Temporal reorganization to overcome monocular demyelination
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ABSTRACT

Objective: To identify the source of delayed visual evoked potential (VEP) latencies in the fellow eyes of patients with optic neuritis (ON) and determine whether these latencies stem from clinically silent demyelination or reflect an adaptive process for synchronization with the affected eyes.

Methods: The study sample comprised 17 patients whom we followed for 12 to 26 months after unilateral first-ever ON diagnosis and 17 age-matched controls. To avoid confounding effects of axonal loss, only intact fellow eyes (except for VEPs) were included. Subjects underwent standard visual evaluation, motion perception, as well as static and time-constrained stereo tasks. Assessments included VEP, optical coherence tomography, high-resolution MRI, and diffusion tensor imaging.

Results: We observed delayed VEP peaks (P100) in both affected and fellow eyes. However, while these were derived from prolonged time-to-start in the affected eyes, supporting the existence of demyelination, time-to-start in the fellow eyes was intact. VEP latencies in the fellow eyes could not be explained by demyelinative lesions along postchiasmal pathways (assessed by diffusion tensor imaging). Delayed peaks in fellow eyes resulted from a wider waveform, which evolved over time and occurred with a concomitant decrease in the gap in time between VEP peaks of both eyes. These changes offered a functional advantage; synchronization of inputs highly correlated with improved time-constrained binocular perception.

Conclusion: Delayed latencies in the fellow eyes may reflect adaptive mechanisms at the cortical level that improve binocular integration over time to adjust for the damage incurred. These data provide a unique demonstration of temporal reorganization that compensates for delayed transmittal of visual information to the cortex. *Neurology* 2013;81:1–8

GLOSSARY

AE = affected eye; DTI = diffusion tensor imaging; FE = fellow eye; logMAR = logarithm of the minimum angle of resolution; MD = mean deviation; ON = optic neuritis; RNFL = retinal nerve fiber layer; TE = echo time; TR = repetition time; VEP = visual evoked potential.

Although the status of the clinically unaffected eye after unilateral optic neuritis (ON) is not well documented in the literature,1–7 there exists sufficient data to term these eyes as fellow rather than unaffected eyes. Delayed visual evoked potential (VEP) latencies in the fellow eyes (FEs) have been demonstrated repeatedly4–7 and researchers suggest that this delay results from localized clinically silent optic nerve demyelination or alternatively reflects a process involving postchiasmal visual pathways.5

Recently, we demonstrated a sustained motion-perception deficit in the affected eyes (AEs) of patients with ON4 in which severity was strongly correlated with VEP latencies, suggesting that optic nerve demyelination affects dynamic visual function.5 If prolonged VEP latencies of the FEs indicate clinically silent demyelination, then motion-perception deficits are expected in these eyes as well. In contrast, delayed latencies in FEs were not accompanied by impaired motion perception and we found no correlation between the two. Moreover, when comparing a group of AEs and FEs with the same VEP latencies, impaired motion perception was evident only in the AEs (figure 1). This discrepancy led us to question whether demyelination is a valid mechanism to explain prolonged VEP latencies in FEs.
We hypothesized that delayed VEPs in affected and fellow eyes stem from different pathophysiologic processes. Whereas the first results from demyelination, the second reflects an adaptive process to compensate for the delayed visual information arrival via the affected side and facilitates binocular inputs synchronization.

**METHODS** Standard protocol approvals and patient consents. The Hadassah Hebrew University Medical Center Ethics Committee approved the experimental procedures, and we obtained written informed consent from all participants.

**Subjects.** This cross-sectional study included 17 patients (aged 20–58 years [36.4 ± 2.6, mean ± SEM] who were studied 12 to 26 months after an ON attack [15.8 ± 1.34 months on average]) as well as 17 age- and sex-matched controls. All patients were hospitalized at Hadassah Hebrew University Medical Center and were followed up in our neurology outpatient clinic, enabling us to retrospectively evaluate visual measurements from the acute phase. We examined all patients acutely and included only those diagnosed with a first-ever unilateral ON by an expert neuro-ophthalmologist. Inclusion criteria were history of an ON attack and age older than 18 years. Exclusion criteria were recurrent ON or other neuro-ophthalmologic defects. To isolate VEP latency and avoid confounding effects of axonal loss in the FEs, patients with impaired vision (visual acuity <0.8 decimal, contrast 10)

![Figure 1 Delayed VEP latencies but intact motion perception in the FEs](image-url)

(A) Longitudinal evaluation of VEP latencies, shown as time-to-peak (A.a) and motion perception (A.b) in the AEs (data taken from reference 9) and FEs of patients with ON. Patients’ performance levels are expressed as a percentage of the mean control subjects’ values. Asterisks denote differences from controls. (B) Correlations between changes in VEP latencies and OFM for the AEs (r = −0.87, p = 0.0005) (B.a) and FEs (r = −0.04, p > 0.05) (B.b). Each symbol corresponds to one subject, indicating the delta between the acute phase and 4 months after diagnosis. (C) Motion perception as a function of VEP latencies in AEs and FEs. Eyes are divided into 5 groups according to time-to-peak values. Numbers below plot indicate the number of eyes in each group. Asterisks denote differences between AEs and FEs. Black symbols — AEs; gray symbols — FEs. *p < 0.05; **p < 0.01; ***p < 0.001. Error bars represent SEM. AE — affected eye; FE — fellow eye; OFM — Object from Motion extraction task; ON — optic neuritis; VEP — visual evoked potential.
sensitivity <1.65 units of logMAR, color vision <100% performance level, and visual field mean deviation (MD) >3.00 dB or impaired retinal nerve fiber layer (RNFL) thickness (>78 μm) in the FEs were also excluded from the cohort.

Study design. We recorded pattern-reversal VEPs using pattern-reversal, full-field, checkerboard stimuli on a Bravo VEP device (Nicolet Biomedical, Madison, WI). Lateral electrodes were placed at O1 and O2, and referenced to Fz. The ground electrode was positioned on the vertex. VEP latencies and amplitudes were averaged across O1 and O2 (figures 1, 2, 3C, and 4). To compare the VEP latencies measured in each hemisphere, we directly compared latencies in O1 and O2 (figure 3D).

To elucidate the mechanism for delayed VEP, we obtained 3 measures for each subject: 1) time-to-peak, which refers to the time from stimulus onset to the maximum positive deflection (P100); 2) time-to-start, which refers to the time from stimulus onset to the start of the positive deflection (N75); and 3) width of the wave, referring to the time from the onset to the end of the positive deflection (N135–N75). VEP measurements were obtained in both patients and controls. The orders of evaluation of study participants’ waveforms were randomized and evaluators were blinded to patient vs control status to avoid bias. To evaluate VEP evolution over time, we retrospectively analyzed VEP data from the early stage (within 2 months of hospitalization for ON) and compared it with late-stage VEP data. VEP data from the early stage were available in all but one patient (for further details, see e-Methods on the Neurology® Web site at www.neurology.org).

Optical coherence tomography. RNFL thickness was recorded on a Spectral-Domain optical coherence tomograph (Heidelberg Engineering, Carlsbad, CA) by a trained technician; an expert independently reviewed all scans to check for artifacts that interfere with RNFL segmentation.

Visual fields were estimated using the automatic Humphrey perimetry test (SITA standard 24-2 protocol with stimulus 3; Carl Zeiss Meditec, Inc., Dublin, CA). We reviewed visual fields for the presence of fixation losses and false-positive and false-negative rates.

MRI data were acquired on a 3-tesla scanner (Triva; Siemens, Erlangen, Germany) using 8-channels standard head-coil. Anatomical MRI sequences included high-resolution T1-weighted images (minimum echo time [TE], flip angle 9°, repetition time [TR] = 2,300 milliseconds, voxel size of 1 × 1 × 1 mm), T2-weighed images (TE = 89 milliseconds, flip angle 180°, TR = 7,000 milliseconds, voxel size of 0.6 × 0.4 × 5 mm), and 3D-Cube fluid-attenuated inversion recovery–weighted images (TE = 395, TR = 5,000 milliseconds, voxel size of 0.9 × 0.9 × 0.9 mm).

Diffusion tensor imaging (DTI) and fiber tractography were used to identify postchiasmal visual pathways (optic tracts and optic radiations) in each patient. We acquired DTI data using a diffusion-weighted imaging sequence and image processing and using the open-source mrVista package (http://vistalab.stanford.edu/software). We performed fiber tractography using the ConTrack algorithm. Identified tracks were superimposed on the T2 and fluid-attenuated inversion recovery sequences to identify demyelinated lesions along the pathways (figure 3A). White matter integrity, assessed by the fractional anisotropy, was calculated separately for the groups with and without lesions along the fibers (figure 3B) (see e-Methods for further details).

Behavioral tests included standard visual testing on a monocular basis: 1) visual acuity (Snellen visual acuity chart); 2) color perception (standard Ishihara pseudoisochromatic plates); and 3) contrast sensitivity (Pelli-Robson chart at 1 m; Metroopia Ltd., Cambridge, UK). Additionally, dynamic visual function was assessed using the Object from Motion extraction task, in which patients viewed motion-defined objects and were asked to identify the objects (for full details, see references 8 and 9).

We included 2 measures of binocular vision: 1) standard static stereopsis evaluation (Randot SO-002; Stereo Optical Co., Chicago, IL); and 2) a novel time-constrained stereo task, in which spatially disparate images are presented for a limited length of time, challenging time-limited binocular integration. Patients viewed geometrical shapes generated on a computer screen, via red/green filtered glasses. One of 4 optional shapes (square, circle, triangle, or a star) was...
presented, at 1 of 6 stimuli durations (20, 30, 40, 60, 100, and 500 milliseconds). No masking was presented before or after stimulus presentation. Subjects were asked to name the object. We defined performance level as the fraction of correct responses in the shortest (20 milliseconds) vs longest (500 milliseconds) stimuli durations (20/500 milliseconds) for each subject (figure 5, B and C). Thus, high scores indicated similar performance levels in the short and long stimulus duration (i.e., no effect of stimulus duration); low stereopsis scores indicated significantly lower performance levels in the short stimulus duration. Normal time-constrained stereopsis perception was defined as the mean control subject values (see e-Methods for further details).

Behavioral tests and VEP measurements were performed on the same day. Completion of DTI and optical coherence tomography recording occurred within 1 month. Control subjects underwent the Object from Motion extraction task and the 2 stereo tests to generate comparable norms.

**Data analysis.** We performed statistical analyses using SPSS 20.0 (IBM Corp., Armonk, NY). At the group level, we compared mean values of VEP measurements, behavioral testing, and fractional anisotropy between control subjects, AEs, and FEs of patients using 1-way analysis of variance, and Tukey test for post hoc comparison. Pearson correlation and linear regression analysis were used to examine relations between VEP measures and binocular visual function. Partial correlations were used to control for possible confounding factors (age and disease duration, sex, and disease type: clinically isolated syndrome or relapsing-remitting multiple sclerosis). Significance was set at \( p < 0.05 \).

**Figure 3**  
Delayed VEP latencies in the FEs are not associated with demyelination in postchiasmal pathways

(A) Optic tracts (light blue) and optic radiations (blue) superimposed on T1-weighted (A.a) and fluid-attenuated inversion recovery–weighted (A.b) images to identify lesions within the pathways (red mark). (B) FA of optic radiations in patients with and without lesions along this tract (red and blue symbols, respectively; \( p = 0.01 \) between groups). Dashed lines represent average FAs in each group. (C) Time-to-peak in FEs of patients with and without lesions along their optic radiations (symbols as in B; \( p > 0.05 \) between groups). (D) Time-to-peak in FEs of patients with lesions along their optic radiations, comparing latencies measured at the hemisphere in which the lesion or healthy optic radiations are synapsing (\( p > 0.05 \) between hemispheres). FA = fractional anisotropy; FE = fellow eye; VEP = visual evoked potential.

**Figure 4**  
Different patterns of VEP changes over time in the 2 eyes

Changes in VEP latencies between the early and late stages of ON (\( n = 16 \)). Black bars = AEs; gray bars = FEs. Asterisks denote differences between stages. The \( p \) values and error bars are as in figure 1. AE = affected eye; FE = fellow eye; ON = optic neuritis; VEP = visual evoked potential.
At the individual level, we calculated the delta between a patient’s mean and we used a 2-tailed t test to test whether deltas were significantly different than zero (figure 2B).

**RESULTS** Visual measures in the affected and fellow eyes. Demographic information and clinical patient data are described in table e-1. As ensured by the inclusion criteria, all FEs had intact visual measurements: mean visual acuity results were 0.99 ± 0.01 decimal (mean ± SEM), contrast sensitivity results were 1.9 ± 0.03 units of logMAR, color vision results were 100% performance level, RNFL thickness results were 89.3 ± 2.76 μm, and visual field results (MD) were −0.7 ± 0.3 dB and median of 0.51 dB. All except one AE had intact visual acuity (0.95 ± 0.03 decimal). Contrast sensitivity was also intact in all cases but one (1.76 ± 0.06 units of logMAR). Color vision was intact in all cases. We noted reduced RNFL thickness in 6 patients (78.25 ± 3.2 μm) and visual field MD was abnormal in 4 patients (−2.47 ± 0.8, median −1.73).

VEP and motion perception in the affected and fellow eyes. VEP amplitudes were intact in both eyes (p > 0.05 compared with controls), but time-to-peak was delayed in both eyes (p < 0.001 compared with controls). Motion perception was impaired in AEs, but not in FEs (72.8% ± 9.2% and 105% ± 6.9% of correct responses for the AEs and FEs, respectively, and p = 0.01 and p > 0.05, respectively, compared with controls). Next, we compared time-to-peak, time-to-start, and the width of wave components. Delayed peaks in AEs derived from prolonged time-to-start (p < 0.001) indicating slowed conduction via the affected optic nerve. In contrast, the time-to-start of the FEs was intact; instead, delayed peaks here resulted from a wider waveform (p = 0.01, figure 2A). This phenomenon was also evident on a subject-by-subject basis in that prolonged time-to-start was found only in the AEs (p = 0.0002) and widening of waveform only in FEs (p = 0.003, figure 2B).

**Postchiasmal pathways.** Postchiasmal visual pathways (optic tracts and optic radiations) were studied in a subgroup of 12 patients. We identified lesions in the optic radiations of 7 patients, but found none in the optic tracts. Furthermore, we noted reduced fractional anisotropy of the optic radiations in the group with lesions compared with the group without lesions or controls (p = 0.01 and p = 0.0008, respectively; figure 3B). We found no differences when comparing the nonlesioned group and controls.
(p > 0.05) and no differences in the VEP latencies of the patients with and without lesions along optic radiations (p > 0.05 for the AEs and FEs; figure 3C). The negligible effect of lesions in the optic radiations on the measured VEP was further evident when we compared the VEP measured at the 2 hemispheres (O₁ and O₂) of patients in the lesion group. We found no differences when comparing VEP for the hemisphere in which the lesion or healthy optic radiations synapse (p > 0.05 for AEs and FEs; figure 3D).

In light of our results that demonstrate 1) normal conduction and intact monocular visual functions for FEs in contrast to what would be expected in a setting of optic nerve demyelination, and 2) a negligible effect of inflammatory involvement of the postchiasmal visual pathways on VEP results, we further tested an alternative explanation. We hypothesized that prolonged VEP latencies in FEs reflect an adaptive process. Thus, we examined 2 elements that characterize adaptive processes. Adaptive processes develop to adjust for incurred damage; furthermore, such processes evolve to improve performance, thus compensating for the acquired deficit.

**Evolution of the VEP waveform in the affected and fellow eyes.** We compared VEP latencies in late and early stages of the disease and found shortening of the time-to-peak in AEs (p = 0.01 between phases, paired t test), along with a trend toward increased time-to-peak in FEs (figure 4). In the AEs, changes in the time-to-peak were due to shortening of the time-to-start (probably reflecting remyelination). In the FEs, however, these were accompanied with widening of the waveform. These processes resulted in decreased time gaps between VEP peaks of the 2 eyes (21- vs 9-millisecond gap in the acute and late stages, respectively; p = 0.01).

**Time-constrained binocular visual functions.** Testing our patients on a standard static stereo task revealed intact function in most patients (76%). In contrast, we found impaired performance on the time-constrained stereo task in most cases (76%; figure 5, A and B).

Furthermore, the ability to perceive short-duration binocular disparity stimuli correlated (r = −0.72, p = 0.003) with the time gap between VEP peaks from both eyes (ΔVEP, figure 5C). Small ΔVEPs co-occurred with better binocular perception, while large ΔVEPs co-occurred with worse binocular perception. Of note, we found small ΔVEPs in patients exhibiting delayed VEP peaks in both eyes, whereas large ΔVEPs were a result of delayed VEP peaks in the AE, but intact latencies in the FE (confounding factors including age, disease duration, sex, and disease type were considered in the correlation analysis). Control subjects had small ΔVEPs and high scores in the time-constrained stereo task. We found no correlation between static stereopsis perception and the time gap between VEP peaks for both eyes (r = −0.01, p > 0.05).

**DISCUSSION** Our results challenge the traditional assumption that delayed latencies in FEs stem from clinically silent demyelination, suggesting that this may not be the only explanation. We demonstrate that the FE VEP waveform rises on time and that the delayed peak stems from widening of the waveform, a process occurring despite intact FE visual function. This finding supports previous studies that failed to find demyelinating MRI lesions in the fellow optic nerve.16,17 Furthermore, postchiasmal pathway integrity did not affect conduction rate according to VEP latency measurements. The mechanism by which optic radiation lesions affect fractional anisotropy but not VEP latencies may derive from the anatomy of the optic radiation itself. While the optic nerve has a compact structure composed of relatively similar fiber bundles, optic radiations have a massive fan-like structure in which a lesion typically occupies only a small part of the pathway.

We also demonstrated varying patterns of VEP evolution over time, including slight lengthening in FEs compared with shortening in AEs. This finding replicates previous reports2,3,6,7 and lends support to the hypothesis that various pathophysiologic processes underlie delayed VEP latency in FEs.

Instead, we suggest that after contralateral demyelinating optic nerve injury, delayed processing of visual data from the unaffected eye may reflect an adaptive process. Reorganization to compensate for reduced visual information inputs arriving at the cortex was previously suggested as a sequel to ON as well as other peripheral visual insults.18–23 While those reports emphasize the importance of spatial reorganization, the current data suggest that temporal reorganization may be a compensatory process for delayed arrival of visual information to the cortex.

Reorganization to enable binocular vision has been suggested as a compensatory mechanism that occurs in patients with strabismus. In such cases of eye deviation, abnormal retinal correspondence may develop to obtain fusion of images from both eyes. This spatial realignment enables a subnormal form of binocular vision.24 In the same way, abnormal latencies may develop in FEs following contralateral ON to allow image fusion. This spatial realignment enables binocular integration, which in turn facilitates binocular vision. Further investigation is required to understand the mechanisms responsible for this temporal realignment.

One possible player in this process is the lateral geniculate nucleus, a visual relay station between the anterior visual pathways and the cortex. Modification of the VEP waveform may take place at the lateral
geniculate nucleus as a result of cortical feedback. Alternatively, adaptation may be a result of cortico-cortical interactions. Studies addressing the cortical sources of pattern-reversal VEP components using advanced imaging techniques (such as fMRI and magnetoencephalography) in combination with VEP recording suggest that the time-to-start and time-to-peak components (equivalent to N75 and P100) may be associated with different brain activity patterns and involve different neuronal populations. Based on these studies and our finding of intact time-to-start but prolonged time-to-peak measurements in FEs, we suggest that input to the visual cortex via FEs is intact and that delayed time-to-peak results originate from corticocortical interactions.

The importance of temporal realignment to binocular visual function was previously illustrated in ON via the Pulfrich effect, wherein lateral motion of an object in the field of view is interpreted by the cortex as having a depth component. This visual stereo illusion, which derives from differing interocular conduction velocities, was described as affecting activities of daily living and sporting abilities and is in line with the reduced performance on the time-constrained stereo task shown here.

Our study is limited by the fact that it included a small subset of patients with ON, all with behaviorally and structurally intact FEs. This selection bias, which was aimed to control for confounding effects, decreases generalizability of results. Thus, the adaptation hypothesis presented here is an additional rather than an exclusive explanation for delayed VEP latencies in FEs. Another drawback of this study is the fact that we used full-field VEP testing, in which the extracted waveform results from a summation of multiple responses derived from different parts of the visual field and may be susceptible to cancellation effects. While this should be taken into account, significant differences were still evident when comparing AE, FE, and control waveforms.

In conclusion, after contralateral demyelinating optic nerve injury, delayed visual data processing in the FE may reflect an adaptive process. This adaptation contributes to temporal synchronization of binocular visual information. In a broader view, our cumulative findings in the affected and fellow eyes suggest that demyelinating ON is an appropriate model to study temporal changes in visual perception.

AUTHOR CONTRIBUTIONS
Dr. Raz: study concept and design, data acquisition, data analysis and interpretation. Dr. Chokron: critical revision. Prof. Ben-Hur: study concept and design, critical revision for important intellectual content, study supervision. Dr. Levin: study concept and design, data acquisition, data analysis and interpretation, study supervision.

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DISCLOSURE
The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

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