Latency of Multifocal Visual Evoked Potentials in Nonoptic Neuritis Eyes of Multiple Sclerosis Patients Associated With Optic Radiation Lesions

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PURPOSE. The aim of the study was to test the hypothesis that latency delay of multifocal visual evoked potentials (mfVEP) in nonoptic neuritis (NON) eyes of multiple sclerosis (MS) patients is related to retrochiasmal demyelinating lesions.

METHODS. A total of 57 MS patients with no history of optic neuritis at least in one eye, and 25 age- and sex-matched healthy controls was enrolled. Probabilistic tractography was used to reconstruct optic radiation (OR) fibers. The MS lesion volume within and outside of OR was calculated. Diffusion tensor imaging (DTI) indices were measured along OR fibers. The relationship of the mfVEP latency with OR lesions and DTI indices was examined.

RESULTS. Average mfVEP latency in the MS cohort was significantly delayed compared to controls ($P < 0.0001$). Of the patients, 77% demonstrated OR lesions. Axial, radial, and mean diffusivity were significantly abnormal in MS patients ($P < 0.001$). Partial correlation demonstrated significant association between mfVEP latency delay and OR lesion load. There was also significant correlation between MfVEP latency and OR DTI. Subgroup analysis revealed significantly higher correlations in patients without a history of ON in either eye compared to the fellow eye of patients with previous ON.

CONCLUSIONS. The findings of this study support our hypothesis that latency delay of the mfVEP in eyes of MS patients without previous ON is related to retrogenicular demyelinating lesions. Additionally, this study demonstrated that a previous episode of ON in the fellow eye may be a significant confounding factor, masking the relationship between the latency and OR lesions.

Keywords: multifocal VEP, optic radiation, multiple sclerosis, latency delay

The pattern visual evoked potential (PVEP) is a response recorded from the brain to repeated visual stimulation with a checkerboard pattern. It is an objective means for measuring function of the visual pathway and is known to be generated at the level of striate cortex by the combined activity of postsynaptic potentials.[1,2] The amplitude of the VEP reflects the number of functional afferent fibers reaching the striate cortex and the degree of synaptic activity in V1. Delayed conduction of the VEP has been found in the majority of patients with optic neuritis (ON) and is thought to reflect demyelination of the optic nerve fibers,[3,4] with a subsequent shortening of latency thought to represent the process of remyelination.[5]

Significant latency delay also has been found in a large proportion of multiple sclerosis (MS) patients with no history of ON (NON).[6–9] It has been suggested that VEP delay in NON eyes of MS patients is caused by subclinical optic nerve involvement[8] or chiasmal spread of inflammation from the ON side.[10]

We recently reported latency delay of the multifocal VEP (mfVEP) in MS patients without a history of ON in either eye.[11] Based on the binocular nature of the delay, and the fact that VEP response is generated at the level of the primary visual cortex and, therefore, possibly influenced by demyelinating lesions along the entire visual pathway, we suggested a possible retrochiasmal origin. The condition of MS is known to affect the entire visual pathway, including the optic tract (OT) and optic radiation (OR). Lesions of the OT are rare and tend to be clinically apparent.[12,13] On the other hand, OR lesions, while often asymptomatic, are very common.[14–16] Thus, autopsy studies demonstrate an incidence of OR lesions of more than 80% in MS patients. However, until recently, studies of OR lesions in vivo were hampered by the fact that OR fibers are undistinguishable from the surrounding white matter.

Diffusion tensor imaging (DTI) is a quantitative magnetic resonance imaging (MRI) technique that measures the diffusion property of water molecules within tissue through the application of multiple diffusion gradients. It is especially

valuable in assessment of central nervous system (CNS) white matter because of its sensitivity to the directionality and integrity of anisotropic tissues. Recent technologic advances in DTI tractography allow OT and OR to be separated from the surrounding white matter in vivo. Determined this way, OT and OR can be coregistered with T1 or T2 FLAIR images and lesion volume within those structures measured.

In addition, the directional diffusivity derived from DTI measurements describes microscopic water movement parallel or perpendicular to the white matter fiber bundle. This is calculated as axial diffusivity (AD) and radial diffusivity (RD) indices, respectively. Since the white matter is composed of well-structured nerve fibers, diffusion is larger along the fiber tract, while it is less in the direction perpendicular to the main axis of nerve fibers. Several additional indices could be derived from RD and AD. A measure of diffusion that is independent of the fiber orientation is provided by the mean diffusivity (MD), while fractional anisotropy (FA) represents a measure of fiber coherence. It is believed that diffusion indices, and RD in particular, represent a measure of primary (lesional) MS damage, since they are severely abnormal within the MS lesions.[17]

Therefore, to confirm our hypothesis of a retrochiasmal origin of the mfVEP binocular latency delay and specify the location of the demyelinated area responsible for it, we structurally identified lesions of OR and examined its relationship with mfVEP latency delay. A similar correlation was performed between latency and diffusion indices.

METHODS

Subjects

Consecutive patients (59) with relapsing–remitting MS with no history of clinical ON, at least in one eye, were enrolled together with 25 age- and sex-matched healthy controls. All participants underwent visual acuity testing and full ophthalmic evaluation, and were tested using brain and spine MRI and mfVEP. Patients with other systemic or ocular diseases that could confound results, such as retinal or optic nerve diseases, were excluded.

All procedures adhered to the tenets of the Declaration of Helsinki. Ethical approval was obtained from The University of Sydney Ethics Committee. A written informed consent was obtained from all participants after study procedures, time involved, and potential risks were discussed.

mfVEP Recording and Analysis

Multifocal VEP testing was performed with Accumap (ObjectiVision Pty. Ltd., Sydney, Australia) as described previously.[18] Briefly, the stimulus consisted of a cortically-scaled dartboard pattern of 58 segments (eccentricity up to 24°). Each segment contained a 4×4 grid of black (1.1 cd/m^2)-and-white (146 cd/m^2) checks (Michelson contrast, 99%), which reversed patterns according to a binary pseudorandom sequence. The visual stimulus was generated on a 21-inch display. All recordings were performed monocularly. Four gold-cup electrodes (Grass Telefactor, West Warwick, RI, USA) were used for bipolar recording, with two electrodes placed 4 cm on either side of the inion, and one electrode 2.5 cm above and one 4.5 cm below the inion in the midline. Electrical signals were recorded along four channels, showing the difference between readings at the superior and inferior electrodes, the left and right electrodes, and, obliquely, the horizontal and inferior electrodes. Visual evoked responses were amplified 1×10^5 times and band-pass filtered 1 to 20 Hz.

Opera software (Accumap; ObjectiVision Pty. Ltd.) correlated the pattern-reversal binary sequence with the electrical signals recorded and a response for each segment was obtained. The largest peak-trough amplitude within the interval of 70 to 210 ms was determined for each channel. One eye was selected randomly for MS patients with no previous ON, while the NON eye was tested in patients with a documented previous ON. Averaged latency values from each segment of the visual field were used for latency analysis.

MRI Recording and Analysis

The MRI data were collected using a 3.0 Tesla GE MR750 scanner (GE Healthcare, Little Chalfont, UK). Three sequences were implemented: Sagittal 3D T1 (GE BRAVO sequence, FOV 256 mm, slice thickness 1 mm, Discovery MR750, TE 2.7 ms, TR 7.2 ms, Flip angle 12°, pixel spacing 1 mm), FLAIR CUBE (GE CUBE T2 FLAIR sequence, FOV 240 mm, slice thickness 1.2 mm, acquisition matrix (frequency × phase) 256×244, TE 163 ms, TR 8000 ms, Flip angle 90°, pixel spacing 0.47 mm), and DTI pulse sequence (spin echo, 64 directions, FOV 256 mm, acquisition matrix (frequency × phase) 128×128, slice thickness 2 mm, TE 83 ms, TR 8325 ms).

Probabilistic tractography, as described by Sherbondy et al.,[19] was used to reconstruct OT and OR fibers. The DTI and FLAIR T2 images were coregistered to high resolution T1 structural image. Prior to the reconstruction of the OT and OR, three regions of interest (ROI) were determined. For OT identification the first ROI (diameter, 10 mm) was placed at the chiasm and deterministic tractography was used to follow the optic tract fibers from the chiasm to the LGN, where a second ROI (7 mm) was placed. For OR reconstruction, a third ROI covering the calcarine sulcus was drawn manually in each hemisphere. Probabilistic tractography software (ConTrack is a part of mrDiffusion package available for download at http://sirl.stanford.edu/software/, in the public domain) was run between the first (chiasm) ROI and the second (LGN) ROI to reconstruct the OT. Five thousand fibers were collected initially and a scoring algorithm was used to select the best 500 fibers. Optic tract fibers were then manually cleaned using Quench software (Quench is a part of mrDiffusion package available for download at http://sirl.stanford.edu/software/, in the public domain). A similar process was employed to reconstruct OR, but second (LGN) and third (calcarine sulcus) ROIs were used instead. Initially, 70000 fibers were collected for OR tractography, of which 30000 best fibers were selected by scoring algorithm. Fibers were again cleaned using Quench software (Fig. 1A).

The MS lesions were identified on coregistered FLAIR T2 and T1 images, and segmented semiautomatically using ITK-SNAP software (ITK-SNAP is a part of mrDiffusion package available for download at http://www.itksnap.org/pmwiki/pmwiki.php, in the public domain). Lesions then were intersected with visual pathway fibers to calculate lesions volume within and outside of OR (Fig. 1B). Averaged (between left and right sides) lesion volume was used for analysis. The DTI indices (FA, MD, AD, and RD) were calculated along OR using function of ConTrack software.

Statistical Analysis

Statistical analysis was performed using SPSS 21.0 (SPSS, Inc., Chicago, IL, USA). As the examined variables followed a normal distribution, Spearman rank correlation and linear regression analysis with adjustment for confounding factors were used to determine correlations between variables. Paired, unpaired Student's *t*-test or ANOVA were used when suitable and a *P* value of 0.05 or less was considered statistically significant.
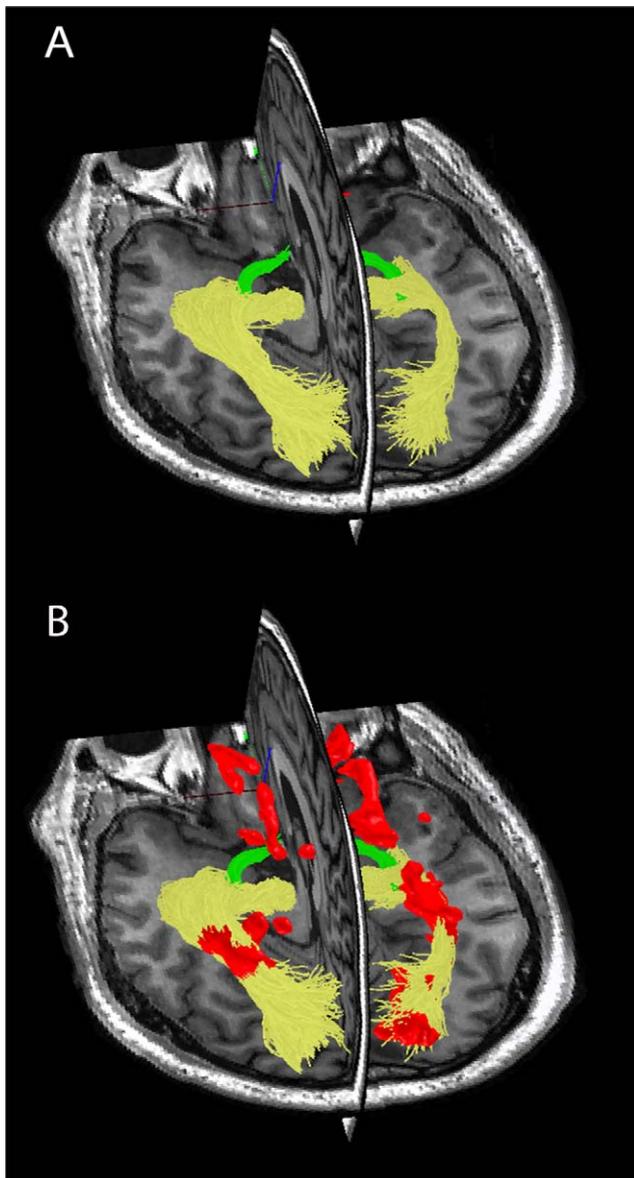
FIGURE 1. (A) 3D tractographic image demonstrates OT fibers in *green* and OR in *yellow*. (B) Lesions (in *red*) were intersected with visual pathway fibers.

RESULTS

Demographic and Clinical Characteristics of Participants

Of the 59 MS patients enrolled in the study, two participants with chiasmal involvement were excluded, 27 had a previous history of ON in one eye, and 30 had no previous history of

TABLE 2. Lesion Volume/mm^3 on T2 FLAIR and T1 Weighted Images

	T2 FLAIR	**T1 Weighted**	**P Value***
OR lesion volume	745 ± 144	525 ± 100	0.001
Lesion volume outside OR	7727 ± 1064	5194 ± 744	<0.00001

* *P* value is the statistical difference between T2 FLAIR and T1 lesion volume/mm^3.

ON. One eye was selected randomly for patients without a history of ON; the NON eye was used in patients with a history of previous ON. These two MS subgroups were analyzed together and then individually for correlations. Demographics are presented in Table 1.

The average mfVEP latency of NON eyes in the entire MS cohort was significantly delayed compared to healthy controls ($P < 0.0001$, Student's *t*-test, Table 1).

No lesions were identified in the OT in any of the patients; however, 77% (44/57) of patients had OR lesions demonstrated on T2 FLAIR images. The lesion volume varied between 24 and 4512 mm^3, and constituted approximately 10% of total brain lesion volume. The T1 OR lesions were detected in 72% (41/57) of patients with lesion volume varying between 20 and 3060 mm^3. The T1 lesion volume also represented appoximately 10% of total T1 brain lesion volume. The T1 lesion volume was significantly less compared to T2 FLAIR within and outside of OR ($P = 0.001$ and < 0.0001, respectively, Table 2).

Correlation Between mfVEP Latency and Lesion Volume

The OR lesion volume was strongly associated with total brain lesion volume for T2 FLAIR and T1 images ($r = 0.85$, $P < 0.001$ and $r = 0.89$, $P < 0.001$, respectively). Therefore, to examine tract-specific relationships between mfVEP latency delay and OR lesion volume, correlation between the two was corrected for lesion volume outside of OR. In addition, correlation also was adjusted for age, sex, and disease duration. Partial correlation demonstrated a significant positive association between mfVEP latency and OR T2 FLAIR lesion load (Table 3). An example is presented in Figure 2. There was also significant (albeit on a lesser scale) correlation between mfVEP latency and OR T1 lesion load.

Since the fellow eye of ON patients may be potentially affected by chiasmal spillover of inflammation from the ON eye, participants were separated into two groups: a group of fellow eyes of ON patients ("ON group") and a group of study eyes of patients who never experienced ON in either eye ("NON group").

The groups demonstrated similar ages, female-to-male ratio, and disease duration. Latency of the mfVEP in the ON and NON groups was significantly delayed, but there was no difference between the groups ($P = 0.8$, Student's *t*-test). The total lesion volumes and OR lesion volumes for T1 and T2 FLAIR also was similar between two groups (Table 4). Correlations between mfVEP latency and OR lesion volume were performed for each group separately. While in the ON

TABLE 1. Demographic and Clinical Characteristics of Participants

	No.	**Age**	**F/M (%)**	**Disease Duration**	**Latency of mfVEP**
Controls	25	39.9 ± 10.2	19/6 (76)		149.3 ± 5.1
MS patients	57	40.8 ± 11.9	42/15 (74)	4.68 ± 3 y	161.2 ± 9
P value		0.7	0.8		<0.0001

TABLE 3. Multifocal Visual Evoked Potentials Latency Correlation With DTI and OR Lesion Volume After Adjusting for Age, Sex, Disease Duration, and Brain Lesion Outside OR

	Entire Cohort		Fellow Eye of ON Patients		Study Eye in Patients Without Previous History of ON	
	Correlation	*P* Value	Correlation	*P* Value	Correlation	*P* Value
T2 OR lesion volume	0.50	<0.001	0.30	0.2	0.69	<0.001
T1 OR lesion volume	0.31	0.03	0.07	0.8	0.53	0.005
FA	−0.34	0.016	−0.3	0.2	−0.34	0.07
MD	0.5	<0.001	0.38	0.1	0.58	0.001
AD	0.42	0.003	0.20	0.3	0.50	0.006
RD	0.48	<0.001	0.38	0.1	0.56	0.002

group the correlation between mfVEP latency of the fellow eyes and OR T2 FLAIR lesions volume lost significance, correlation for the study eye in the NON group considerably increased compared to the entire cohort. A similar result was observed for T1 lesions: There was loss of significance for the fellow eyes of the ON patients group, but there was an increased correlation for the study eyes of NON-patient group

FIGURE 2. An MS patient with no history of ON showing (**a**) mfVEP latency delay (*darker zones*) and (**b**) left OR lesions (in *red*, tract fibers in *yellow*) with corresponding increase of RD.

(Table 3). Noticeably, even for the study eyes of NON patients, the correlation of T1 lesion volume with mfVEP latency was less, compared to T2 FLAIR lesion volume.

Correlation Between mfVEP Latency and DTI Metrics

There was significant and very similar increase of axial and radial diffusivity in the entire patient cohort compared to normal controls. As a result, MD (i.e., diffusion in all direction) also increased, while FA (relative directional diffusivity) remained stable (Table 5).

All four indices correlated significantly with mfVEP latency. The RD and MD demonstrated strongest association, followed by AD. The FA showed weakest correlation with latency (Table 3).

Group analysis of the relationship between the DTI indices and the mfVEP latency demonstrated behavior similar to the one described above for the lesion volume; that is, correlation increased for the NON group, but became nonsignificant for fellow eyes of ON patients (Table 3; example in Fig. 3).

Except for FA, all DTI indices in both groups remained significantly different from normal controls (ANOVA, Tukey post hoc test, $P < 0.0001$). However, diffusivity changes in fellow eyes of ON patients displayed larger deviation from normal controls compared to study eyes of NON patients, particularly for RD, for which the difference between the two groups demonstrated tendency for significance (0.64 ± 0.01 vs. 0.6 ± 0.01 for fellow eyes of ON and NON patients, respectively ANOVA, Tukey post hoc test, $P = 0.06$).

DISCUSSION

In this study we analyzed the relationship between latency of the multifocal VEP and structural markers of primary MS-related damage in the posterior visual pathway. We hypothesized that the latency delay of the mfVEP in eyes of MS patients without previous ON may be caused by retrochiasmal demyelinating lesions. This assumption was based on binocular nature of the mfVEP latency delay in MS patients without ON in either eye, which we reported previously.[11]

The findings of the current study support our hypothesis. Thus, apart from confirming extensive latency delays in NON eyes compared to normal controls, we found a significant association between latency of the mfVEP and lesion volume of the OR as determined by T1 and T2 FLAIR MRI images. Since lesion volume within OR correlates highly with volume of the lesions in the rest of the brain, correction for non-OR white matter lesion volume was necessary to determine a tract-specific relationship. This correction, as well as adjustment for age, sex, and disease duration, had minimal effect on the revealed association.
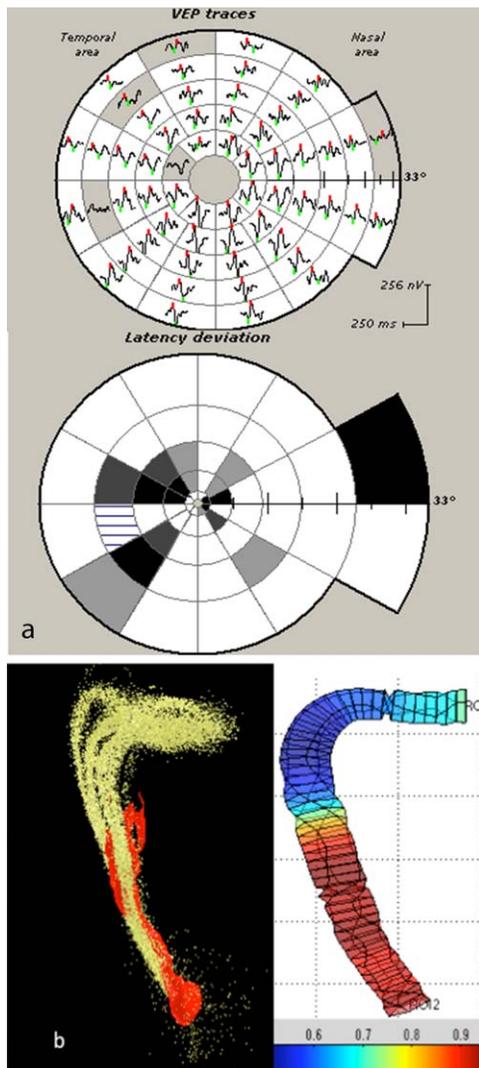
TABLE 4. Demographic and Clinical Characteristics of MS Participants With and Without History of ON in Fellow Eye

	No.	Age	F/M (%)	Disease Duration	Latency of mfVEP	T2 OR Lesion Volume	T2 Total Lesion Volume	T1 OR Lesion Volume	T1 Total Lesion Volume
Fellow eye of ON patients	27	40.1 ± 11.3	21/6 (76)	4.71 ± 3.1	161.6 ± 8.2	874	9327	603	6508
Study eye of NON patients	30	41.3 ± 12.4	21/9 (72)	4.66 ± 3.0	160.0 ± 9.7	653	7988	417	4853
P value			0.7	0.8	0.9	0.8	0.5	0.6	0.4	0.3

TABLE 5. Diffusion Tensor Imaging Characteristics of Participants

	MS Patients	Controls	*P* Value
FA	0.49 ± 0.04	0.50 ± 0.02	0.16
MD	0.88 ± 0.07	0.82 ± 0.03	<0.0001
Axial diffusivity	1.4 ± 0.07	1.32 ± 0.05	<0.0001
Radial diffusivity	0.62 ± 0.07	0.56 ± 0.04	<0.0001

Lesion volume determined on T2 FLAIR sequence was generally larger and the OR part of it demonstrated a higher degree of correlation with the mfVEP latency delay as compared to T1 lesion volume. This is probably related to the fact that, while T1 and T2 lesions have low histopathologic specificity, chronic T1-weighted lesions ("black holes") are associated with severe tissue destruction and axonal loss, while T2 lesions are more linked to demyelination.[20-22]

Another novel finding of this study is the demonstration of a significant correlation between the latency of the mfVEP and OR diffusivity indices. Changes of DTI indices in the OR of MS patents have been reported previously.[23,24] Reich et al.[23]
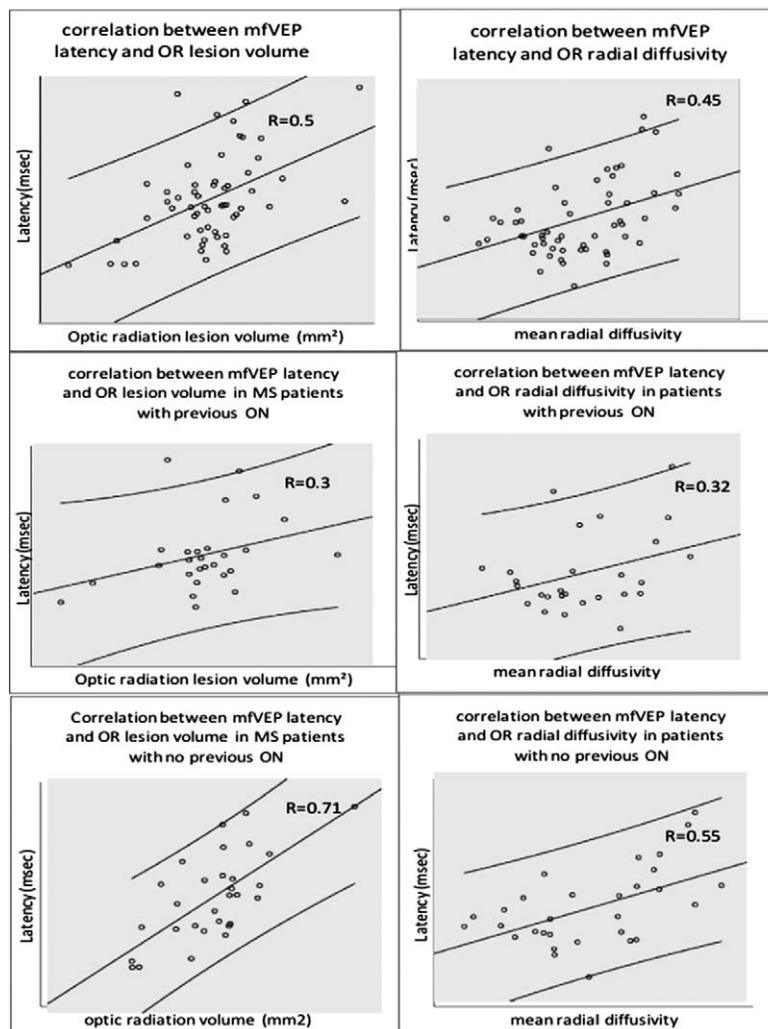

FIGURE 3. Partial regression plots for entire study participants and subgroup analysis according to the presence or absence of previous ON in fellow eyes.

demonstrated significant abnormality of all DTI indices in OR of MS patients (lower FA, and higher MD, AD, RD values). Similar alterations of OR DTI indices in MS patients were confirmed recently by Rocca et al.[24] More importantly, both studies also demonstrated strong association of DTI changes (RD in particular) with presence of the OR lesions. Therefore, correlation between latency delay of the mfVEP and DTI indices provides another evidence linking the mfVEP delay with retrogeniculate inflammatory demyelination.

An important observation is also related to subanalysis based on the history of ON: Patients without previous ON in either eye demonstrated considerably stronger (and more significant) correlation between mfVEP latency and OR lesion load compared to the entire cohort. On the other hand, when only fellow eyes of ON patients were analyzed, the correlation between mfVEP latency and OR lesions became nonsignificant. This trend was similar for all lesional measures, including T2 and T1 lesions, and DTI indices. Since both groups have a similar demographics and disease burden, it is likely that the presence of ON may mask the relationship between mfVEP latency and OR lesions in the fellow eye. A potential chiasmal spill over of the inflammatory demyelination from the ON eye, even in a few cases, may dramatically change mfVEP latency, but would not have any effect on OR lesions. It also has been suggested that adaptive cortical mechanism may contribute to the VEP latency delay in the fellow eye of ON patients (particularly to the late VEP waves, which are measured in this study). It was proposed that the delay in cortical processing of the visual information from the unaffected eye may compensate for the slowdown of visual input from the ON eye caused by demyelination of the optic nerve.[25]

In addition, the negative effect of ON on posterior visual pathway, which results in significant alteration of OR diffusivity, has been demonstrated in several studies. Those changes potentially could affect the correlation between mfVEP latency and DTI metrics.[23,26]

There are several limitations in this study. Firstly, magnetization transfer imaging (MTI) has not been used. However, while MTI potentially may help in lesion identification, we believe that combination of T2 FLAIR and DTI-reconstructed OR allowed us to detect and measure the majority of the lesions in the posterior visual pathway.

Secondly, cortical damage, which potentially may affect OR, has not been analyzed. However, current detectability of cortical lesions (even using the most sensitive double inversion recovery sequence) is very poor. In addition, DTI has not been shown to identify cortical damage of the occipital brain.

Thirdly, a potential effect of cortical plasticity and subclinical ON on correlation between the latency of the mfVEP and lesions of the posterior visual pathway has not been investigated. In addition, severe damage to axons in some lesions may result in axonal loss and decline of mfVEP amplitude, rather than latency delay, which also may have an impact on correlation.

In conclusion, the result of this study supported our hypothesis that OR lesions are related to latency prolongation in NON eyes of MS patients. Previous ON, however, may have significant contribution to latency delay even in the fellow eye. Therefore, care should be taken to adjust for this factor if mfVEP latency is to be used as a marker of demyelination in the posterior visual pathway.

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