseline and follow-up. Particularly, in each RSN, the difference examinations were restricted to only including the voxels within a mask, which was defined by the RSN mask

gather from the group ICA. We used brain regions with significant differences in RSN as masks ($Z > 2.3$, $p < 0.05$, TCFE corrected) and extracted the average functional connectivity values of these masks at baseline and follow-up of the patients. To identify RSNs that predict changes in clinical indicators, we calculated the Pearson correlation between the altered functional connectivity values of these networks and changes in patients' clinical indicators ($p < 0.05$).

Changes in seed-based whole-brain voxel functional connectivity

We defined regions in RSNs that were significantly different and predicted changes in clinical symptoms as seeds, calculated functional connectivity between these seeds and the entire brain region, and compared differences between NMOSD patients and HCs ($p < 0.05$, TFCE corrected). The brain regions with significant differences were further used as masks to extract changes in functional connectivity between baseline and follow-up. The Pearson correlation of altered functional connectivity of these brain regions with altered clinical symptoms was subsequently calculated to find extensive networks that predicted clinical assessment ($p < 0.05$).

Statistical analysis of demographic and clinical data

Statistical analyses performed using SPSS version 22.0. The variables (age and sex) between the NMOSD patients and the HC participants were compared using the independent sample t test and chi-square test. Changes in patients' clinical assessment were assessed using the Wilcoxon matched-pairs signed rank test. Differences were considered statistically significant at $p < 0.05$.

Results

Demographic variables and clinical assessment

Comprehensive demographic information for the participants is detailed in Table 1. There were no significant differences in gender and age between patients and HCs. There were no significant differences in the EDSS scores ($W = -103$, $p > 0.05$) or visual acuity scores ($W = 84$, $p > 0.05$) between baseline and follow-up assessments among patients, as shown in Table 1. Details of the clinical data are provided in Table S1.

Table 1 Summary of participant characteristics

Characteristics	HC (n=20)	NMO (n=31) Baseline/Follow-up	p value
Female sex number (%)	16 (80.00)	27 (87.10)	0.50[a]
Age (years)	32.95 ± 9.53	39.35 ± 13.31	0.07[b]
Number of relapses	-	3.68 ± 2.48	-
EDSS	-	3.13 ± 1.78/2.71 ± 1.96	0.22[c]
Visual Acuity	-	0.35 ± 0.17/0.39 ± 0.23	0.29[c]

Data are represented as mean ± standard deviation

HC healthy controls, *NMO* neuromyelitis optica patients, *EDSS* Expanded Disability Status Scale

[a] Chi-squared test

[b] Two-sample t-test

[c] Wilcoxon matched-pairs signed rank test

Changes in intra-RSN functional connectivity

The final 31 participants received a statistical power of 0.77. The spatial maps of the 8 RSNs are depicted in Fig. 1. According to the classification proposed by Beckmann et al., these 8 networks can be classified as the medial visual network, lateral visual network, auditory network, sensory motor network, default mode network, executive control network, right dorsal visual network, and left dorsal visual network [18].

The results of the difference tests (baseline vs. HC, follow-up vs. HC, baseline vs. follow-up) for these RSNs are shown in Fig. 2. With the exception of the auditory network, there were significant differences in functional connectivity within each other network. HCs exhibited significantly higher functional connectivity within the medial visual, lateral visual, sensory motor, executive control, and left dorsal visual networks. The extent of significantly affected brain regions observed at baseline was reduced at follow-up (shown on the right side of Fig. 2).

In the medial visual network, the range of brain regions exhibiting significantly lower connectivity in patients compared to HCs at baseline expanded during the follow-up. Similarly, in the right dorsal visual network, while patients showed no significant differences from HCs at baseline, they exhibited a significant decrease in functional connectivity in some areas during the follow-up (Fig. 2, upper and lower left).

Initially, patients' default mode network showed no significant differences from HCs. At follow-up, some regions, particularly BA23, exhibited increased functional connectivity in patients compared to controls (Fig. 2, left middle).

The RSNs of a patient may be influenced by a multitude of factors. In order to test the association between patients' functional networks and clinical symptoms, we calculated the Pearson's correlation between changes in the functional networks of these significantly different brain regions and changes in clinical behavioral assessment (Fig. 3). It can be observed that only the brain regions exhibiting significant differences in the default network, namely alterations in functional connectivity in BA23, exhibited a significant positive correlation with alterations in patients' EDSS scores ($r = 0.53$, $p < 0.01$,

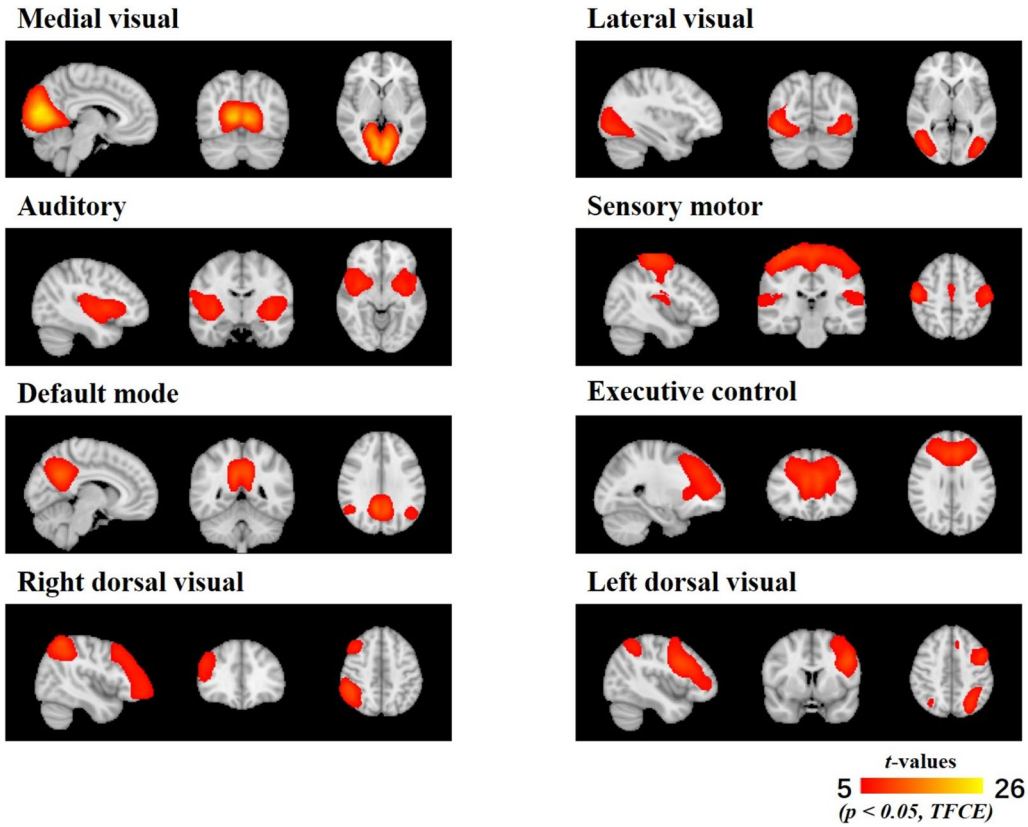

Fig. 1 Spatial maps of selected resting-state networks. Group-level networks, displayed in MNI standard space, were derived by analyzing combined data from healthy controls, NMOSD patients at baseline, and NMOSD patients at follow-up ($p < 0.05$, TFCE corrected). The right side of the image represents the left side of the actual brain

Fig. 3a), while no significant correlation was observed with alterations in visual acuity ($r = 0.27$, $p > 0.05$, Fig. 3b). No significant associations were found between altered connectivity in other brain networks and changes in clinical performance.

Changes in seed-based whole-brain voxel functional connectivity

We directly employed ROI identified through thresholding at $p < 0.05$ (TFCE corrected) on the DMN, where significant differences in intra-RSN functional connectivity were observed. Thus, we utilized BA23, which has shown potential in predicting changes in patients' EDSS scores, as a seed to calculate the functional connectivity of this region to the whole brain and further compared the differences (Fig. 4). Functional connectivity of the BA23 region with both the lingual and fusiform was significantly higher in HCs than in the patient group at the follow-up stage. However, no significant differences were observed between patients and HCs at baseline, nor between baseline and follow-up of NMOSD patients. Subsequently, we calculated functional connectivity changes in these regions and correlated them with changes in patients' clinical behavioral assessments (Fig. 5). We observed significant negative correlations between changes in functional connectivity in these regions and changes in both EDSS scores ($r = -0.38$, $p < 0.05$) and visual acuity ($r = -0.45$, $p < 0.05$).

Discussion

NMOSD presents considerable challenges due to its severe impact on visual and neurological functions, necessitating ongoing research to uncover the complex brain functional changes in affected patients. Our longitudinal study, building on the foundation laid by previous cross-sectional research, offers new insights into the evolving patterns of brain function in NMOSD patients over time. It reveals correlations between changes in functional connectivity and alterations in clinical assessments, deepening our understanding of the brain mechanisms involved in NMOSD.

At baseline, NMOSD patients exhibited significant disruptions in visual and sensorimotor networks, consistent with previous studies indicating reduced functional

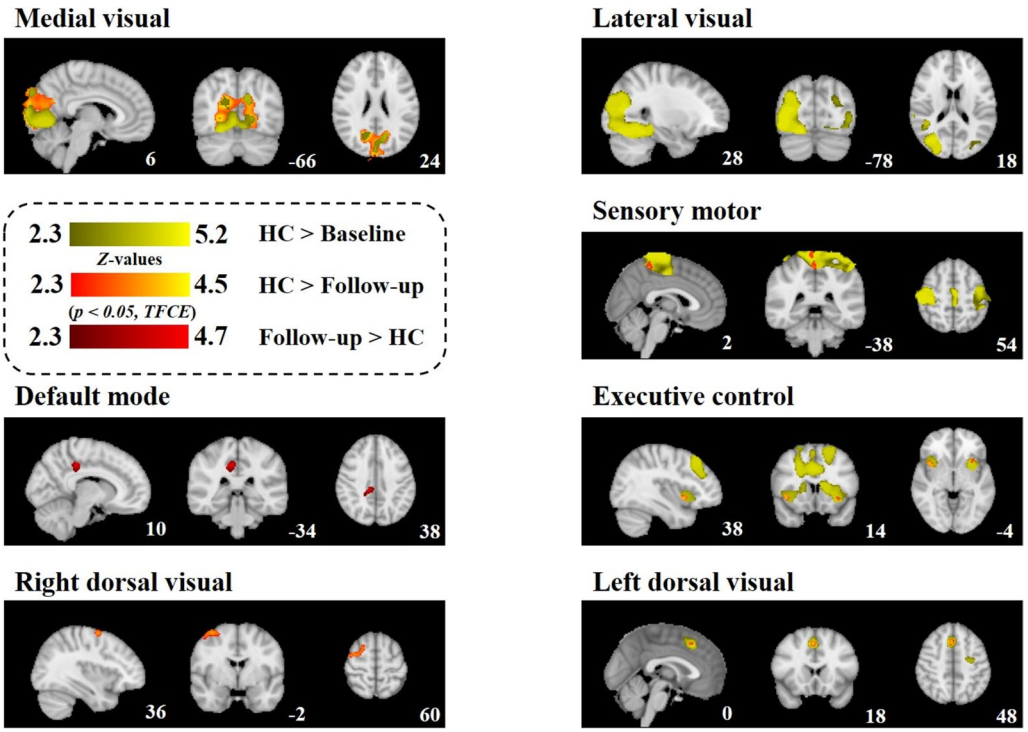

Fig. 2 Comparison of functional connectivity within resting-state networks. Patients had significantly lower connectivity within networks such as medial visual, lateral visual, sensory motor, executive control, right dorsal visual and left dorsal visual systems than healthy controls. In particular, patients' default mode network was not significantly different from healthy controls in baseline. However, the functional connectivity in right BA23 within the default network was higher in the patients' follow-up. Yellow colormap (row 1): HC > NMOSD baseline; red-yellow colormap (Row 2): HC > NMOSD follow-up; red colormap (row 3): NMOSD follow-up > HC. The right side of the image shows the left side of the actual brain. $p < 0.05$, TFCE corrected

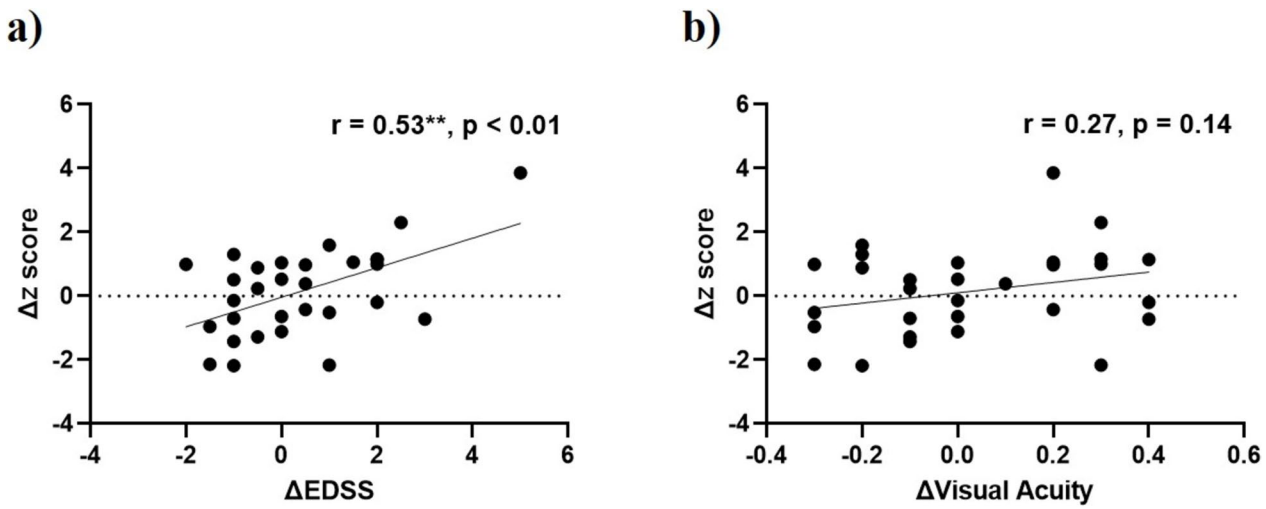

Fig. 3 Correlation analysis of changes in functional connectivity within BA23 with clinical indicators in patients. **a** Improvements in EDSS; **b** Improvement in visual acuity. EDSS = Expanded Disability Status Scale. *p < 0.05, **p < 0.01

connectivity in these areas [19, 20]. These reductions correlated strongly with visual impairment and motor dysfunction observed in cross-sectional studies [20]. Our longitudinal study revealed that regions with initially diminished connectivity showed a narrower range of disruption at follow-up, involving lateral visual, sensory

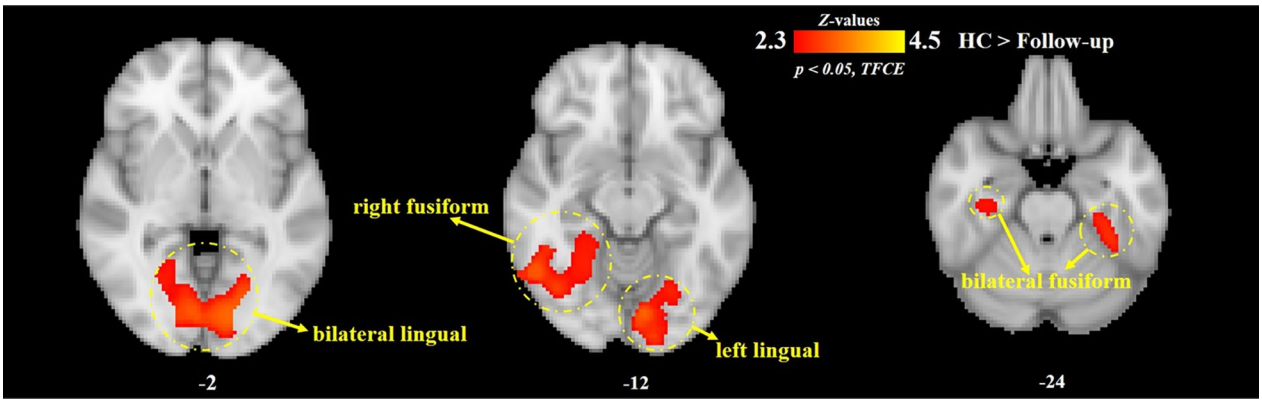

Fig. 4 Comparison of whole-brain functional connectivity using BA23 as a seed region. During the follow-up phase, connectivity between the bilateral lingual and fusiform gyri and the right BA23 was significantly lower in patients compared to healthy controls. p < 0.01, TFCE corrected

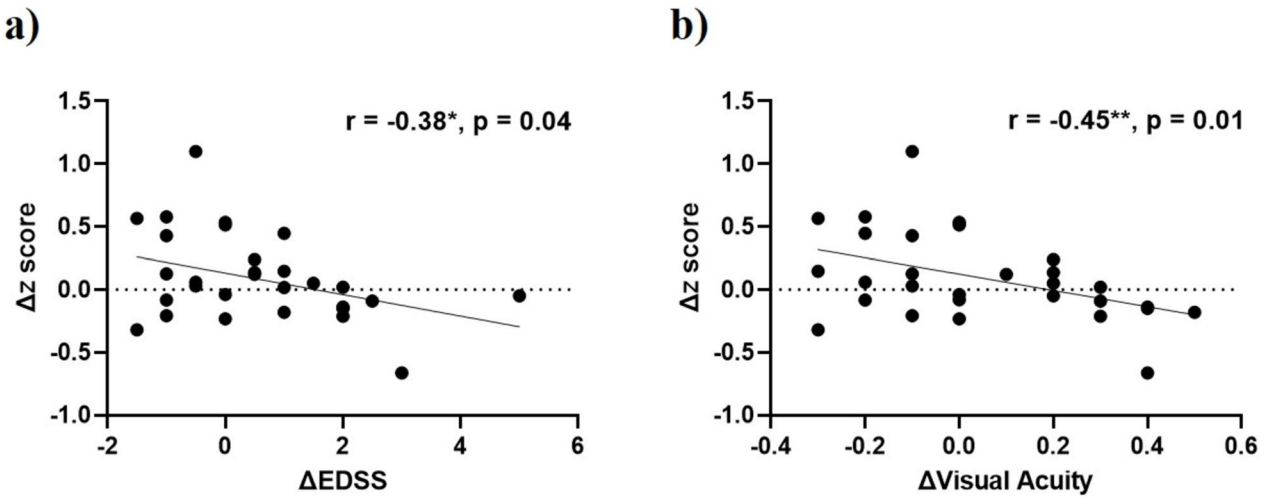

Fig. 5 Correlation between changes in functional connectivity of BA23 with lingual and fusiform gyri and clinical indicators in patients. **a** Improvements in EDSS; **b** Improvement in visual acuity. EDSS = Expanded Disability Status Scale. *p < 0.05, **p < 0.01

motor, executive control and left dorsal visual networks. This pattern supports the role of neural plasticity in curtailing connectivity disruptions, possibly by strengthening alternative pathways or enhancing the remaining connections within these networks [21]. Such findings suggest neural adaptation or compensation in NMOSD.

While most networks showed recovery or reduced disparity in connectivity compared to HCs over time, medial and right dorsal visual networks exhibited increased differences at follow-up. This indicates that these visual processing networks may be more significantly impacted by the disease progression, and pathology worsening over time [22]. These findings align with previous studies showing heterogeneous connectivity changes in NMOSD, where some networks show preservation or improvement, and others progressive disruption [23]. Such heterogeneity reflects the complex effects of NMOSD pathology across different brain regions and functional systems [19, 20].

Although most networks showed reduced connectivity, the DMN in NMOSD patients displayed increased connectivity at follow-up, particularly in the BA23 region. Disruptions in the DMN, associated with cognitive impairments and alterations in self-referential mental activity, highlight the disease's impact on crucial brain regions for identity and memory processing [24]. The increase may suggest a compensatory mechanism aiming to preserve cognitive function amidst ongoing neural damage. Such increased connectivity within the DMN supports hypotheses from previous studies that

heightened activity in certain brain areas may represent an adaptive response to maintain neurological functions [21, 25]. Importantly, the positive correlation between increased functional connectivity in the BA23 area and improvements in EDSS scores highlights the significance of this compensatory mechanism, suggesting that increased connectivity could be linked to slower disability progression. These findings provide a promising direction for future therapeutic strategies that focus on enhancing or maintaining connectivity in specific brain regions to mitigate disease progression.

The absence of significant correlations between changes in visual acuity and overall functional connectivity underscores the complexity of NMOSD pathology. This suggests that neural adaptations may support specific functions without uniformly improving all clinical outcomes, indicating a nuanced interaction among brain regions [23]. In particular, changes in functional connectivity between BA23 and visual regions may help explain variations in visual acuity.

We observed significant declines in functional connectivity between BA23 and the fusiform and lingual gyri over the study period. These regions are critical for visual processing and object recognition [26, 27]. The fusiform gyrus, often referred to as the "visual word form area", is essential for object, face, and word recognition [28, 29], while the lingual gyrus is involved in processing low-level visual features such as color and shape [30]. Importantly, declined connectivity between these areas and BA23 was negatively correlated with visual acuity, suggesting that disruption of these visual pathways may contribute to progressive visual impairments in NMOSD.

At baseline, functional connectivity between BA23 and these regions did not differ between NMOSD patients and HCs. However, the observed decline in patient group during follow-up likely reflects progressive neurodegeneration and weakening of visual processing pathways [19, 31], highlighting the importance of these regions in maintaining visual function and the potential of targeted interventions to mitigate visual decline.

Although NMOSD and MS both exhibit network reorganization, their distinct inflammatory mechanisms and lesion distributions result in divergent connectivity outcomes. NMOSD is an astrocytopathy triggered by AQP4-IgG and complement-mediated astrocyte destruction, predominantly affecting the optic nerves and spinal cord while sparing the cortex and juxtacortical white matter [32, 33]. Consequently, key hubs within the DMN remain structurally intact, leading to increased connectivity observed in this study, which correlates with lower disability scores. These findings align with the resilience reported by Wang et al. [34] and the compensatory hyper-connectivity described by Savoldi et al. [35]. In contrast, MS involves T-/B-cell-mediated attacks on myelin, extensive cortical-subcortical demyelination, microglial activation, and axonal transection [36], which directly impact DMN hubs, resulting in early 'network collapse' that correlates with cognitive decline [37]. Thus, the astrocyte-targeted, optic-spinal pathology in NMOSD supports focal DMN compensation, whereas the widespread myelin-targeted damage in MS leads to DMN decoupling. These mechanistic distinctions clarify the unique hyper-connectivity observed in BA23 in NMOSD and underscore the need for disease-specific neuroprotective or remyelination strategies.

This study has several limitations that should be considered. Firstly, it did not explore correlations between changes in functional connectivity and neuropsychological measures like cognition, sensorimotor skills, memory, and emotional processing. Understanding these correlations could elucidate the relationship between neural adaptations and clinical symptoms in NMOSD. Secondly, the small sample size and single-site nature of the study may limit the generalizability of our findings. Future studies should utilize advanced MRI techniques and involve larger, multisite cohorts to better assess the underlying brain pathology and its links to NMOSD's clinical manifestations. Thirdly, our focus was solely on NMOSD patients in remission, excluding those experiencing acute relapses that could significantly affect brain structure and function. Including patients across different disease phases in future research will provide a more comprehensive view of NMOSD's impact on brain function. Lastly, by only including right-handed participants, the study's applicability to the general population may be restricted. Future research should incorporate a more diverse participant pool to assess the potential influences of handedness on brain connectivity and clinical outcomes.

Conclusions

Our longitudinal findings reveal significant changes in brain functional connectivity in NMOSD patients, reflecting a dynamic balance between compensatory adaptations and functional impairments. In particular, alterations within the BA23 region and its network interactions were closely associated with clinical outcomes, suggesting its central role in the brain's functional response to NMOSD. These findings suggest that targeted neuromodulation or rehabilitation strategies aimed at BA23 connectivity could be explored in future therapeutic trials.

Abbreviations

NMOSD	Neuromyelitis optica spectrum disorder
fMRI	Functional magnetic resonance imaging
ICA	Independent component analysis

FC	Functional connectivity
RSNs	Resting-state networks
EDSS	Expanded disability status scale
TFCE	Threshold-free cluster enhancement
ICs	Independent components

Supplementary Information

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Additional file1 (DOCX 17 KB)

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Author contributions
Conceptualization, J.W. and J.L.; methodology, J.L.; resources, H.D.; MRI-acquisition, X.K; MRI-evaluation, J.H.; clinical assessment, H.D.; formal analysis, J.W.; writing—original draft preparation, J.W.; writing—review and editing, J.W., J.H. and J.L.; supervision, J.L.; funding acquisition, J.L. All authors have read and agreed to the published version of the manuscript.

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Availability of data and materials
Data will be available upon reasonable request from the corresponding author.

Declarations

Competing Interests
The authors declare no competing interests.

Ethics approval and consent to participate
The study was approved by the Ethics Committee of Xuanwu Hospital. Ethics approval is not applicable. All participants provided informed consent.

Clinical trial number
Not applicable.

Consent for publication
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