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Retinal ganglion cell function in recovered optic neuritis: Faster is not better

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HIGHLIGHTS

- Patients with Multiple Sclerosis and past history of optic neuritis (ON) can have normal clinical vision.
- Pattern Electroretinogram (PERG) responses, reflecting mass retinal ganglion cell responses, show shortened latency in eyes with resolved ON.
- Faster function, as measured by PERG, is not better, as this implies loss of smaller axons in the optic nerve.

ABSTRACT

Objective: To assess residual retinal ganglion cell (RGC) function in patients with recovered optic neuritis (ON) and multiple sclerosis (MS).
Methods: Age-matched controls (C, $n = 32$) and MS patients ($n = 17$) with history of ON in one eye but normal visual acuity and color vision were tested with steady-state Pattern Electroretinogram (PERG). Light Emitting Diodes (LED)-generated bar gratings, robust signal averaging and Fourier analysis were used to assess response amplitude and latency.
Results: PERG amplitude was similar for C, ON and fellow eyes (FE) ($P = 0.4$), but PERG latency was shortened in ON by 3.2 ms ($P = 0.002$) and in FE by 2.0 ms ($P = 0.02$) and was correlated ($P < 0.01$) with both Retinal Nerve Fiber Layer (RNFL) and Ganglion Cell Inner Plexiform Layer (GCIPL) thicknesses. PERG latency shortening could be simulated in control subjects ($n = 8$) by dioptrically blurring the edges of gratings (high spatial frequencies), which reduced activity of parvocellular RGCs with smaller/slower axons. The blurred PERG latency was shorter than baseline by 2.9 ms ($P = 0.01$).
Conclusions: PERG latency is shortened in both eyes of MS patients with recovered unilateral ON, suggesting relative dysfunction of RGCs with slower axons and sparing of RGCs with faster axons.
Significance: Assessment of PERG latency in MS and ON may help identifying and monitoring RGC dysfunction. PERG latency shortening in FE suggests primary retinopathy in MS.

1. Introduction

Multiple sclerosis (MS) is a chronic demyelinating disease affecting neurons and their axons at multiple sites in the central nervous system (Peterson et al., 2001; Martinez-Lapiscina et al., 2014). The visual system is highly susceptible to damage from MS (Balcer et al., 2015; Graham and Klistorner, 2017). In fact, optic neuritis (ON) is a common ophthalmological feature in MS patients, which is characterized by loss of visual acuity (VA) and visual field (Chen and Gordon, 2005; Jasse et al., 2013) that generally recover to normal after several months. Despite normal VA and visual field, recovered ON eyes may have decreased axonal density and volume as measured by Optical Coherence Tomography (OCT) (Akçam et al., 2014) (Klistorner et al., 2014; Graham et al., 2016), suggesting loss of retinal ganglion cells (RGCs). Abnormal OCT in eyes with recovered ON imply abnormal function of RGCs and their axons that is still poorly understood.

RGC function can be assessed with Pattern Electroretinogram (PERG) (Fiorentini et al., 1981; Maffei and Fiorentini, 1981). However, information about residual RGC function as assessed by PERG in eyes with recovered ON is inconclusive. Most PERG applications in ON used the standard transient PERG (Bach et al., 2013), whose

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waveform is characterized by a positive peak about 50 ms after each pattern reversal (P50) followed by a broad negative trough peaking at about 95 ms (N95). The majority of PERG studies to test RGC function in MS and ON report decreased P50 + N95 PERG amplitude and delay of P50 PERG latency (for review see (Hokazono et al., 2013)). Assessment of PERG latency in ON using the P50 wave of transient PERG may lead to misleading interpretation, as the P50 wave is poorly related to RGC activity (Viswanathan et al., 2000) and is little altered in optic nerve disease (Holder, 1987). The N95 wave has higher specificity for RGC dysfunction in optic nerve disease compared to P50 (Holder, 1987) but the N95 latency is difficult to measure accurately due to the broad shape of this component (Holder, 2001).

The steady-state PERG (SS-PERG) offers an opportunity to address the problem of PERG latency assessment. The relevant component of the steady-state PERG is a sinusoidal wave at the frequency as the reversal rate (typically around 16/s) whose phase (latency) can be precisely and objectively measured with Fourier analysis. Compared to the transient PERG, the SS-PERG has a relatively higher signal-to-noise ratio and higher sensitivity and specificity for RGC dysfunction in disease (Bach and Hoffmann, 2008). The SS-PERG may be at noise level in advanced stages of optic nerve diseases such as Leber Hereditary Optic Neuropathy (LHON) (Guy et al., 2017) and Non Arteritic Ischemic Optic Neuropathy (NAION) (Monsalve et al., 2017). Recently, patterned visual displays based on Light Emitting Diode (LED) technology have been introduced (Toft-Nielsen et al., 2011) that have much higher luminance and temporal resolution compared to standard Cathode Ray Tube (CRT) displays. Higher luminance results in a signal with higher amplitude, and synchronous pattern reversal over the entire stimulus field results in higher precision of phase (latency) measurement (Toft-Nielsen et al., 2011). In contrast, with CRT displays the contrast-reversal occurs in a sweeping manner over several ms (Ito et al., 2013) resulting in asynchronous activation of PERG generators.

Here we report results obtained using SS-PERG in response to LED-generated pattern reversal in a population of MS patients with recovered ON compared to similarly aged healthy subjects. It will be shown that PERG latency is substantially shorter than normal in both ON and FE eyes. PERG latency shortening can be simulated in healthy subjects with optical defocus, which deteriorates contrast for the edges of the stimulus bar grating (high spatial frequencies) leaving the smoothed bars (low spatial frequency) relatively unaffected (Brodie and Conte, 1992; Bach and Mathieu, 2004).

2. Subjects

2.1. Subjects

Study subjects were 17 patients with unilateral recovered ON, that were selected from a larger cohort of patients with relapsing remitting multiple MS. The first episode of ON occurred 7.5 ± 5 years before testing, and the most recent episode occurred 7.3 ± 6 years. At the time of testing, patients had normal clinical vision (visual acuity $\geq$ 20/20, full visual field, normal Ishihara color vision) in both ON eyes and fellow eyes (FE). Control subjects (C) were similarly aged healthy subjects with normal clinical vision. Patients significantly differed from controls in the thickness of Retinal Nerve Fiber Layer (RNFL) (C > ON, $P = 0.0002$; C > FE, $P = 0.23$; FE > ON, $P = 0.053$), thickness of the Ganglion Cell Inner Plexiform Layer complex (GCIPL) (C > ON, $P < 0.00001$; C > FE, $P = 0.0039$; FE > ON, $P = 0.01$), and marginally differed in intraocular pressure (IOP) (C > ON, $P = 0.041$; C > FE, $P = 0.045$; FE > ON, $P = 0.6$) as summarized in Table 1. An independent group of healthy subjects ($n = 9$, mean age: 29 ± 8.9 years) was used to test the effect of dioptric defocus on PERG. The study followed the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of the University of Miami. Informed written consent was obtained from all subjects.

2.2. PERG recording

A SS-PERG was simultaneously recorded from each eye as previously described (Monsalve et al., 2017). The visual stimulus was a pattern of black-white horizontal square-wave gratings generated on a 14 × 14 cm LED display (1.6 cycles/deg, 15.63 reversals/s, 98% contrast, 800 cd/sqm mean luminance, 25 deg field – Jorvec Corp., FL, USA) presented binocularly at 30 cm viewing distance in a dimly lit room. Subjects looked at the center of the stimulus with natural pupils and blinking and wore corrective lenses as needed for the viewing distance to obtain a Jaeger J1+ visual acuity. PERG signals were recorded from gold cup skin electrodes (9 mm diameter, Grass) taped over the lower eyelids (reference ipsilateral temples, common ground central forehead) and averaged in sync with the pattern reversal over 1024 epochs (~2.18 min) by automatically rejecting epochs occasionally contaminated by blinking artefacts. Noise signals were simultaneously recorded by averaging odd and even epochs in counterphase (Schimmel, 1967). A sketch of the PERG set up and an example of response are summarized in Fig. 1 together with the response components that were assessed. PERG and noise waveforms were Fourier analyzed to retrieve the 15.63 Hz frequency component at the reversal rate and measure the corresponding zero-to-peak amplitude (μV) and phase delay (degrees) compared to the stimulus reversal. As one reversal period (360 degrees) corresponded to 1/15.63 Hz = 0.064 s, phase delays could be converted to latency delays using the formula [latency (ms) = (360 − phase (deg))/360 * 64 ms]. PERG latency converted from phase coincided with the time-to-peak of the 15.63 Hz Fourier-isolated sinusoidal component shown in Fig. 1. For experiments on the effect of optical blur on PERG, one eye of each subject was added with positive lenses to reduce visual acuity to J5 (20/50 equivalent), while the other eye had visual acuity of J1+ (20/20 equivalent). Contrast sensitivity for edges rapidly deteriorates with increasing blur (Jansonius and Kooijman, 1997). With dioptrical blur resulting in a J5 visual acuity, the edges of the square-wave grating were no longer visible, whereas the contrast of the smoothed grating did not appear substantially altered. Removing edges from the square-wave pattern had the effect of

Table 1
Summary of main demographic and clinical characteristics of patients.

	C ($n = 32$)	ON ($n = 17$)	FE ($n = 17$)	ON vs C (P-value)	FE vs C (P-value)	ON vs FE (P-value)
Age (years)	42 ± 12.69	43 ± 9.43	43 ± 9.43	0.91	0.91	0.91
RNFL (μm)	99.09 ± 8.88	81.88 ± 10.86	92.25 ± 12.05	0.0002	0.231	0.053
GCIPL (μm)	85.34 ± 6.60	68.23 ± 7.50	77.64 ± 7.79	<0.0001	0.0039	0.01
IOP (mm Hg)	17.03 ± 2.86	15.52 ± 1.80	15.25 ± 1.86	0.041	0.045	0.6

RNFL, Retinal Fiber Layer Thickness; GCIPL, Ganglion Cell Inner Plexiform Layer Thickness; IOP, Intraocular pressure; C, Controls; ON, Optic Neuritis eyes; FE, Fellow Eyes; P-values, Significance levels of Mixed Model ANOVA statistics and post-hoc Tukey multiple comparisons.