

# Visual Fixation Instability in Multiple Sclerosis Measured Using SLO-OCT

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**PURPOSE.** Precise measurements of visual fixation and its instability were recorded during optical coherence tomography (OCT) as a marker of neural network dysfunction in multiple sclerosis (MS), which could be used to monitor disease progression or response to treatment.

**METHODS.** A total of 16 MS patients and 26 normal subjects underwent 30 seconds of scanning laser ophthalmoscope (SLO)-based eye tracking during OCT scanning of retinal layer thickness. Study groups consisted of normal eyes, MS eyes without prior optic neuritis (MS wo ON), and MS eyes with prior optic neuritis (MS + ON). Kernel density estimation quantified fixation instability from the distribution of fixation points on the retina. In MS wo ON eyes, fixation instability was compared to other measures of visual and neurologic function.

**RESULTS.** Fixation instability was increased in MS wo ON eyes (0.062 deg<sup>2</sup>) compared to normal eyes (0.030 deg<sup>2</sup>,  $P = 0.015$ ). A further increase was seen for MS + ON eyes (0.11 deg<sup>2</sup>) compared to MS wo ON ( $P = 0.04$ ) and normal ( $P = 0.006$ ) eyes. Fixation instability correlated weakly with ganglion cell layer (GCL) volume and showed no correlation with low-contrast letter acuity, EDSS score, or SDMT score.

**CONCLUSIONS.** Fixation instability reflects the integrity of a widespread neural network germane to visual processing and ocular motor control, and is disturbed in MS. Further study of visual fixation, including the contribution of microsaccades to fixation instability, may provide insight into the localization of fixation abnormalities in MS and introduce innovative and easily measured outcomes for monitoring progression and treatment response.

**Keywords:** visual fixation, fixation instability, multiple sclerosis, optic neuritis, central visual pathways

Visual fixation, the process by which the human visual system stabilizes images on the retina, is essential to normal foveal vision. Classes of fixational eye movements, including microsaccades, act continually to maintain foveation on stationary targets, with microsaccades also functioning to prevent sensory adaptation and perceptual fading.<sup>1,2</sup> Abnormalities in visual fixation are well-described in retinal disorders that cause macular scotomas from geographic atrophy.<sup>3-5</sup>

We recently described a method using confocal scanning laser ophthalmoscope (SLO)-based eye tracking during the performance of optical coherence tomography (OCT) to characterize changes in fixation instability and foveation in patients with optic neuropathy.<sup>6</sup> Visual fixation abnormalities, including the presence of square-wave jerks, also are well-recognized in neurologic disorders, including Alzheimer dementia<sup>7-9</sup> and the Parkinsonian syndromes,<sup>10,11</sup> and it is recognized increasingly that changes in microsaccade characteristics also may occur.<sup>11,12</sup> Demyelination related to multiple sclerosis (MS) is recognized as the most common cause of acquired pendular nystagmus,<sup>13-16</sup> but it is less understood

how visual fixation is affected in MS patients without nystagmus. Fixation instability, microsaccades, and foveation are likely to be disturbed as a result of inflammatory and neurodegenerative effects on the optic nerve and the widespread network of central afferent and efferent visual and oculomotor control pathways that are necessary for normal fixation.

OCT devices that use SLO-based eye tracking are increasingly ubiquitous in MS clinics and offer the ability to bring precise measurements of eye movement control to clinical practice. For example, during image acquisition with the Spectralis SLO-OCT (Heidelberg Engineering, Heidelberg, Germany), the retinal position is calculated from the SLO during the scan to stabilize multiple B-scans on the same retinal location, improve image signal/noise characteristics, and reduce measurement variability (a key feature for longitudinal assessments in clinical practice and in clinical trials). These tracking data can be analyzed to provide for the first time, objective measurement of visual fixation instability and the degree of eccentric fixation relative to the anatomic fovea.<sup>6</sup> In



this study, we assessed visual fixation instability in MS patients, recorded during SLO-OCT, as a potential indicator of neurologic dysfunction.

## METHODS

### Subjects

A total of 16 subjects with relapsing-remitting MS (RRMS) based upon the 2010 revision to the McDonald criteria<sup>17</sup> and 26 normal subjects were recruited prospectively from the University of Iowa Department of Ophthalmology and Visual Sciences. Six of the RRMS subjects had a single prior episode of unilateral optic neuritis occurring more than 1 year before enrollment. All patients underwent a detailed neuro-ophthalmic examination (by MJT or RHK), and no patient had clinically evident fixational nystagmus or internuclear ophthalmoplegia. OCT tracking data were available for all eyes tested, except for the single eye of one MS patient. Three study groups consisted of 52 unaffected eyes from normal subjects, 25 eyes without prior optic neuritis from MS subjects (MS wo ON eyes), and six eyes with prior optic neuritis from MS subjects (MS + ON eyes).

The research adhered to the tenets of the Declaration of Helsinki, and was approved by the institutional review board (IRB) at the University of Iowa. Written, informed consent was obtained from the subjects after explaining the nature and possible consequences of the study.

### Retinal Tracking During OCT

For each eye studied, 30 seconds of visual fixation were recorded using the Spectralis SLO-OCT platform (Heidelberg Engineering) before obtaining a macular volume OCT scan. Each subject was instructed to fixate on the internal central blue fixation target, and the contralateral eye was occluded with an eye patch. The fixation target was focused on the retina as part of the image acquisition, eliminating effects of refractive error. The SLO and OCT B-scans were recorded at the high-resolution (HR) setting (1536 × 1536 pixels for the SLO image and 1024 × 496 pixels for each B-scan). At the HR setting of the Spectralis SLO, retinal position was acquired by Heidelberg's Automatic Real-time Tracking (ART) system at a frequency of 4.8 Hz, based upon the line scan speed of the SLO (8000 lines/s) and the time equivalent required to reset the scanning laser between video frames (125 lines). A program logged the retina position into a tracking log, with each row containing values representing an affine transformation (a mapping method used to preserve collinearity; whether of points, lines, or planes) of the reference SLO image of the OCT to the active SLO video frame, providing horizontal, vertical, and torsional representation of eye position. To prevent distraction from the red scan lines that appeared during OCT B-scan acquisition, fixation was recorded for 30 seconds before acquiring each macular volume. Each macular volume consisted of 49 vertically oriented B-scans, with each B-scan consisting of a mean of 9 images.

### Localization of the Fovea and Calculation of Ganglion Cell Layer (GCL) Volume

Segmentation of each macular volume was performed using the Heidelberg Eye Explorer software (HEYEX), and the fovea location was determined as the thinnest portion of the retina between the internal limiting and basement membranes (ILM-BM) within the foveal zone, calculated from the vertical and horizontal B-scan reconstructions. The automated segmenta-

tion of the GCL was inspected for errors and manually corrected if needed. GCL volume (mm<sup>3</sup>) was calculated for each macular OCT.

### Determining Retinal Fixation Points and Fixation Instability

For each 30-second sample of visual fixation, a two-dimensional scatterplot of the retinal points used for fixation was derived from the affine transformations in the tracking log and colocalized to the SLO reference image. This was achieved by applying the affine transformations in the tracking log to the location of the initial fixation point, which is defined as the center of the SLO reference image and which corresponds to the optical center of the SLO and the location of the central fixation target of the Spectralis. Kernel density estimation (KDE), a nonparametric method, was used to derive a continuous two-dimensional function of the density of the retinal fixation points. The density of fixation was represented as a contour or isoline plot. Based on an established method, fixation instability was defined as the area of the 68% isoline of the KDE. The 68% isoline encloses an area on the retina in which 68% of the visual fixation is estimated to occur.<sup>6,18</sup> Figure 1 demonstrates how KDE models the density of the retinal fixation points and shows the relationship between the area of the 68% isoline and increasing amounts of fixation instability.

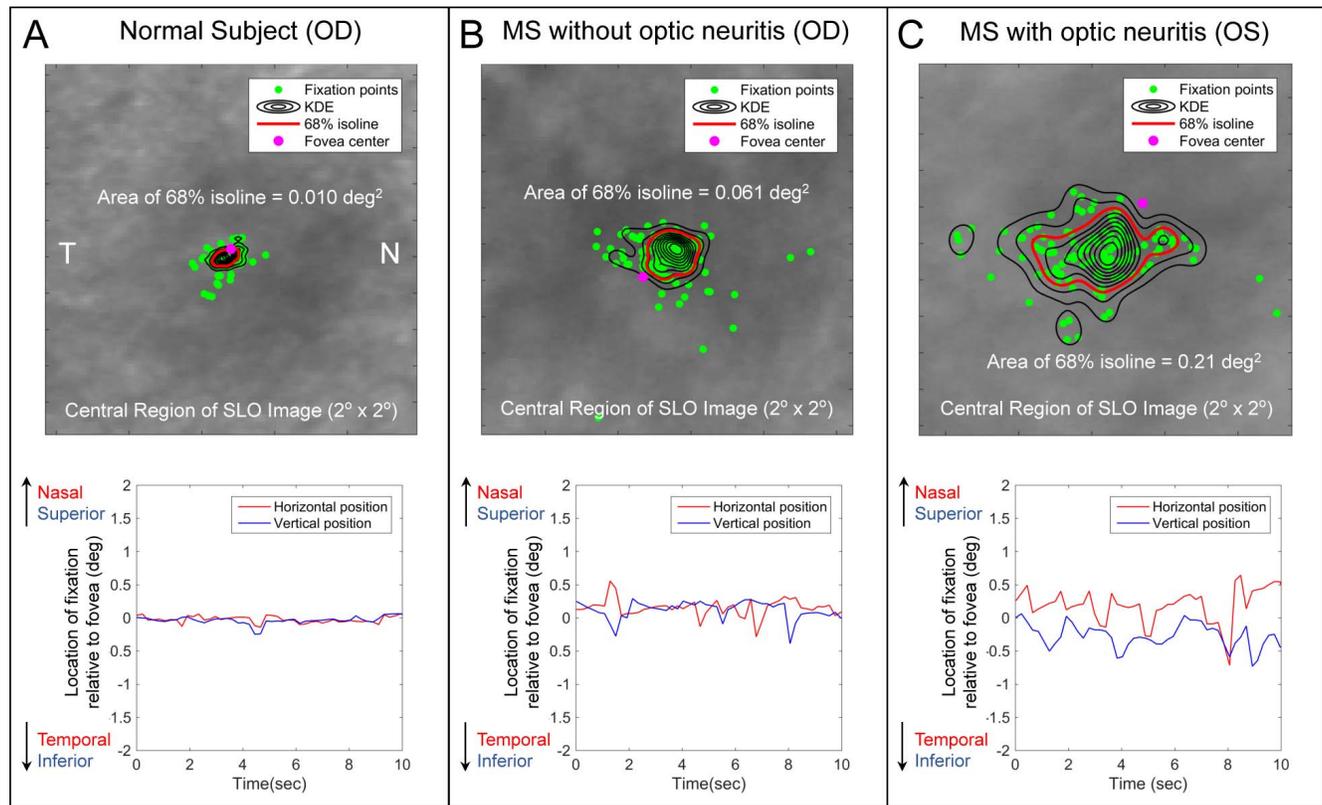
### Measures of Visual and Neurologic Function

Best-corrected visual acuities were measured in all patients, and MS patients underwent additional testing to characterize visual and neurologic dysfunction, including measurement of the expanded disability status scale (EDSS), symbol digit modality test (SDMT), and low-contrast letter acuity (2.5% Sloan).

### Computational Methods and Statistics

Image processing and calculation of fixation instability was performed using custom written code in MATLAB R2015b (Mathworks, Inc., Natick, MA, USA). Statistical analysis was performed using STATA Version 14 (StataCorp., College Station, TX, USA) and SAS (SAS Institute, Inc., Cary, NC, USA). Nonparametric Wilcoxon rank sum tests were used to compare median fixation instability for normal, MS wo ON, and MS + ON eyes. A binomial method was used to calculate 95% confidence intervals (CI) for median values. A mixed effects model was used to compare the mean fixation instability for normal, MS wo ON, and MS + ON eyes, accounting for within subject correlation between right and left eyes. The mixed effects model for fixation instability was defined by  $Y_{gij} = \mu + \alpha_g + s_i + \varepsilon_{gij}$  where  $\mu$  is the mean of all subjects,  $\alpha_g$  is the fixed group effect ( $g = 1, 2, 3$  for normal, MS wo ON, and MS + ON eyes),  $s_i$  is the random subject effect of subject  $i$  with variance  $\sigma_s^2$ , and  $\varepsilon_{gij}$  is the error with variance  $\sigma_e^2$ . Eyes with fixation instability values greater than 3 SD from the mean were excluded from each group.

Mixed linear models were used to compare fixation instability in MS wo ON eyes with GCL volume and low-contrast letter acuity (Sloan 2.5%). The sandwich estimator was used to calculate the standard errors of the regression slopes,<sup>19</sup> and two different assumptions about the errors in the regression model were considered: (1) independent errors across the 25 eyes and (2) correlated errors among eyes from the same subject. Spearman's rank correlation was used to compare fixation instability in MS wo ON with EDSS score and SDMT score. Statistical significance was assumed at  $P < 0.05$ .



**FIGURE 1.** Measurement of fixation instability with the Spectralis SLO-OCT. **(A)** In this normal subject, the cluster of fixation points on the retina obtained from 30 seconds of retinal tracking is shown by *green dots*. The close relationship of fixation with the fovea (*magenta dot*) is evident. The density of fixation at each retinal location is calculated using KDE, represented as *black isolines*. *Inner isolines* enclose regions of greater density. Fixation instability is defined as the area of the 68% isoline of the KDE (shown in *red* in each Figure). In this normal eye, fixation instability measured 0.010 deg<sup>2</sup>. A representative tracing of 10 seconds of visual fixation for this normal subject is shown in the lower panel; positive values represent nasal or superior displacement of the retinal fixation points relative to the fovea center, and negative values represent temporal or inferior displacement. **(B)** In this patient with MS and a history of left optic neuritis, fixation instability in the unaffected right eye measured 0.061 deg<sup>2</sup>. The tracing of visual fixation shown in the lower panel demonstrates greater fixation instability. **(C)** Fixation instability in the fellow left eye previously affected by optic neuritis measured 0.21 deg<sup>2</sup>; this further increase in fixation instability is evident in the tracing in the *lower panel*.

Repeated measurements of fixation instability collected in the right eye of five normal subjects also were analyzed by a random effects model to assess the within eye variability of the measurement of fixation instability (Supplementary Fig. S1).

**RESULTS**

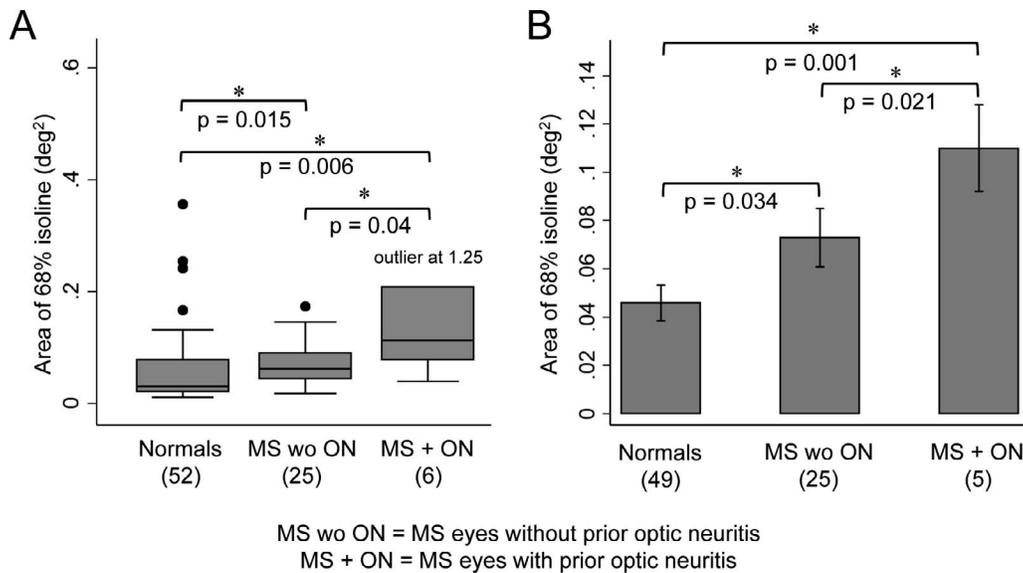
Mean age was 47 years (SD 11 years) for normal subjects and 42 years (SD 6 years) for MS subjects. Mean Early Treatment of Diabetic Retinopathy Study (ETDRS) visual acuity at 4 m was -0.04 logMAR for the MS wo ON eyes (range, -0.2 to 0.1 logMAR) and 0.07 logMAR for the MS + ON eyes (range, 0.0-0.2 logMAR). Median EDSS score was 2 (interquartile range [IQR], 1.5-3.5) for the MS subjects.

A representative plot of visual fixation instability for a patient from each study group is shown in Figure 1. Median fixation instability was increased in MS wo ON eyes (*n* = 25, median = 0.062 deg<sup>2</sup>; CI, 0.045-0.086 deg<sup>2</sup>) compared to normal eyes (*n* = 52, median = 0.030 deg<sup>2</sup>; CI, 0.024-0.051 deg<sup>2</sup>; *P* = 0.015, Wilcoxon rank sum test; Fig. 2A). A further increase in fixation instability was seen for MS + ON eyes (*n* = 6, median = 0.11 deg<sup>2</sup>; CI, 0.043-1.15 deg<sup>2</sup>) compared to all MS wo ON eyes (*P* = 0.04) and to normal eyes (*P* = 0.006).

The mixed effects model showed that mean fixation instability was increased in MS wo ON eyes (*n* = 25, estimated

mean = 0.073 deg<sup>2</sup>; *P* = 0.034) and MS + ON eyes (*n* = 5, estimated mean = 0.11 deg<sup>2</sup>; *P* = 0.001) compared to normal eyes (*n* = 49, estimated mean = 0.046 deg<sup>2</sup>; Fig. 2B). Mean fixation instability also was increased in MS + ON compared to MS wo ON eyes (*P* = 0.021). The probability value for testing the equality of the three means was *P* = 0.003. The estimated variances of the random effects implied correlation between eyes of the same subject ( $\rho$  = 0.55). These results confirmed the findings from the nonparametric group median fixation instability comparisons, which are unable to account for the fact that some eyes come from the same subject.

Linear regression using the mixed model and assuming independent errors showed a significant, but weak relationship (*R*<sup>2</sup> = 0.19, *P* = 0.028) between fixation instability and GCL volume in MS wo ON eyes (Fig. 3A). The relationship between fixation instability and GCL volume in MS wo ON was less significant under the assumption of correlated errors from eyes of the same subject (*P* = 0.096). There was no correlation between fixation instability and Sloan 2.5% low contrast visual acuity using either independent (*R*<sup>2</sup> = 0.0006, *P* = 0.91) or correlated (*P* = 0.60) errors (Fig. 3B). Spearman's rank correlation showed no significant correlation between fixation instability and EDSS score ( $\rho$  = 0.28, *P* = 0.17; Fig. 3C), or between fixation instability and SDMT score ( $\rho$  = 0.11, *P* = 0.59; Fig. 3D).



**FIGURE 2.** Fixation instability in MS eyes and normal eyes. **(A)** Box plot showing that median fixation instability is increased in MS wo ON eyes compared to normal eyes ( $P = 0.015$ ). There is an additional increase in median fixation instability in MS + ON eyes ( $P = 0.04$  for comparison with MS wo ON eyes;  $P = 0.006$  for comparison with normal eyes). **(B)** A mixed effects model to account for within subject correlation between right and left eyes confirmed that mean fixation instability is increased in MS wo ON ( $P = 0.034$ ) and MS + ON ( $P = 0.001$ ) eyes, each compared to normal eyes. Fixation instability also is increased in MS + ON compared to MS wo ON eyes ( $P = 0.021$ ). Mean and standard error values estimated from the model are shown in the bar chart.

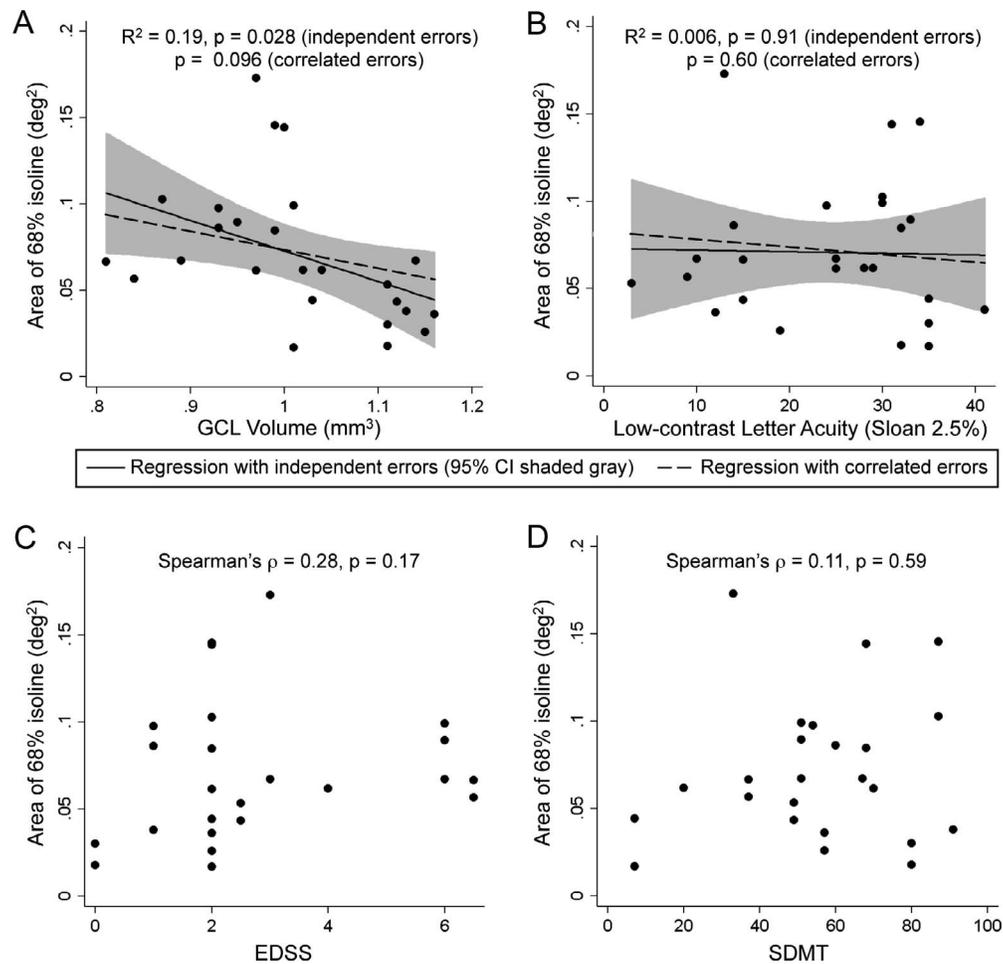
## DISCUSSION

Quantifiable measures of neurologic function are critical to better monitor disease status in MS and to serve as outcome measures for new therapeutics targeted at remyelination and neuroprotection. As more than 50% of the brain participates in the sensory or motor aspects of vision, metrics that assess visual function offer insight into the neurologic status of individuals with MS. Visual outcomes, such as low-contrast letter acuity, are well-recognized as correlating with visual disability and lesion burden on MRI,<sup>20</sup> and OCT offers the ability to measure retinal nerve fiber layer and retinal GCL thinning, which correlates with visual function and vision-specific quality of life measures.<sup>21,22</sup> A current challenge is to combine the structural changes that occur at the level of the retina, as well as the brain, with functional measures to better assess the visual dysfunction that is reported by most patients with MS.

SLO-OCT is well-suited for interrogating the structure and function of the visual system. OCT provides an assessment of the structural integrity of the retinal ganglion cells and their axons, and visual fixation data are byproducts of the OCT testing. The ability to measure visual fixation provides a functional measure of the neural structures involved in fixation, including the retina, optic nerves, subcortical white matter, visual cortices, dorsolateral prefrontal cortex, frontal eye fields, superior colliculi, brainstem reticular formation, and cerebellum (i.e., a strategy for interrogating processing elements and their integrity while functioning across neural networks that span both sides of the sensorimotor visual system apparatus).<sup>23</sup> Our study demonstrates that abnormalities in visual fixation may be measured in MS patients undergoing routine clinical OCT. Fixation instability was increased by nearly 2-fold in patients with RRMS without prior optic neuritis, suggesting that fixation instability may be a useful marker of central neurologic dysfunction in MS. While a weak correlation between fixation instability and GCL volume in MS wo ON eyes was suggested by our mixed linear model under the assumption of independent errors across the eyes ( $P$

$= 0.028$ ,  $R^2 = 0.19$ ), this effect was less evident when assuming correlation among eyes of the same subject, and there was no correlation with low-contrast visual acuity, a measure that is considered sensitive to optic nerve dysfunction. Therefore, it is likely that fixation instability in MS patients without prior optic neuritis is due in large part to demyelination or neurodegeneration affecting central pathways. While not in the scope of this study, comparison of fixation instability with MRI white matter lesion burden or other central signs of ocular motor dysfunction, such as impaired smooth pursuit, saccadic dysmetria, or abnormal visual-vestibulo-ocular reflexes (or their cancellation during cosynchronization of eye and head movements during the tracking of an object moving through space), may confirm correlation of fixation instability with demyelination in central pathways involved in visual fixation.

Fixation instability offers an appealing metric to assess the integrity of a widespread neural network and provide a global measure of function, but a change in fixation instability may be the result of multiple factors, including optic neuropathy, demyelination in subcortical white matter tracts, cortical atrophy, reduced inhibition of brainstem saccadic generators, or change in feedback control of the neural integrator of eye movements as in the case of pendular nystagmus.<sup>16</sup> Central adaptation to promote binocular integration also may have a role in patients with prior optic neuritis.<sup>24</sup> The low frequency (4.8 Hz) SLO-based eye tracking method provided by the Spectralis OCT is well-suited for calculating fixation instability over 30 seconds and is a convenient addition to clinical OCT testing, but characterizing the broader spectrum of visual fixation features in MS, including individual microsaccades, will allow the full diagnostic benefit of measuring visual fixation during OCT. Clinical OCT devices, including the Spectralis SLO-OCT, allow the capture of SLO video during fixation, which can be analyzed to derive highly-precise fixation tracings at higher-frequency (>250 Hz, which is recognized widely as necessary to measure all classes of saccades accurately, including microsaccades).<sup>5,25</sup> We currently are refining such an image-registration method to derive microsaccade and ocular drift data from SLO video at higher



**FIGURE 3.** Comparison of fixation instability with GCL volume, low-contrast letter acuity, EDSS score, and SDMT score in MS eyes without prior optic neuritis (MS w/o ON). (A) Fixation instability shows a weak relationship with retinal GCL volume ( $R^2 = 0.19$ ,  $P = 0.028$  assuming independent errors across the 25 eyes;  $P = 0.096$  assuming correlated errors among eyes of the same subject). (B–D) There is no correlation between fixation instability and Sloan 2.5% low-contrast letter acuity ( $R^2 = 0.006$ ,  $P = 0.91$  assuming independent errors across the 25 eyes;  $P = 0.60$  assuming correlated errors among eyes of the same subject), EDSS score (Spearman's  $\rho = 0.28$ ,  $P = 0.17$ ), or SDMT score (Spearman's  $\rho = 0.11$ ,  $P = 0.59$ ).

temporal frequency, to better understand the cause of fixation instability, and to elucidate other features that more completely characterize the pathobiological underpinnings of visual fixation derangements in patients with MS.

While our study is limited to only 16 patients with MS, the vast majority had low disability (median EDSS of 2) and none had secondary progressive MS. As such, it is expected that some of the MS patients tested will have visual fixation that is similar to normal subjects. Nevertheless, a nearly 2-fold increase in fixation instability was evident in MS patients. Assessment of fixation instability in patients with more advanced RRMS or secondary-progressive MS may allow a relationship with MS disability outcomes to be more apparent. In secondary progressive MS, where patients accrue disability without experiencing a clinical relapse or MRI exhibiting new or worsening demyelination, progression of fixation instability may represent a dynamic signature with face and construct validity for documenting advancing disease pathophysiology, or alternately its prevention in response to the application of novel neurotherapeutic strategies.

Variation in fixation instability also was seen among normal subjects in our cross-sectional data, but test repeatability was reassuringly high in five subjects undergoing repeated testing. This may suggest that longitudinal worsening of fixation instability in an individual patient may be of greater use than

the magnitude of any individual measurement. Further longitudinal study of visual fixation in MS patients using high spatial and temporal resolution tracings derived from SLO video will help clarify the causes of variability of fixation instability between and within subjects, as well as the relationship of changes in visual fixation with changes in other measures of disease severity.

In conclusion, retina tracking during SLO-OCT allows the quantification of visual fixation instability, providing an additional measure of the integrity of the visual system in patients with MS. This measure of visual function assesses the integrity of a widespread neural network, which becomes affected in MS. Further study of visual fixation, including the contribution of microsaccades to fixation instability, will provide additional insight and potentially new outcomes for monitoring the progression of MS and assessing the response to future treatments.

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