

Sustained motion perception deficit following optic neuritis

Behavioral and cortical evidence



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ABSTRACT

Objective: To assess the recovery process in patients after an acute optic neuritis (ON) attack, comparing static and dynamic visual functions.

Methods: In this prospective controlled study, 21 patients with unilateral, first-ever ON were followed over the course of 1 year. Standard visual tests, visual evoked potentials, and optical coherence tomography were assessed repeatedly. In addition, we developed a novel set of motion perceptual tasks to test dynamic visual deficits. fMRI examinations were performed to study the neuronal correlates for the behavioral findings.

Results: Four months after the acute phase, the affected eyes had returned to normal performance levels in the routine visual testing. However, motion perception remained impaired throughout the 12-month period. In agreement with the clinical findings, fMRI studies showed recovery in cortical activation during static object recognition, as opposed to sustained deficit in tasks that require motion perception.

Conclusions: Sustained motion perception deficit following ON may explain the continued visual complaints of patients long after recovery of visual acuity. Cortical activation patterns suggest that if plastic processes in higher visual regions contribute to the recovery of vision, this may be limited to static visual functions. Alternatively, cortical activation may reflect the visual percept (intact for visual acuity and impaired for motion perception), rather than demonstrating plastic processes. We suggest that motion perception should be included in the routine ophthalmologic tests following ON. *Neurology*® 2011;76:2103-2111

GLOSSARY

AE = affected eye; **ANOVA** = analysis of variance; **CS** = contrast sensitivity; **FE** = fellow eye; **OCT** = optical coherence tomography; **OFM** = object from motion; **ON** = optic neuritis; **RNFL** = retinal nerve fiber layer; **ROI** = region of interest; **VA** = visual acuity; **VEP** = visual evoked potential.

Optic neuritis (ON) is a demyelinating disease of the optic nerve, causing acute visual loss. Though considered transient when using standard visual testing,¹ patients continue to perceive difficulties in performing everyday visual tasks,² such as participating in sports with moving targets and while driving a car.^{3,4} A specific deficit in motion perception was later verified^{5,6} but was not assessed longitudinally.

Motion perception begins in the retina, mediated through the magnocellular pathway, containing cells with transient responses and fast-conductive axons. Cortically, the visual area MT (middle temporal) likely plays a major role in the integration of local motion signals into global percepts.⁷

fMRI has been used to demonstrate dynamic relationships among structure, clinical outcome, and functional activation. Recently, fMRI was used to evaluate the cortical response following an ON attack,⁸⁻¹² suggesting that changes in cortical organization may have an adaptive role in visual recovery after ON, in addition to the remyelinating process in the nerve itself.

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Supplemental data at
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Table 1 Visual tests along the study follow-up, affected eyes^a

	Median (range)				Normal values
	Acute (n = 21)	1 mo (n = 21)	4 mo (n = 15)	12 mo (n = 13)	
Visual acuity (Snellen) ^b	0.4 (0.0025-1.2)	1 (0.005-1.5)	1 (0.005-1.5)	1.2 (0.005-1.5)	1
	40 (0.25%-100%)	100 (0.5%-100%)	100 (0.5%-100%)	100 (0.5%-100%)	100%
	$p = 6 \times 10^{-5}$				
Visual field (0°-10°) (Humphrey) ^c	94 (0%-100%)	100 (13%-100%)	100 (13%-100%)	100 (38%-100%)	100%
	$p = 0.003$				
Color (Ishikawa) ^d	47.5 (0%-100%)	100 (0%-100%)	100 (0%-100%)	100 (0%-100%)	100%
	$p = 0.001$ [4]				
Contrast sensitivity (Pelli-Robson) ^e	1.35 (0-1.95)	1.65 (0-1.95)	1.65 (0-1.95)	1.8 (0-1.95)	1.84 ²⁰
	69.2 (0%-100%)	84.6 (0%-100%)	84.6 (0%-100%)	92.3 (0%-100%)	94.4%
	$p = 7 \times 10^{-5}$	$p = 0.01$			
MD ^f	23.6 (0%-83.3%)	55.5 (0%-100%)	72.2 (0%-100%)	55.6 (0%-100%)	84%
	$p = 5 \times 10^{-7}$ [3]	$p = 0.0007$ [3]	$p = 0.047$ [3]	$p = 0.02$ [1]	
OFM ^f	5 (0%-46.5%)	26.7 (0%-60%)	33.3 (0%-66.7%)	33.3 (0%-68.3%)	59.5%
	$p = 4 \times 10^{-8}$	$p = 9 \times 10^{-6}$	$p = 0.0008$ [1]	$p = 0.002$	
OCT (μm)			97 (51.7-107.3)	75.25 (36-102.8)	100.1 ¹⁶
			[3]	$p = 0.004$ [1]	
VEP amplitude: AE/FE	67.2 (0%-137.3%)		94.8 (56.6%-192.9%)	116.5 (57.2%-172%)	
	$p = 0.001$				
VEP latency(ms)	145 (133-166) $p = 7 \times 10^{-7}$		138 (122-151)	137 (126-140)	103.8 ²¹
			$p = 2 \times 10^{-7}$	$p = 3 \times 10^{-5}$	

Abbreviations: AE = affected eye; FE = fellow eye; MD = motion detection; OCT = optical coherence tomography; OFM = object from motion; VEP = visual evoked potential.

^a The p values denote significant differences in comparison to the normal values, as defined in the right column. The p values in the VEP amplitude (AE/FE) denote significant differences from 100%.

^b In units of decimal. Normal range is according to the Ranges of Vision Loss by the International Council of Ophthalmology (resolution adopted by the International Council of Ophthalmology, Sydney, Australia, April 20, 2002. Available at: www.icoph.org/pdf/visualstanres.pdf. Accessed May 7, 2009). Acuties expressed as the percentage from optimal vision are given below. Optimal vision was defined for this purpose as 1 decimal (acuties ≥ 1 decimal were considered as 100%).

^c The percentile of the field detected (i.e., points in the visual field detected at above a chance level: more than 15 out of 30 stimulations²²). Similar results were also obtained when testing the whole visual field (0°-24°).

^d The percentile of correct responses (out of the total of 10 items in the test).

^e In units of logMAR. Contrast sensitivity expressed as the percentage from optimal vision (1.95) given below.

^f Motion detection and OFM tests: the percentiles of correct responses are given. Normal mean was defined as the mean performance level of the matched control subjects. Number of participants with missing data, when applicable, is given in squared parentheses at the bottom of each cell.

Our study aims to assess motion perception longitudinally following an ON attack, and to document its associated cortical response.

METHODS Standard protocol approvals, registrations, and patient consents. The Hadassah Hebrew University Medical Center Ethics Committee approved the experimental procedure. Written informed consent was obtained from all subjects.

Subjects. Twenty-one patients aged 18–41 (mean \pm SD 28.9 \pm 6.6) years presenting with a first-ever episode of acute ON participated in the study. All patients presented with unilateral visual loss, a relative afferent pupillary defect, and an otherwise normal neuro-ophthalmologic examination (table e-1 and e-Methods on the *Neurology*[®] Web site at www.neurology.org). Twenty-one control subjects who matched the patients for age,

gender, and dominant eye on a subject-by-subject basis were included in the study.

Procedure and data analysis. Four types of examination were performed. Subjects were evaluated monocularly in each test, according to the timeline described in figure e-1.

1. Standard visual tests, including visual acuity (VA, measured by Snellen VA chart); visual fields estimation (by the automatic Humphrey perimetry visual field test 24–2); color perception (standard pseudoisochromatic plates, by Ishikawa); and contrast sensitivity (CS, Pelli-Robson chart at 1 meter, Metrovia Ltd., Cambridge, UK).
2. Additional laboratory tests: optical coherence tomography (OCT)—retinal nerve fiber layer (RNFL) thickness was recorded on a Zeiss Stratus OCT 3 with version 4 software; pattern visual evoked potentials (VEPs)—the amplitudes and

latencies of the major positive component (P100) were recorded to pattern reversal full-field checkerboards; VEP latencies—patients in whom the VEP waveform was unobtainable due to poor vision were excluded from the VEP latency analyses ($n = 7$ in the acute phase and $n = 2$ in later phases); and VEP amplitudes—due to the wide range of variability within a normal population, to best study the effect of ON over time, VEP amplitudes from the affected eye (AE) were expressed as a percentage of that from the fellow eye (FE).¹³

Patients' performance level in the standard visual and additional laboratory tests was compared to the mean normal population values, when available from the literature (in the VA, CS, VEP, and OCT measures). For the visual fields and color perception measures, patients' performance levels were compared to the optimal score available in each test (see table 1 and table e-2 for details). Note that comparison with the mean normal population value or the optimal score is a rigorous criterion. In the clinical constellation, normal visual levels are defined as those above the lower limit of the normal range. A delta score, representing the differences between the subject's data and the given norm, was calculated for each subject. This was done separately for the affected and fellow eyes. Significant differences were defined when the deltas of the group were significantly different from zero.

3. Behavioral tests—motion perception: a) motion detection—subjects were presented with either coherent moving dot arrays (moving noise) or stationary dots and were asked to state whether or not they identified movement in each stimulus; b) object from motion (OFM) extraction: this test is a variation of the one used by Regan et al.⁵ Subjects viewed motion-defined objects and were asked to recognize and name the object. An array of dots composed an object, by moving the dots within the image rightward while moving the dots outside the image leftward at velocity deg/s (or vice versa). The dot pattern generates a camouflaged object that cannot be detected when the dots are stationary or moving as a whole. Importantly, object recognition is dependent on motion perception (for full details, see e-Methods and videos 1 and 2). The percentile of correct responses was calculated for each subject and then averaged across subjects. A delta score, representing the difference between the patient and matched control, was calculated. Significant differences were defined as cases in which the deltas of the group were significantly different from zero.

To address the relative deficit of the AEs in the different visual measures, we further represented performance level at all visual measures in a percent correct scale (actual performance/optimal score available in the test, see table 1 and table e-2).

A repeated-measures analysis of variance (ANOVA) with within-groups factors of eye (AE vs FE), test (VA, CS, color perception, visual field, OFM, and motion detection), and time since the event (0 or 4 months) was used to compare changes along time in the different visual measures. This was performed using SPSS 11.0 for Windows (SPSS, Chicago, IL).

4. fMRI—several tasks were performed: a) viewing flickering checkerboard, known as preferred stimulus for activating primary visual regions; b) viewing an expanding-contracting array of dots, a preferred stimulus for activating the motion-related higher visual area (MT); c) static object recognition: subjects viewed objects whose contours are defined by luminance differences, and were asked to covertly name them.

This stimulus is known to preferentially activate the object-related higher visual area (LOC); d) OFM extraction: subjects viewed motion-defined objects, and were asked to press a response button when they recognized the object and to covertly name it. All experimental conditions were presented in a monocular display.

Data analysis. Data analysis was performed using the Brain-Voyager QX software package (Brain Innovation). Significance levels were calculated according to the cluster size correction (Monte Carlo stimulation)¹⁴ at $p < 0.005$. Across-subject statistical parametric maps (figures 2 and 3) were calculated using a hierarchical random effects model,¹⁵ allowing a generalization of the results to the population level. Three regions of interest (ROIs) within the visual cortex were defined: V1 ROI, representing the primary visual cortex; LOC and MT, representing the object and motion-related regions, respectively (see e-Methods). The individual activation level in each subject, assessed as β weights, was calculated in each ROI. Activation levels were then averaged across subjects (figures 2 and 4).

RESULTS Routine visual functions 4 months following the acute episode are normal, yet VEP latencies are prolonged. In the AEs, visual acuities, visual field, and color perception were significantly impaired at the acute phase and recovered completely after 1 month. Contrast sensitivity displayed a longer deficit and recovered completely after 4 months (see detailed information in table 1). In the FEs, all visual functions were within the normal range at all time phases (see detailed information in table e-2). While the group as a whole had recovered at the 12-month phase, 2 patients had a sustained severe visual impairment.

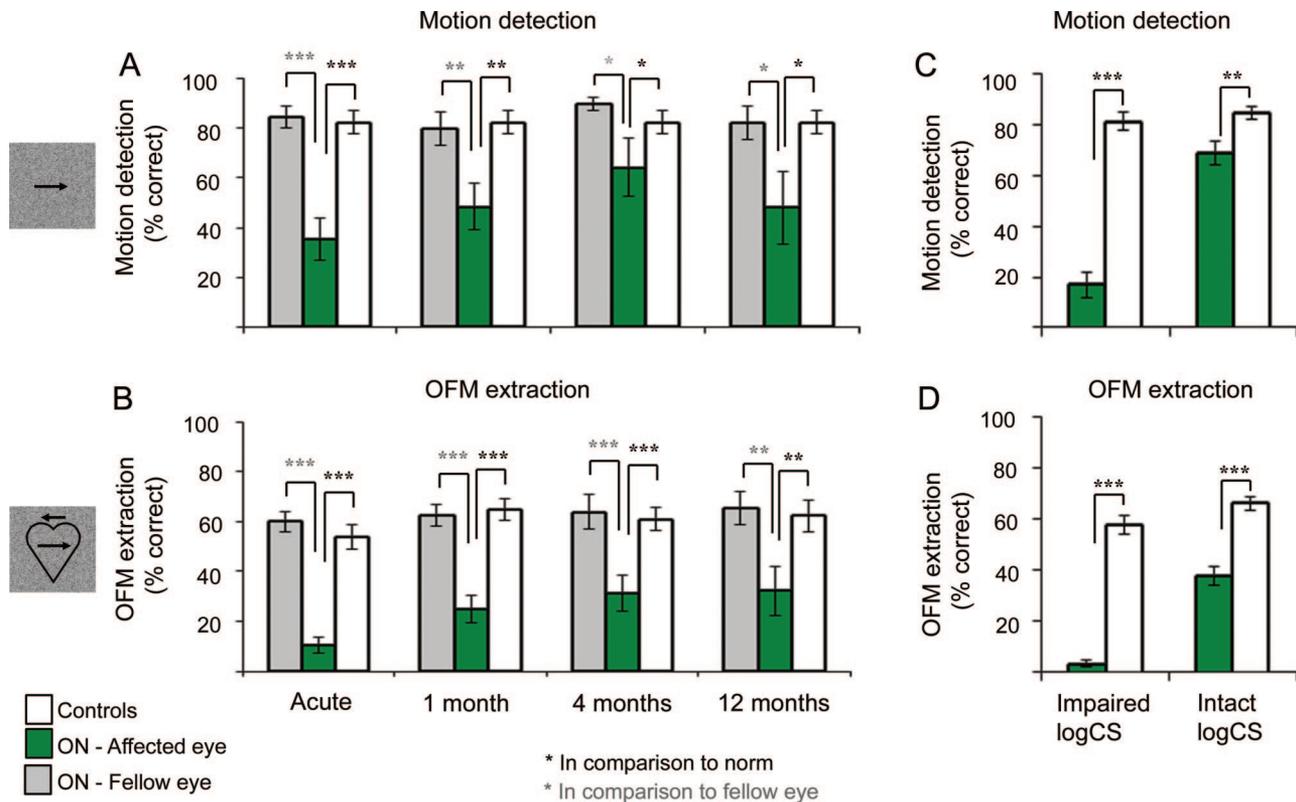
At the 12-month phase, the RNFL thickness of both eyes was reduced when compared to the normal mean,¹⁶ but was within the normal range (table 1 and table e-2).

The VEP amplitudes of the AEs were decreased in the acute phase but not subsequently. Both affected and fellow eyes had significantly prolonged VEP latencies at all testing phases (table 1 and table e-2).

Motion perception in the affected eye is impaired 1 year following the acute episode. Improvement occurred in both routine visual tests and motion perception. This was evident up to the 4 months phase ($p < 0.05$, paired t tests between phases), but not subsequently. However, improvement was disparate across measures, as revealed by an eye \times test \times time interaction ($F = 2.44$, $p = 0.045$, repeated-measures 3-way ANOVA).

In contrast to routine visual tests, motion perception was impaired during the entire follow-up period (table 1 and figure 1, A and B). The AEs were impaired in both motion detection and OFM extraction tasks during all testing phases, in comparison to the normal mean of the matched control subjects and to the FEs.

Figure 1 A sustained deficit in motion perception independent of contrast sensitivity (CS) levels



Performance levels in the 2 motion-related tasks: motion detection (A) and object from motion (OFM) extraction (B) during the 4 testing phases. (C) Motion detection and (D) OFM extraction results for the affected eyes (AEs) when grouped according to their CS levels (averaged across all testing phases). The figure plots motion perception levels of AEs with impaired and intact CS, as compared to their matched control subjects. White bars, matched control subjects; green bars, AE of patients with optic neuritis (ON); gray bars, fellow eyes of patients with ON. Asterisks denote significance level: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

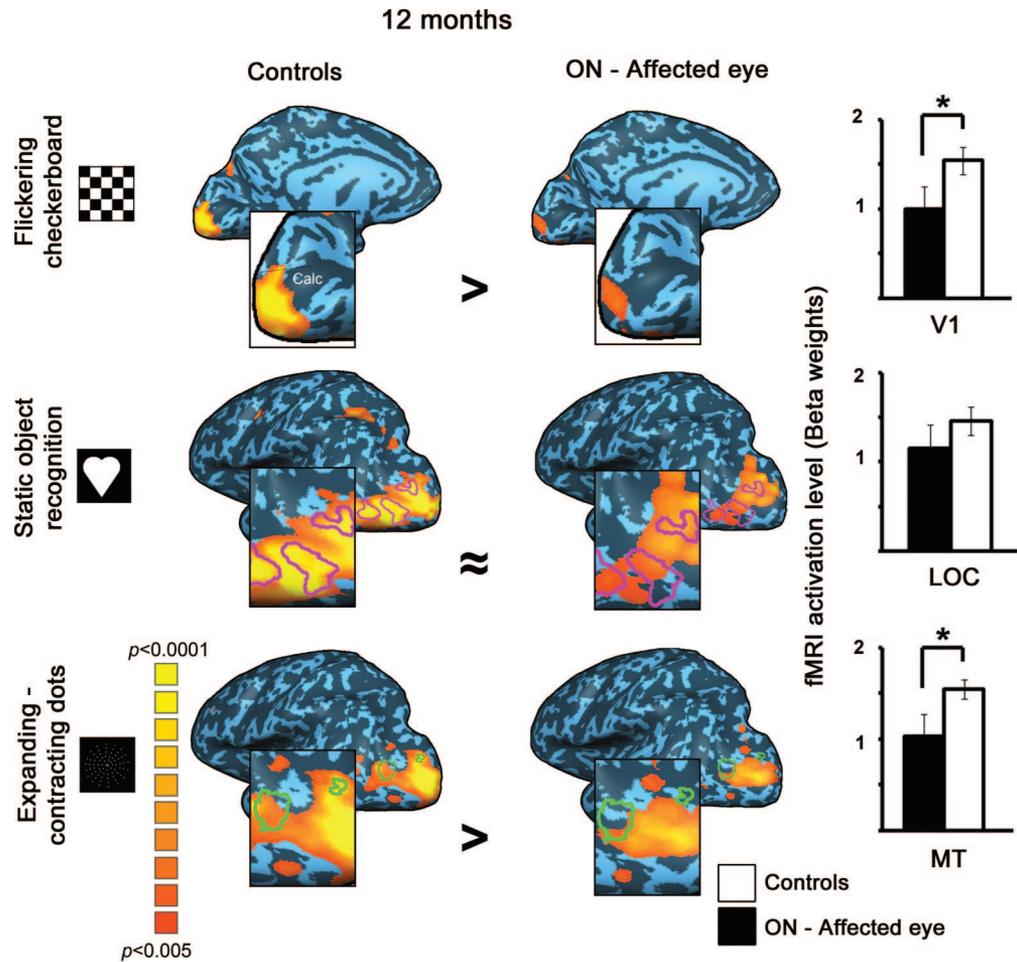
The sustained deficit in motion processing might have resulted from the combination of 2 factors. First, a disproportionate deficit in the acute episode was found in motion perception when compared to the other visual functions (e.g., $p = 5 \times 10^{-5}$ and $p = 4 \times 10^{-5}$ for comparison of OFM with VA and CS, paired t tests; all measures were represented in a percent correct scale). Second, there was less recovery of motion processing in comparison to the other visual measures. Thus, the OFM recovery level (defined as the deltas between the acute and 4 months phases) was lower in comparison to the recovery of VA or CS functions ($p = 0.03$, $p = 0.045$, respectively, paired t test between deltas).

There was no direct relationship between the severity of visual impairment during the acute episode and the severity of impairment later in the disease. However, severity of impairment in later phases (e.g., 12 months) was strongly correlated with severity at the 1-month phase (linear least-squares regression with calculation of the correlation coefficient, $r = 0.93$, 0.97 , and 0.91 for VA, CS, and OFM; $p < 10^{-4}$ in all).

Motion perception deficits are independent of the contrast sensitivity function. Does the motion perception deficit relate to the impaired CS in the AE? In order to test this, we separated all the AEs into 2 groups according to their CS levels: eyes with intact (>1.6) and impaired (≤ 1.6) CS. Figure 1, C and D, plots the motion perception functions in the 2 groups compared to their matched control subjects. Both groups of AEs with impaired or intact CS levels exhibited a deficit in motion perception tasks. Furthermore, analysis of covariance revealed that the effect of group (AE vs matched controls) was significant after taking into account CS levels of the AEs. Thus, motion perception deficit is independent of CS levels ($F = 157.3$, $p < 0.001$; $F = 165.7$, $p < 0.001$ for OFM and motion detection, respectively).

Cortical activation associated with motion perception is reduced 1 year following the acute episode. fMRI studies were performed on a subgroup of 13 patients and their matched control subjects. The patient subgroup was indistinguishable from the whole group of patients in all visual functions, VEP, and OCT measures. This was

Figure 2 An intact cortical activation level in LOC and reduced cortical activation in V1 and MT 12 months following the acute phase



fMRI activation maps are presented, showing activation within the primary visual cortex (V1), object-related (LOC) and motion-related (MT) regions during their preferred stimulus presentation. The data are presented on a full Talairach normalized inflated brain of the left hemisphere. V1 is anatomically defined in the Calcarine sulcus (Calc), presented on a medial view of the cortex (upper row). LOC and MT are outlined on the lateral view of the cortex (LOC, purple lines; MT, green lines, second and third rows, correspondingly). Blow-ups highlight activation in the 3 ROIs. Activation above $p = 0.005$ (corrected for multiple comparison) is presented; color scale denotes significance levels. Activation is seen for control subjects and affected eyes of patients with optic neuritis (ON). Histograms on the right denote the activation levels (β weights) within each region of interest for the 2 groups. For comparison, fMRI activation levels in V1, LOC, and MT measured at the acute phase are presented in figure e-2).

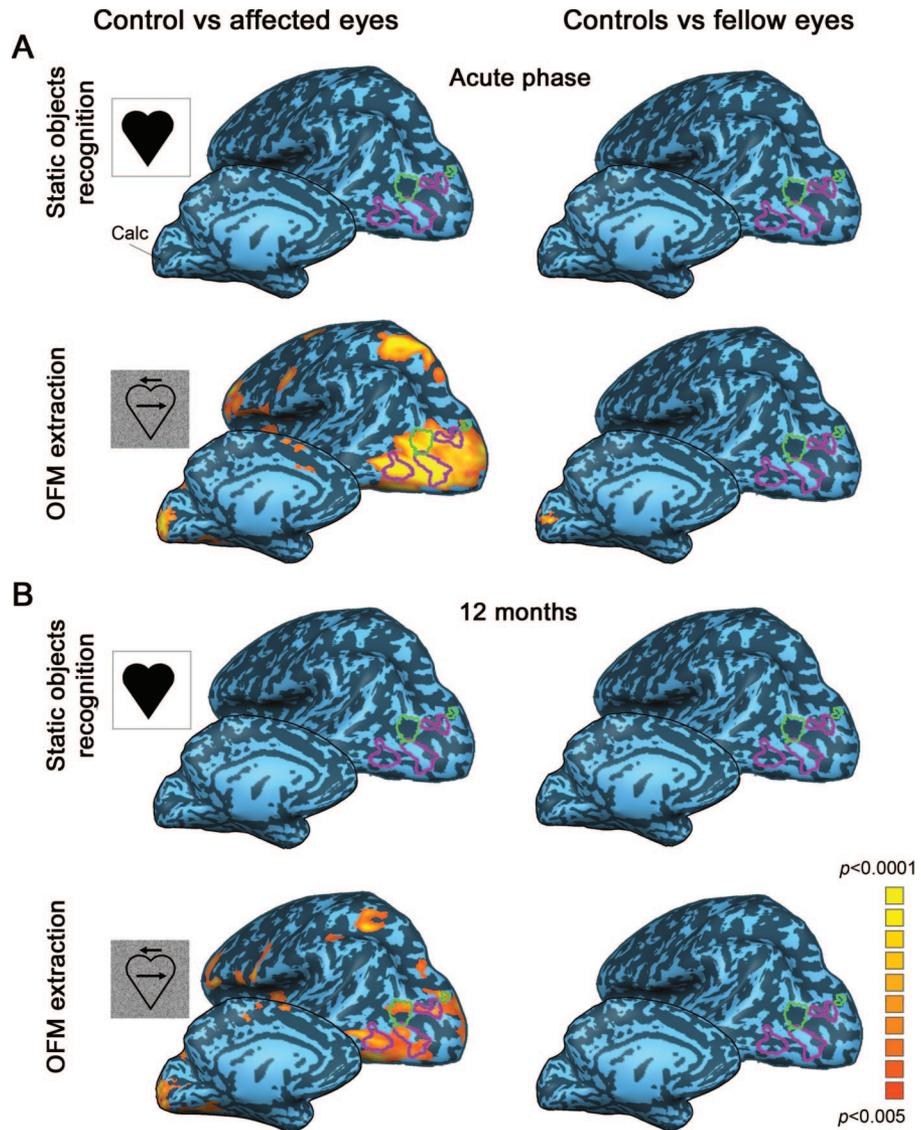
true for both AEs and FEs during all testing phases (2-sample t tests, $p > 0.3$ in all comparisons).

During the fMRI scan, subjects viewed flickering checkerboard, static objects, or an expanding-contracting array of dots (preferred stimuli for activating V1, LOC, and MT, respectively). Figure 2 shows the cortical activation in the 3 ROIs for control subjects and for patients with ON during AE stimulation 12 months following the acute phase. Viewing static objects elicited robust activation in LOC in patients with ON and controls. While activation was slightly reduced during AE stimulation, a major part of LOC was activated. On the contrary, viewing moving stimuli via the AE elicited activation only in a small part of MT. This co-occurs with the

reduced activation in V1 during checkerboard presentation to the AE. In addition to the multi-subjects' cortical activation maps, we quantitatively assessed the fMRI activation levels on a subject-by-subject basis. Activation levels were measured as the β weights in the 3 ROIs: V1, MT, and LOC. Reduced activation for the AE, as compared to controls, is seen in V1 and MT but not in LOC.

Cortical activation for motion-defined objects verifies the psychophysical findings. In order to address the neuronal basis of the behavioral OFM task, an fMRI using this same paradigm was performed. Subjects viewed either luminance or motion-defined objects (OFM). If patients experience a specific deficit in

Figure 3 A sustained reduction in cortical activation while processing motion-defined forms projected to the affected eye (AE): Cortical maps

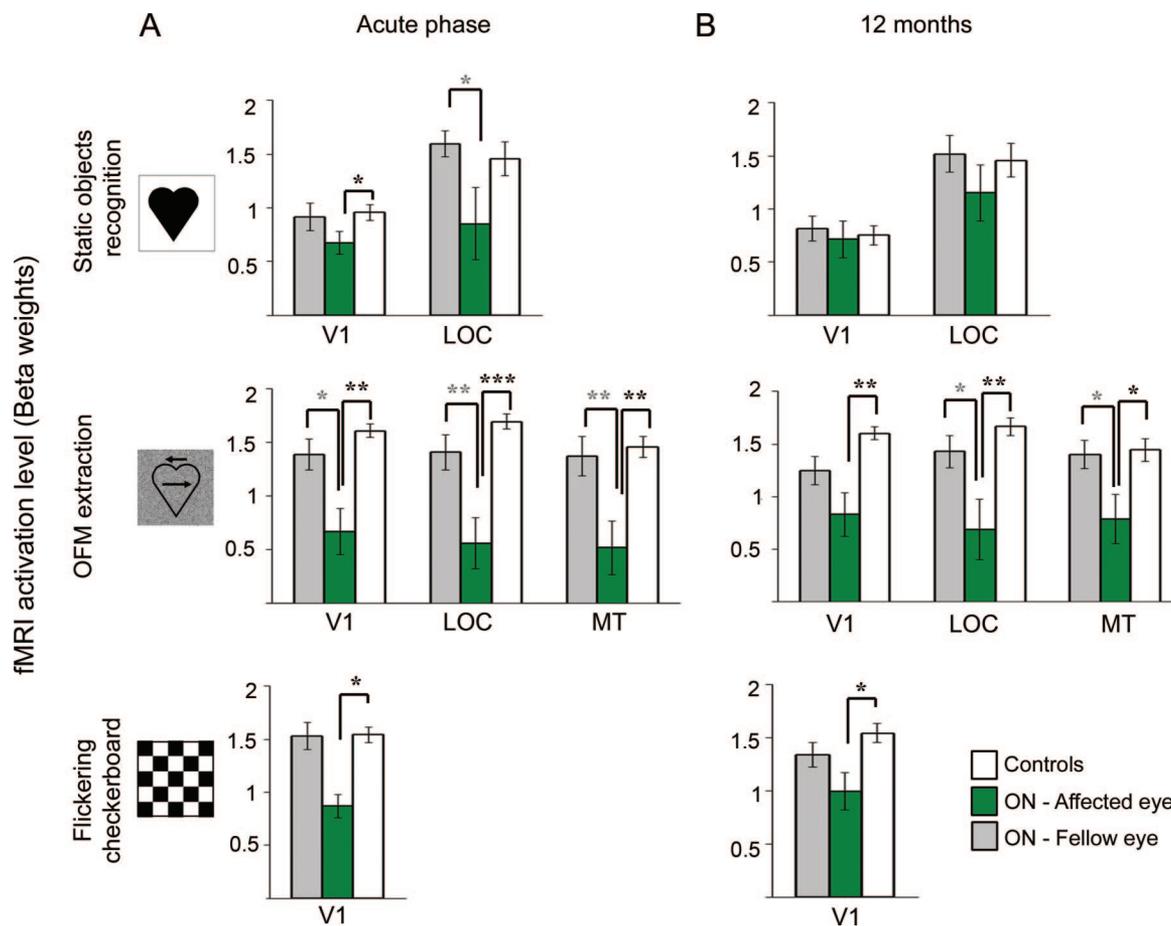


Differential fMRI activation maps are presented showing activation for controls vs patients with optic neuritis (ON) (controls > patients with ON) during static object and object from motion (OFM) viewing. The cortical activation obtained during AE and fellow eye stimulation (in comparison to controls) is shown for the acute (A) and 12-month (B) phases. The data are presented on a full Talairach normalized inflated brain of the left hemisphere. Lateral and medial views (upper and lower views for each stimulation) are shown. Activation above $p = 0.005$ (corrected for multiple comparison) is presented; color scale denotes significance levels. The figure plots regions which have increased activation in the matched control subjects in comparison to the affected or fellow eyes of the patients with ON (left and right columns, respectively). Regions of interest are outlined as in figure 2.

motion perception, reduced cortical activation will be seen only for the second stimulus type, since motion perception is required to recognize OFM but not luminance-defined objects. Since OFM combines both motion and object perception, this stimulus is expected to activate both MT and LOC (in addition to primary visual cortex). Figure 3 presents the group results of the cortical activation during these tasks, at the acute and 12-month phases. A differential activation map is shown, highlighting voxels with greater activation in the controls compared with

the ON group. Cortical activation levels obtained when subjects viewed static objects via the AE were not different from those obtained in controls. This was found at all testing phases, including the acute phase. In comparison, viewing OFM stimuli via the AE resulted in robust differential cortical activation in various occipital regions including V1, LOC, and MT. (Differential activation is also seen in sensorimotor regions since subjects were instructed to press a response button when they identified the OFM.) A reduced cortical activation while processing OFM

Figure 4 A sustained reduction in cortical activation while processing motion-defined forms projected to the affected eye (AE): fMRI activation levels



Activation levels (β weights) during viewing of static objects, object from motion (OFM), and flickering checkerboard in the 3 ROIs: V1, LOC, and MT during the acute (A) and 12-month (B) phases. White bars, matched control subjects; green bars, AE of patients with optic neuritis (ON); gray bars, fellow eyes of patients with ON. Asterisks denote significance level: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

stimuli was found as long as 12 months following the acute phase, indicating the sustained impairment in motion processing. fMRI activation patterns 4 months following the acute phase were similar to those obtained at the 12-month phase (data not shown).

fMRI activation levels on a subject-by-subject basis were also assessed. Activation levels, measured as β weights, were then averaged across subjects, in all 3 ROIs (V1, MT, and LOC; figure 4). Reduced activation during static object viewing occurred during the acute phase only. Reduced activation levels during OFM processing occurred in all ROIs at the 12-months phase.

The results in the acute phase, as demonstrated in figures 3 and 4, indicate that while some patients demonstrated reduced cortical activation during static objects processing (reduced averaged β weights in V1, figure 4), this is not a general phenomenon and thus does not survive the random-effect model (figure 3). Reduced activation during dynamic object

processing, on the other hand, is common to all patients and can be generalized to the ON population level.¹⁵

DISCUSSION We have presented evidence for a sustained motion perception deficit following ON, while static visual functions recovered. This effect was demonstrated using novel tests developed in our laboratory. Verification of these tests on a wider scale is necessary to establish norms; currently the deficit was evaluated relative to a small group of 21 control subjects. The behavioral deficit in motion perception was associated with reduced cortical activation during motion processing. This was evident using different kinds of motion-related stimulation and different data analyses.

Previous longitudinal studies suggested that measures of low-contrast vision may be the most sensitive markers of visual dysfunction following ON.¹⁷⁻¹⁹ We also found that CS continued to be impaired in comparison to visual acuity, visual field, and color per-

ception. However, testing motion perception, which is not included routinely in ON assessment, revealed the most significant and prolonged impairment. Furthermore, the motion perception deficit was independent of CS levels.

A motion perception deficit following ON was suggested in 2 previous reports.^{5,6} A significant proportion of these eyes had normal visual and low contrast acuities. Our longitudinal prospective study further demonstrates that the deficit in motion perception is sustained 1 year after the attack, indicating a severe prognosis for motion perception, as compared to other visual functions.

Previous fMRI studies on patients who recovered clinically from ON showed an intact activation level in the object-related visual regions during stimulation of the AE.⁹⁻¹² This was evident when activation in early visual areas was intact^{11,12} but also when it was reduced.^{9,10} Intact activation in LOC was considered as evidence of cortical plasticity, where cortical adaptation to a persistent abnormal input contributes to the recovery process.^{8-10,12} Recovery from ON was mainly related to intact visual acuity levels⁸⁻¹² and intact visual fields,⁹⁻¹¹ known to recover relatively fast following the attack. We confirmed an intact activation level in the object-related visual regions during stimulation of the AE. However, sustained reduction in cortical activity was still evident in the motion-related area (MT), responsible for dynamic processing. Thus, if higher cortical visual regions play a role in visual recovery, it seems to be limited to static visual functions. An alternative hypothesis may be that the cortical activation level reflects the visual percept (intact for visual acuity and impaired for motion perception), rather than demonstrating cortical plasticity. Recently, a correlation between LOC activation levels during the acute phase of ON and visual outcome (visual acuity 12 months after the attack) was demonstrated.¹² This baseline LOC activation was posited as a predictive measure for visual recovery. Of note, however, is that visual outcome correlated not only with baseline LOC activation, but also with the degree of visual loss at the acute phase. Thus, the LOC activation may reflect the severity of visual acuity at the acute phase. (Indeed, the authors specifically showed that after adjusting for the interaction variable of baseline acuity, baseline LOC activation did not significantly predict visual outcome). This may be in accordance with the suggestion that cortical activation levels reflect the visual percept.

We suggest that sustained deficit in motion perception may explain patients' persistent visual complaints, even when standard testing is normal. Motion perception, using OFM recognition, may be

a valuable addition to routine ophthalmologic tests following ON.

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DISCLOSURE

Dr. Raz, Dr. Dotan, T. Benoliel, and Dr. Chokron report no disclosures. Prof. Ben-Hur serves on a scientific advisory board for and holds stock options in BrainWatch Ltd.; serves on the editorial boards of the *Journal of the Neurological Sciences*, *Multiple Sclerosis*, and *Neurology Research International*; is listed as an author on a patent re: Use of human embryonic stem cells or cells derived from in neurodegenerative and neuroimmunological disorders; and receives research support from the Israel Science Foundation. Dr. Levin reports no disclosures.

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UNUSUAL BRAIN GROWTH PATTERNS IN EARLY LIFE IN PATIENTS WITH AUTISTIC DISORDER: AN MRI STUDY

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Objective: To quantify developmental abnormalities in cerebral and cerebellar volume in autism. *Methods:* The authors studied 60 autistic and 52 normal boys (age, 2 to 16 years) using MRI. Thirty autistic boys were diagnosed and scanned when 5 years or older. The other 30 were scanned when 2 through 4 years of age and then diagnosed with autism at least 2.5 years later, at an age when the diagnosis of autism is more reliable. *Results:* Neonatal head circumferences from clinical records were available for 14 of 15 autistic 2- to 5-year-olds and, on average, were normal (35.1 ± 1.3 cm versus clinical norms: 34.6 ± 1.6 cm), indicative of normal overall brain volume at birth; one measure was above the 95th percentile. By ages 2 to 4 years, 90% of autistic boys had a brain volume larger than normal average, and 37% met criteria for developmental macrocephaly. Autistic 2- to 3-year-olds had more cerebral (18%) and cerebellar (39%) white matter, and more cerebral cortical gray matter (12%) than normal, whereas older autistic children and adolescents did not have such enlarged gray and white matter volumes. In the cerebellum, autistic boys had less gray matter, smaller ratio of gray to white matter, and smaller vermis lobules VI-VII than normal controls. *Conclusions:* Abnormal regulation of brain growth in autism results in early overgrowth followed by abnormally slowed growth. Hyperplasia was present in cerebral gray matter and cerebral and cerebellar white matter in early life in patients with autism.

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Comment from Jonathan W. Mink, MD, PhD, FAAN, Associate Editor: This is a large comprehensive study of brain development in autism using volumetric MRI. The finding of different patterns of brain growth at different developmental stages was an important contribution to the understanding of autism as a neurodevelopmental disorder.