An Eye on Brain Integrity: Acute Optic Neuritis Affects Resting State Functional Connectivity

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Submitted: December 22, 2014

Accepted: March 20, 2015

Citation: Wu GF, Brier MR, Parks CA-L, Ances BM, Van Stavern GP. An eye on brain integrity: acute optic neuritis affects resting state functional connectivity. *Invest Ophthalmol Vis Sci*. 2015;56:2541–2546. DOI:10.1167/iov.14.16315

PURPOSE. Currently, the ability for imaging to capture brain adaptations to injury that occurs in multiple sclerosis (MS) is limited. In particular, how the brain initially contends with the earliest clinical manifestations of white matter injury has yet to be defined. The purpose of this study was to determine the impact of acute optic neuritis (ON) on resting state functional connectivity magnetic resonance imaging (rs-fcMRI).

METHODS. Fifteen patients with a clinically isolated syndrome of acute ON were evaluated at an academic center in a prospective study. Subjects were assessed with structural and functional vision measures, including optical coherence tomography (OCT), high- and low-contrast letter acuity testing, and visual fields and quality-of-life measures (VFQ-25). The rs-fcMRI was compared with age- and sex-matched healthy controls.

RESULTS. We observed reduced functional connectivity within the visual system and a loss of anticorrelations between the visual system and nonvisual networks. Stronger functional connectivity between visual regions correlated with better quality of life, as measured by the VFQ-25, and better acuity scores for both high- and low-contrast testing in the affected eye.

CONCLUSIONS. The rs-fcMRI functional connectivity changes within (intranetwork) and between (internetwork) resting state networks occur after acute ON, indicating immediate cortical responses to focal inflammatory demyelination. Thus, focal white matter injury in the central nervous system acutely results in widespread network alterations that may lead to functional neurologic changes seen in MS.

Keywords: optic neuritis, multiple sclerosis, fcMRI, connectivity

Multiple sclerosis (MS), an immune-mediated demyelinating disease of the central nervous system (CNS), causes significant disability in younger adults.¹ Multiple sclerosis pathology results from demyelination and axonal damage.² The genesis of neurologic disability from inflammatory demyelinating plaques in MS remains unclear. In particular, how acute focal white matter damage leads to higher-order cortical dysfunction is poorly understood.^{3,4} Functional imaging studies support the concept that neurologic insults from varied disease states result in disruptions in the organization of spontaneous brain activity. Neurodegenerative conditions, including Alzheimer's disease, have served as prototypic examples of network derangements that are correlated with neurologic dysfunction,⁵ typically with a reduction in synchrony between nodes of a cortical network in comparison with healthy controls. Yet in other neurologic diseases, including MS, a different pattern emerges. For example, MS and depression have been linked with increases as well as decreases in functional connectivity using resting state functional magnetic resonance imaging (rs-fcMRI)^{3,4}; however, the time-course and functional significance of these alterations in

functional connectivity organization remain unclear. In this study, we investigated the effects on brain network connectivity of a specific, focal demyelinating event (optic neuritis [ON]) occurring at the earliest clinical time point in the course of MS.

Structural neuroimaging changes in MS are modestly associated with disability.⁶ The rs-fcMRI quantifies correlations of spontaneous blood oxygen level-dependent (BOLD) fluctuations.⁷ The rs-fcMRI can be used to investigate physiologic changes in brain networks due to disease.⁸ Although relatively few rs-fcMRI studies have been performed in MS patients, this technique has shown promise in identifying features associated with MS disability.^{9–11} However, rs-fcMRI studies are complicated by the presence of multifocal and diverse lesion locations and an inability to relate white matter injury to cortical dysfunction. Furthermore, most rs-fcMRI studies have focused on the later stages of MS,^{9,12–14} which may not be as beneficial for predicting disease progression.

The visual system is appealing to study early functional connectivity changes in MS.¹⁵ Visual dysfunction can be quantified using common tests (e.g., Sloan low-contrast letter acuity) or by optical coherence tomography (OCT).¹⁶ Optic

neuritis is frequently the first clinically isolated syndrome (CIS) leading to a diagnosis of MS and is an ideal candidate for studying early CNS changes due to MS. We hypothesized that during acute ON, functional connectivity changes occur in visual networks and are correlated with visual dysfunction.

METHODS

Study Participants

Acute ON ($n = 15$) patients, using standard clinical criteria,¹⁷ were prospectively recruited. Patients with a previous MS diagnosis, preexisting vision loss, or eye diseases were excluded. All patients underwent a baseline clinical MRI, with seven (47%) having no white matter lesions. Healthy controls (HCs; $n = 18$) were recruited from existing cohorts and were matched according to age and sex. Available legacy control subjects were not subjected to visual testing. All participants provided written informed consent to participate in this study, which was approved by the institutional review board of Washington University in St. Louis and adhered to the tenets of the Declaration of Helsinki.

Clinical Outcome Measures

Quality of Life. All ON patients responded to a series of questions concerning impairment due to visual dysfunction (Visual Function Questionnaire [VFQ-25]). An interviewer scored responses based on published procedures.¹⁸

Functional and Structural Vision Measures. Only ON patients had a standardized, comprehensive neuro-ophthalmic examination by a single examiner (GPV). Vision measurements were obtained at nadir and after returning to baseline. We divided the visual metrics into those obtained at the nadir of visual function and those obtained either at baseline examination (defined as either partial or complete recovery) or at the time of the rs-fcMRI. The rationale for this decision was that some patients were examined after they had begun to recover their visual function, and we were interested in determining whether visual function at nadir would correlate with changes in functional connectivity. Visual function at nadir was defined as the worst-documented visual function within 2 weeks of onset of visual loss, the time frame during which a typical episode of ON might progress, and when most patients reach their nadir.¹⁷ For some patients, this information was extracted from the referring ophthalmologist's or optometrist's records. Monocular visual acuity testing was assessed using Snellen high-contrast letter acuity (HCLA) and Sloan low-contrast letter acuity (SLCLA). All patients also underwent automated perimetry testing with Humphrey Visual Field Analyzer (Swedish Interactive Threshold Algorithm Standard, 24-2; Carl Zeiss Meditec, Dublin, CA, USA) or Goldmann kinetic (if visual acuity was $<20/200$). Although automated and static perimetry are difficult to compare statistically, we were interested in determining whether there was a correlation with visual field loss and connectivity. We therefore assigned a value of -30 dB to the patients receiving Goldmann static perimetry. This method allowed for a general assessment of overall loss of field sensitivity compared with change in connectivity. Some patients ($n = 11$) also underwent OCT testing (Carl Zeiss Meditec; Cirrus Spectral Domain, Dublin, CA, USA) using the fast retinal nerve fiber layer thickness (RNFL) program. Three repetitions of optic disc cube 200×200 scans (capturing 6×6 mm of data) in each eye were performed using the Cirrus HD OCT. Average RNFL thickness measurements were recorded. Good-quality scans were defined as signal strength greater than 7, centering of the scan, and uniform brightness.

TABLE 1. Demographic and Clinical Characteristics of Subjects

Subject Features	ON, $n = 15$	HC, $n = 18$
Age, y, median (range)	35 (24–56)	39 (23–52)
Female, n (%)	9 (42)	42
Ethnicity, n (%)		
Caucasian	12 (80.0)	9
African American	2 (13.3)	9
Hispanic	1 (6.6)	0
Education, y, median (range)	16 (12–18)	14 (10–20)
Right-handed, n (%)	15 (84)	84
Eye affected, n (%)		
OS	8 (53.3)	NA
OD	6 (40.0)	
OU	1 (6.6)	
Normal brain MRI, n (%)	7 (46.6)	

Magnetic Resonance Image Acquisition, Preprocessing, and Quality Assurance

Functional and structural MRIs were collected according to established parameters and initial preprocessing was performed as previously described^{19,20} (see Supplementary Material). Reduction of head motion artifact was accomplished by regression of the time-series derived by retrospective realignment and removal of high-movement frames.^{21–23} Additionally, nuisance signals extracted from white matter, cerebrospinal fluid, and the global signal were regressed from the BOLD time-series²⁴ (see Supplementary Material).

Functional Connectivity and Statistical Analysis

The BOLD time-series was extracted from a 6-mm radius spherical seed placed in the left primary visual cortex (L-V1; $-8, -83, 0$). The Pearson correlation coefficient (r) was calculated between the extracted region of interest (ROI) time-series and the time-series from all other voxels in the brain. This value was then transformed using the Fisher z transform $z(r)$, creating a $z(r)$ volume for each subject. These volumes were then subjected to random-effects t -tests (ON versus HC) on a voxelwise basis, generating a parametric map consisting of t and P values. Statistical significance was determined by using threshold-free cluster enhancement²⁵ with a critical $P = 0.05$. For assessment of functional connectivity relationships with visual function, we adopted an ROI-ROI based approach. Pairwise Fisher z transformed correlations were calculated between BOLD signals extracted from ROI pairs.⁵ A Pearson correlation coefficient was generated for comparisons between functional connectivity values and visual function outcome measures. All statistics were performed in MATLAB 2014A (Mathworks, Natick, MA, USA).

RESULTS

Subject Characteristics

Demographic data of ON and HC individuals were similar (Table 1). All ON patients were assessed on average 50 ± 25 (mean $\pm$ SD) days after onset of symptoms. Patients presented with unilateral ON except one who had bilateral ON. Neuromyelitis optica (NMO) was originally suspected in the patient with bilateral ON, but serum NMO antibodies were negative, and the patient has been followed for nearly 5 years with no further events and normal brain and spinal MRI scans.

FIGURE 1. Functional connectivity with the primary visual cortex is disrupted in acute ON. *Upper row (A)* shows mean Fisher z transformed correlation values between L-V1 and the rest of the brain for HCs. Correlation values near 0 (e.g., $z(r) < |0.1|$) are not displayed for clarity. *Middle row (B)* shows results using the same seed for the acute ON group. *Bottom row (C)* shows the t values for the difference (HC – ON). The data are masked at a voxelwise $P < 0.05$, as determined by threshold-free cluster enhancement.

Analysis of rs-fcMRI

Spontaneous brain activity exhibits a complex correlation structure, with activity from sets of brain regions highly synchronous with other brain regions categorized as belonging to the same resting state network, termed intranetwork connectivity. Activity within a network exhibits negative correlation or no correlation with other regions, termed internetwork connectivity.⁸

We first assessed if changes in functional connectivity were seen in ON patients with the hypothesis that inflammatory demyelination of the optic nerve would result in visual network changes. Mean functional connectivity from a seed placed in area V1 was assessed in HC subjects (Fig. 1A). The mean topography in HC subjects was consistent with strong positive correlations observed between the V1 seed and the rest of the visual system. In addition, prominent negative correlations were observed between the V1 ROI and frontal, parietal, and subcortical regions. Assessment of L-V1 in ON patients revealed a similar topography (Fig. 1B). However, ON patients had a loss of homotopic connectivity between left and right V1 ROIs compared with HCs (Fig. 1C). Similar results were obtained when placing a seed in right visual cortex (R-V1) (data not shown). In addition, we identified a loss of anticorrelation between the V1 seed and extravisual regions in ON subjects, including motor and fronto-parietal areas (Fig. 1C). Thus, after an acute CIS event of ON, functional

connectivity changes were seen not only within the visual system but also in its interactions with other networks.

Relation Between rs-fcMRI and Visual Function Outcome Measures

We next examined the relationship between functional connectivity changes and outcome measures of visual function. Functional measures of vision were consistent for ON patients (Table 2). Worse HCLA in the affected eye at baseline was associated with reduced functional connectivity between left and right V1 ROIs ($r = -0.67$, $P = 0.0094$; Fig. 2A). Although a trend toward an association between functional connectivity between V1 hemispheres and nadir HCLA in the affected eye was observed, no statistically significant relation was present ($r = -0.48$, $P = 0.082$; Fig. 2B). However, a statistically significant correlation was seen between functional connectivity between the left and right V1 hemispheres and baseline SLCLA for the affected eye ($r = -0.57$, $P = 0.032$; Fig. 2C), although not for the unaffected eye baseline SLCLA ($r = -0.37$, $P = 0.22$; Fig. 2D). Notably, higher functional connectivity between left and right V1 was correlated with a greater quality of life as measured by the VFQ-25 ($r = 0.62$, $P = 0.018$; Fig. 2E).

We also examined whether acute functional connectivity changes after ON were associated with structural changes in the eye as revealed by OCT. Retinal nerve fiber layer thickness in the affected eye measured by OCT correlated with

FIGURE 2. Relation between functional visual outcome measures and homotopic primary visual cortex functional connectivity in acute ON patients. Scatterplots of clinical assessments of visual function as a function of homotopic functional connectivity between L-V1 and R-V1. AE, affected eye; UE, unaffected eye; VFQ, visual quality of life.

FIGURE 3. Homotopic primary visual cortex functional connectivity is correlated with OCT in acute ON patients. Scatterplots between OCT and connectivity between L-V1 and R-V1 are shown along with lines of best fit.

functional connectivity between L-V1 and R-V1 in ON patients ($r = 0.63$, $P = 0.049$; Fig. 3).

DISCUSSION

Much attention has been directed at understanding functional connectivity changes that occur after cerebral inflammatory demyelination in MS.^{9–11,13} We hypothesized that brain network connectivity changes are affected during the earliest clinical manifestations of MS. In this study, we observed reduced functional connectivity within the visual system during acute ON. A selective reduction in network connectivity, particularly in the visual system, has been observed in patients with relapsing-remitting MS (RR-MS).^{12,14} Visual system connectivity alterations may serve as a hallmark for RR-MS, as ON is common in MS patients¹⁵ and could produce persistent reductions in functional connectivity. Our data demonstrate that a reduction in functional connectivity within the visual system precedes structural lesions identifiable with traditional MRI.²⁶ These results are in parallel with findings in other neurodegenerative diseases, where functional connectivity changes are often observed early in the disease course.^{27,28} Overall, our results indicate that functional connectivity is reduced early in CIS and may continue to persist with progression to RR-MS.

Our results also suggest that not only intranetwork changes in the visual system but also internetwork connections are affected in acute ON. Although we did not observe an increase in functional connectivity within discrete networks, as has been seen in RR-MS,^{10,13,29} we identified a loss of anticorrelations between V1 and extravisual regions following acute ON. This early loss of anticorrelation resulting from acute ON may eventually drive an elevation in connectivity strength among select networks, perhaps by strengthening remaining core connections within those networks or by nonspecific compensatory mechanisms.³⁰ Hence, a pathway toward “hyperconnectivity” that has been proposed as a general response to CNS injury³ could be established during acute ON and ultimately contribute to increased connectivity within the default mode network that is consistently identified in RR-MS.^{13,29}

There is growing evidence that axonal and neuronal loss in the anterior visual pathways reflects similar structural changes in the rest of the brain, which ultimately leads to the disruption in neuronal connections underlying functional disability in MS.^{26,31,32} The visual system serves as an optimal model for studying axonal and neuronal injury in the brain. In addition to its ease of accessibility, the visual system allows for quantitative assessment of structural and functional changes after insult. We demonstrate that loss of functional connectivity in the earliest

TABLE 2. Vision Outcomes for Patients With ON

Study	Outcome
VFQ-25 composite score	80 ± 21
SF-36	
Physical component score	50 ± 11
Mental component score	48 ± 12
Average RNFL thickness, μm	
Affected eye	96 ± 28
Unaffected eye	96 ± 15
RNFL symmetry,* %	83 ± 10
Snellen VA of affected eye, logMAR	
Nadir	1.2 ± 0.9
Time of scan	0.3 ± 0.5
Sloan VA of affected eye, logMAR	
Time of scan	1.6 ± 0.8
Visual field, dB	
Nadir	−22 ± 10
Time of scan	−7 ± 10

All values are mean ± SD. SF-36, short form-36; VA, visual acuity.

* RNFL symmetry refers to intereye comparisons.

stage of MS is clinically relevant, with worse visual acuity measures and lower visual quality of life correlating with reduced functional connectivity within the visual network. Interestingly, we found that connectivity changes associated with acute ON are correlated with RNFL thickness, even in unaffected eyes. This is perhaps not surprising, as previous studies have shown that the eyes of MS patients that have not experienced a clinical episode of optic neuritis still exhibit thinner RNFL and reduced macular volume compared with HCs, indicating that axonal and neuronal loss are present in clinically “normal” eyes.^{32,33} Although previous studies have failed to demonstrate a role for OCT in predicting the future course of the disease,^{34,35} the correlation between connectivity and quality of life demonstrated here raises the possibility that rs-fcMRI might play a prognostic role, providing insight into future disease course.

One interesting result was an apparent greater correlation between change in connectivity and RNFL thickness in the unaffected eye. This may simply reflect our small sample size, but could also reflect pathophysiology: optic disc edema can influence RNFL thickness. Although we excluded patients with visible optic disc edema from OCT analysis, it is possible that the affected eye may have had microscopic disc swelling, resulting in RNFL thickening and masking RNFL thinning over the short term. Theoretically, the unaffected eye would be less likely to have such swelling and might prove a truer correlation with connectivity. Future work with larger sample sizes and the use of macular OCT and retinal ganglion cell layer thickness measurements will be more optimal to clarify this finding.

One subject included in our cohort of ON had bilateral disease. Testing and follow-up have excluded NMO from diagnostic consideration. We have performed independent analysis excluding the data from this subject and have found no significant change in connectivity pattern (data not shown). However, excluding this subject from analysis of the relation between vision outcome measures and connectivity changes results in loss of statistical significance for quality of life ($r = 0.34$, $P = 0.26$) and baseline HCLA for the affected eye ($r = -0.46$, $P = 0.12$), suggesting the functional impact of connectivity changes during acute ON in relation to these outcome measures is borderline. Nonetheless, the subject with bilateral ON does not significantly influence the relation

between V1 connectivity and measures of HCLA at nadir or baseline SLCLA of the affected eye ($r = -0.55$, $P = 0.05$; $r = -0.55$, $P = 0.049$, respectively, excluding the subject with bilateral ON). Further assessment in acute ON of the impact of laterality on connectivity changes with respect to clinical outcomes deserves additional consideration using a larger cohort.

Although our study is the first to show changes in connectivity in brain networks in a cohort of acute ON patients, a well-defined and well-characterized CIS, we recognize several limitations of this work. First, our sample size does not permit extensive examination of the wide range of clinical outcomes that characterize CIS. In particular, we were not able to discriminate correlations for connectivity exclusively for patients without additional white matter lesions beyond the optic nerve. These subjects represent just under half of the CIS patients imaged in this study and may be more suitable for conclusions related to the broader effects within the CNS after singular insults. Second, this is a cross-sectional study that limits our ability to assess functional connectivity changes over time in patients who have experienced CIS. Longitudinal analysis will be critical to determine whether the changes observed acutely are transient or persistent, and whether changes in functional connectivity in patients with isolated ON and other CIS can predict the future development of clinically definite MS. Finally, we were unable to isolate all anatomic regions within the visual system for image analysis, namely the second-order neurons of the lateral geniculate nucleus (LGN). However, the well-characterized anatomy of the visual system allows for an exploration of the functional disruptions downstream of the LGN, as its projections are well understood.

In summary, this study is the first to show clinically relevant changes in functional connectivity in brain networks in a group of subjects with CIS manifesting as acute ON. Notably, we have shown that higher visual network connectivity is related to improved patient ability at the initiation of MS, as measured by several established clinical measures of visual function. In addition, ON was associated with wider network effects that extended beyond the visual system. These results suggest that acute ON not only leads to focal injury but also can have broad effects throughout the brain. Future studies aimed at understanding the long-term effects of changes in functional connectivity could be used as a biomarker to evaluate therapeutic interventions.

Acknowledgments

Supported by a pilot award from the National Multiple Sclerosis Society (GPV) and Just-In-Time funding from the Washington University in St. Louis Institute of Clinical and Translational Sciences. Additional support was provided by the Alzheimer's Association New Investigator Grant NIRP 12 257747 (BA) and by National Institutes of Health Grants R01NR014449, R01NR012657, R01NR012907, and R21MH099979 (BA). The authors alone are responsible for the content and writing of the paper.

Disclosure: **G.F. Wu**, None; **M.R. Brier**, None; **C.A.-L. Parks**, None; **B.M. Ances**, None; **G.P. Van Stavern**, None

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