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Study of Critical Flicker Fusion (CFF) Function and P100 latency of Visual Evoked Potential (VEP) in Normal subjects and Patients who Recovered from Acute Optic Neuritis

Yanjun Chen[1]*, Kevin A Buhr[2] and James Ver Hoeve[1]

[1]*Department of Ophthalmology & Visual Sciences, University of Wisconsin, USA*

[2]*Department of Biostatistics and Medical Informatics, University of Wisconsin School of Medicine and Public Health, USA*

***Corresponding author:** *Yanjun Chen, M.D, Ph.D, Department of Ophthalmology and Visual Sciences University of Wisconsin School of Medicine and Public Health, 2828 Marshall Ct. Suite 200, Madison, WI 53705, USA, Tel: 608263148, E-mail: ychen344@wisc.edu*

Abstract

Objective: Critical Flicker Fusion (CFF) function has been used to assess visual function in patients with impaired vision. The purpose of this study is to seek further evidence to support the role of the CFF in the assessment of optic nerve function by comparing CFF to implicit time of the P100 of Pattern Reversal Visual Evoked Potential (PRVEP) in normal subjects and patients who recovered from acute optic neuritis.

Methods: 4 healthy adult subjects and 11 patients (14 affected eyes) who recovered from acute optic neuritis underwent PRVEP and CFF, as well as Snellen visual acuity and Ishihara color testing. For normal subjects, neutral density filters (NDF) of 0.6 to 3.0 log unit were used to control stimulus luminance to obtain response vs. stimulus intensity curve for each measurement. The CFF and PRVEP P100 latency were compared between the normal subjects and patients.

Results: In normal subjects, CFF decreased 7.8 Hz (95% CI [7.4, 8.3], $p < 0.001$) and P100 latency increased 17.9 ms (95% CI [9.7, 26.0], $p < 0.001$) per log unit increase in NDF. Increasing NDF was also associated with decreasing logMAR acuity and decreasing P100 amplitude (both $p < 0.001$). In patients recovering from unilateral acute optic neuritis, CFF was significantly lower in affected than unaffected eyes. For all patients, affected eyes had significantly lower CFF than healthy eyes in normal subjects. PRVEP P100 latency did not differ significantly in the affected eyes of patients from the unaffected eyes of patients and normal subjects.

Conclusion: Both CFF and PRVEP P100 latency are linearly correlated with log luminance. CFF is significantly decreased in the affected eyes of patients who recovered from acute optic neuritis. CFF may complement the currently used office tests to facilitate the assessment of optic nerve dysfunction.

Keywords

Critical flicker fusion, Visual evoked potential, P100 latency, Neutral density filter, Optic neuritis

Introduction

When the eye is exposed to rapidly alternating light a sense of flickering is produced. As the frequency of the intermittent light increases to a threshold value, the flickering light becomes indistinguishable from a steady light. The threshold frequency beyond which flickering light transforms to steady light is called critical flicker fusion (CFF) function [1]. Multiple levels of the visual pathway and cortical involvement have been proposed to contribute the physiologic mechanism of CFF, such the retinal photoreceptors and ganglion cells [2-5], primary visual cortex [6], and temporal, parietal and other extra striate cortices [6-9].

Using CFF to assess optic nerve function has been studied in cataract [7-9], age-related macular degeneration [10,11], glaucoma [12-15], and optic neuropathies [12,16-18] with varying results. Study of CFF in cataract found little impact of dense cataract on CFF [8-10]. Studies on multiple sclerosis (MS) associated demyelinating optic neuritis found decrements of CFF in not only the acute stage of visual loss, but also after visual acuity recovered to normal, as well as in those who do not report a history of optic neuritis [19,21-23]. The above results suggest that CFF could be a sensitive measure of optic nerve function.

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Table 1: The demographic and clinical features of the patients group.

#	Age (years) Sex	Eye affected	VA at presentation	HVF (MD, dB): presentation	MRI CE	Diagnosis	Steroids	Interval* (month)	VA at test	HVF (MD, dB) at test:	CFF (Hz)
1	66, F	OD	20/40	-30.65	Y	folicular lymphoma	Y	18	20/20	-9.47	20.1
		OS	20/60	-31.11	Y		Y		20/25	-11.46	20.3
2	63, F	OD	2/200	29.48	Y	idiopathic	Y	5	20/30	-3.21	28.7
3	44, M	OD	20/40	-18.87	Y	MS	Y	14	20/20	-3.09	31.9
4	40, F	OD	20/20	-15.04	Y	idiopathic	Y	3	20/20	-0.79	13.2
5	48, M	OD	20/20	-24.29	Y	idiopathic	Y	24	20/20	-2.03	12.6
		OS	20/400	-32.87	Y		Y		20/20	-5.56	12.5
6	47, F	OD	counting finger	-16.44	Y	idiopathic	Y	5	20/100	-9.49	19.9
7	47, F	OD	severe	-	-	MS	Y	204	20/20	-3.50	22.9
8	33, F	OS	light perception	unable	Y	MS	Y	16	20/800	-20.68	11.2
9	36, F	OD	20/200	-33.86	Y	MS	Y	33	20/20	-5.41	34.4
10	56, F	OD	20/60	-9.71	Y	idiopathic	Y	6	20/20	-4.03	27
		OS	20/30	-2.61	Y		Y		20/20	-0.88	26.9
11	49, M	OD	hand motion	-26.84	Y	idiopathic	Y	48	20/25	-20.22	29.6

#Patient number, *The interval between patient's initial presentation and the time of the study; -Unavailable; M: Male; F: Female; OD: Right eye; OS: Left eye; CE: Contrast enhancement of the optic nerve; MS: Multiple sclerosis; Idiopathic: Idiopathic optic neuritis.

The purpose of the present study was to compare CFF with PRVEP, a widely accepted electrophysiologic measurement of optic nerve function [19,20], in normal subjects and patients who recovered from acute optic neuritis. In addition, CFF was compared to logMAR acuity and color vision, the two most commonly used visual function testing in clinical practice.

Materials and Methods

Subjects

The study recruited two groups of subjects. Group 1 included 4 healthy adult subjects (2 males and 2 females) ranging in age from 31 to 60 years (mean ± SD, 43.8 ± 12.0). Group 2 included eleven patients (3 males and 8 females, fourteen affected eyes) who recovered from acute optic neuritis, with age ranging from 33 to 66 years (mean ± SD, 48.1 ± 10.3) (Table 1). The exclusion criteria included history of ocular disease other than refractive error, eye trauma or ocular surgery, or concurrent use of ophthalmic solutions other than artificial tears. Those who had a history of ocular disease other than optic neuritis were excluded from the patient group. All healthy subjects had normal eye examination including visual acuity, slit lamp and undilated fundus exam. The procedures conformed to the tenets of the Declaration of Helsinki. The study was approved by the University of Wisconsin-Madison Institutional Review Board. Written consent form was obtained after the details of the tests were explained in detail.

CFF and PRVEP testing

CFF function was measured at a fixed luminance level using a white light flicker fusion device (Flicker Fusion Analyzer, Lafayette Inc., Loughborough, UK). The white electroluminescent lamps produce even illumination over a ½ inch diameter viewing area on a dark background with luminance of 58 cd/m^2. The stimulus subtends a visual angle of 1.9 deg in the area of fixation and was viewed separately by each eye through viewing chamber from 15 inch away. CFF threshold was assessed using a standard ascending and descending method. For ascending method, the stimulus was set at 0 Hz, increased by 1 Hz/sec, and the subjects indicated when the stimulus stopped flickering and fused to a uniform, steady light stimulus. For descending method, the stimulus was set at 60 Hz, which is well above the fusion threshold and appears as a uniform, steady light stimulus. The stimulus decreased by 1 Hz/sec, and the subjects indicated when stimulus began flickering. In each trial, the CFF threshold was tested twice by both ascending and descending method; the average between ascending and descending threshold of the two repeats was taken as the CFF threshold for that trial [19].

PRVEP recordings were made in accordance with the respective ISCEV standards [20,21]. The PRVEP was recorded from gold cup electrodes place at O1, Oz, and O2 sites, with the reference electrode placed at Fz and ground at Cz. The PERG was recorded from DTL fiber electrodes [22] draped over the inferior fornix and referenced to a gold cup electrode near the ipsilateral outer canthus. Amplification gain was 20 K with a bandpass filter of 1 to 100 Hz. The stimuli were high contrast (> 90%) checkerboard patterns. Stimuli were displayed on a customized LED display of the E3 electrodiagnostic system (Diagnosys, LLC, Lowell, MA). The luminance of the white squares was 100 cd/m^2; the dark squares were < 0.1 cd/m^2. Check sizes subtended 30 min arc and the reversal rate was at 2 Hz. The display monitor is 81 cm wide × 65 cm high and placed 1.5 meters away from subjects, subtending a visual angle of 30.2 by 24.8 deg. The

average of 100 sweeps was obtained for each trial. During the visit, two immediate PRVEPs were recorded in normal subjects and one in patients.

For CFF and PRVEP testing, the subjects were dark adapted for 15 min before recording began.

Testing protocol

For group 1 normal subjects, Snellen visual acuity, color vision (Ishihara plate) and CFF were measured in the left and right eye in routine eye exam room illuminated by ceiling light. Snellen visual acuity was transformed to logarithm of the minimum angle of resolution (*log*MAR) for further analysis. PRVEP were conducted in both the left and right eye in two subjects, and in the right eye for the other two. The PRVEP recordings were similar between the left and right eye for a given subject; the PRVEP recordings from the right eye from each of the four normal subjects were used for the analysis. During each test, a series of neutral density filter (NDF) of 0.6, 1.2, 1.8, 2.4 and 3.0 log unit were placed over the tested eye to modulate the luminance level of the stimulus, with higher NDF producing greater reduction in stimulus luminance. For each test, the sequence of the neutral density filter was first randomized using a random number generator, followed by randomization of the eye tested and the sequence of ascending/descending method (for CFF). The sequence of neutral density filter and the order of eye tested were counterbalanced to minimize any effect of sequence (e.g., fatigue or practice effect).

For group 2 patients, Snellen visual acuity, color vision (Ishihara plate) and CFF were measured in the left and right eye in routine eye exam room illuminated by ceiling light. PRVEP were recorded in the left and right eye without neutral density filter. The sequence of the eye tested as well as ascending/descending method for CFF was randomized using a random number generator for each measurement.

Statistics

For group 1 normal subjects, intraclass correlation coefficients (ICC) were calculated for CFF threshold, logMAR acuity, and Ishihara color vision. ICCs were calculated using an ICC (1,1) model in the sense of Shrout, et al. for classes defined by subject and NDF level within subject (evaluating the correlation across eyes and repeats within eyes) [23] Based on these results, all further analyses used data from normal subjects' right eyes averaging over repeats.

CFF, logMAR acuity, Ishihara color plate testing, and PRVEP P100 latency and amplitude measurements were plotted against NDF by subject. Means and 95% confidence intervals (CIs) for CFF and PRVEP P100 latency at baseline (NDF = 0) were calculated, and ANCOVA models (with a single fixed subject effect and a continuous NDF covariate) were used to evaluate the relationships between NDF and each of CFF, logMAR acuity, and P100 latency and amplitude with point estimates and 95% CIs given for selected coefficients. The relationship between NDF and Ishihara scores was summarized descriptively.

Statistical analysis was performed with R version 3.3.0. Testing was conducted at an $\alpha = 0.05$ significance level. For group 2 patients, critical flicker fusion and PRVEP P100 latency were plotted for unaffected and affected eyes, with results for normal (group 1) subjects at NDF = 0 provided for comparison. Two-group t-tests were used to compare CFF and P100 latency values between right eyes in normal subjects (at NDF = 0) with unaffected eyes in unilaterally affected patients and with all affected eyes (averaging for bilaterally affected patients). For unilateral patients, paired t-tests were used to compare CFF and P100 latency values between affected and unaffected eyes. Mean differences and 95% CIs were summarized.

CFF and P100 latency were plotted for normal eyes across NDF values ranging from 0 to 2.4, as well as for affected and unaffected eyes in patients. For normal eyes, a multivariable regression of the CFF and P100 latency dependent variables against the independent NDF variable was performed to construct a regression line relating CFF and P100 latency for normal eyes under varying NDF. This regression was used to construct 95% and 99% profile prediction bands (i.e., prediction bands for the CFF/latency relationship profiled across possible NDF values) to serve as a reference range for the CFF/latency relationship in normal eyes subject to varying NDF conditions. Affected and unaffected eyes (n = 22) in patients were compared against this model using a profile Z-test against the prediction distribution, using a Bonferroni corrected $\alpha = 0.05/22 = 0.002$ adjusted for n = 22 patient eyes.

Results

Part 1. Normal subjects

CFF, Ishihara color plate and logMAR acuity vs. log stimulus luminance: Across classes defined by subject and NDF filter, the intraclass correlation for CFF, logMAR, and Ishihara measurements on left and right eyes and repeat measurements on the same eye was high (ICC = 0.994, 0.982, and 0.986 for CFF, logMAR, and Ishihara respective). For this reason and for simplicity of presentation, measurements for normal subjects' right eyes averaged across repeats were used for all subsequent analysis.

Figure 1 shows the CFF, logMAR acuity and Ishihara color plate testing measurements by NDF for four normal subjects. At baseline (NDF = 0), the mean CFF was 34.5 Hz (95% CI [29.5, 39.5]). An ANCOVA analysis of CFF versus NDF indicated no evidence of different slope by subject ($p = 0.19$) with evidence of different per-subject intercepts ($p < 0.001$); the shared slope of the fitted model represented a 7.8 Hz decrease (95% CI [7.4, 8.3],

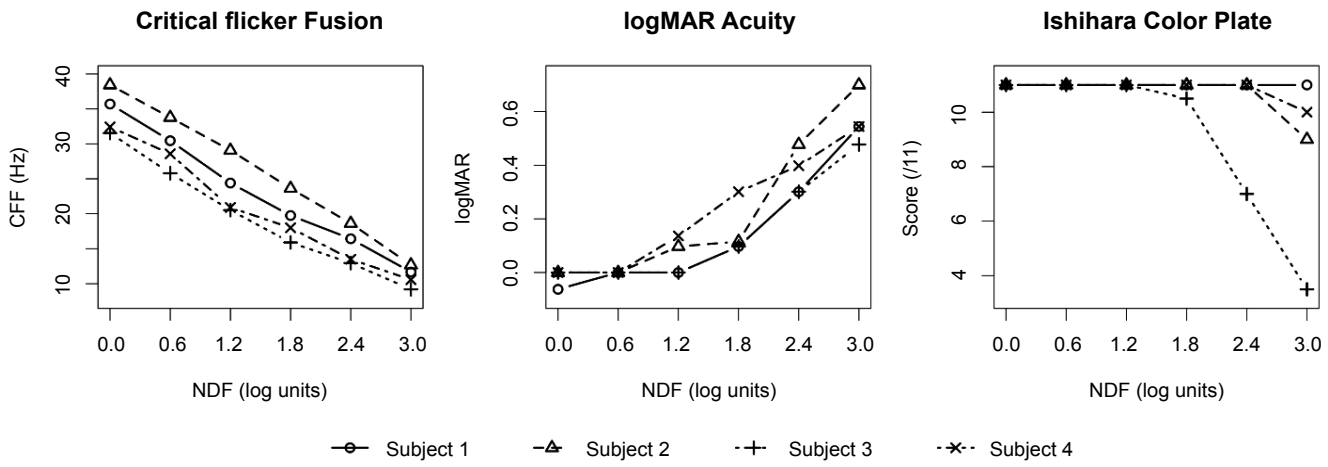

Figure 1: Measurements of CFF, logMAR acuity and Ishihara color plate by NDF observed for each of four subjects (average of both repeats for right eye). The CFF vs. log stimulus luminance function (left) demonstrated a linear correlation, showing a 7.8 Hz decrease (95% CI [7.4, 8.3], $p < 0.001$) per log unit increase in NDF. Color vision was least affected by changes in log stimulus luminance (right), and logMAR acuity increased minimally as NDF increased up to 1.2 log, above which acuity increased precipitously (middle).

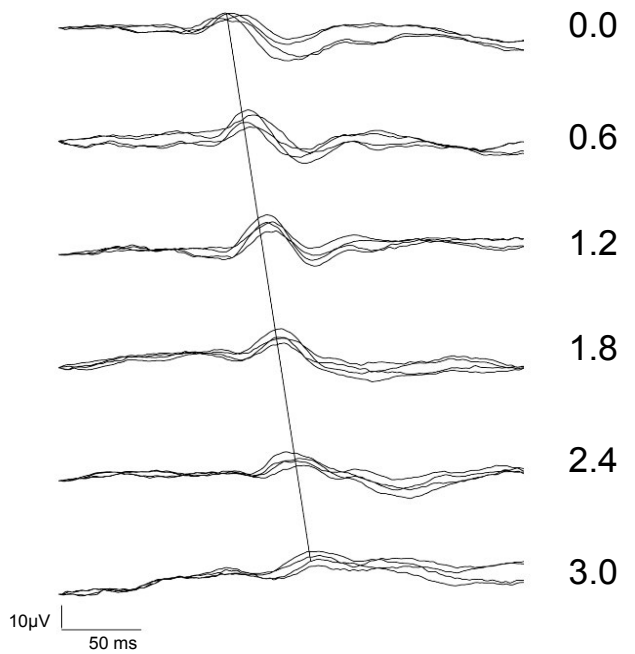

Figure 2: Examples of PRVEP recording to 30 min arc checkerboard stimulus in S1 (right eye). Four repeats of PRVEP were overlapped for log stimulus intensity produced by NDF (marked in numbers to the right of each recording). P100 response is demonstrated as distinct positive deflection. Gradual prolongation of the P100 latency with increasing NDF is marked by the line traversing the P100 responses.

$p < 0.001$) per log unit increase in NDF. The logMAR acuity increased with increasing NDF ($p < 0.001$), with minimal increase between NDF = 0.0 and 1.2 and rapid increase for NDF > 1.2. For the Ishihara color plate test, three of four subjects experienced no decrease in score except at NDF = 3.0. The fourth subject experiences a decrease for NDF > 1.2.

PRVEP P100 latency and amplitude vs. log stimulus luminance: Figure 2 shows PRVEP recordings for a particular subject, indicating the effect of decreasing stimulus luminance/increasing NDF on P100 latency and amplitude. Increasing NDF caused progressive delay of arrival of P100, i.e., prolongation of the P100 latency, as marked by the dashed line drawing through the peak of the P100 waves, as well as decrease in resulting P100 response amplitude. At the highest NDF of 3.0 log (dimmest stimulus), the P100 response is often difficult to discern. For this reason, PRVEP response at NDF = 3.0 was excluded from subsequent analysis.

For PRVEP P100 latency, the average baseline (NDF = 0) value was 129 ms (95% CI [124, 134]). Increasing NDF was associated with increasing P100 latency ($p < 0.001$) (Figure 3). An ANCOVA analysis indicates a mild trend of different slope by subject ($p = 0.04$) with an average fitted slope representing a 17.9 ms increase in latency (95% CI [9.7, 26.0]) for each log unit increase in NDF. Similarly, an ANCOVA analysis indicated a decrease in P100 amplitude with increasing NDF ($p < 0.001$), although individual subjects had markedly different trajectories.

Patients

The patient group included 14 affected and 8 unaffected eyes from 11 patients (3 affected bilaterally, and 8 affected unilaterally) who recovered from acute optic neuritis (Table 1). Patients were diagnosed with acute optic neuritis based on the history of acute visual loss, normal fundus examination at the presentation, and improvement of vision after steroid therapy. Nine of eleven patients had contrast enhancement of the affected optic nerve on orbital magnetic resonance imaging (MRI). The MRI is not available in one patient and did not reveal contrast enhancement of the affected optic nerve in another. Multiple sclerosis (MS) was diagnosed in four and idiopathic optic neuritis in six patients. The diagnosis of MS was made by neurologists shortly after the

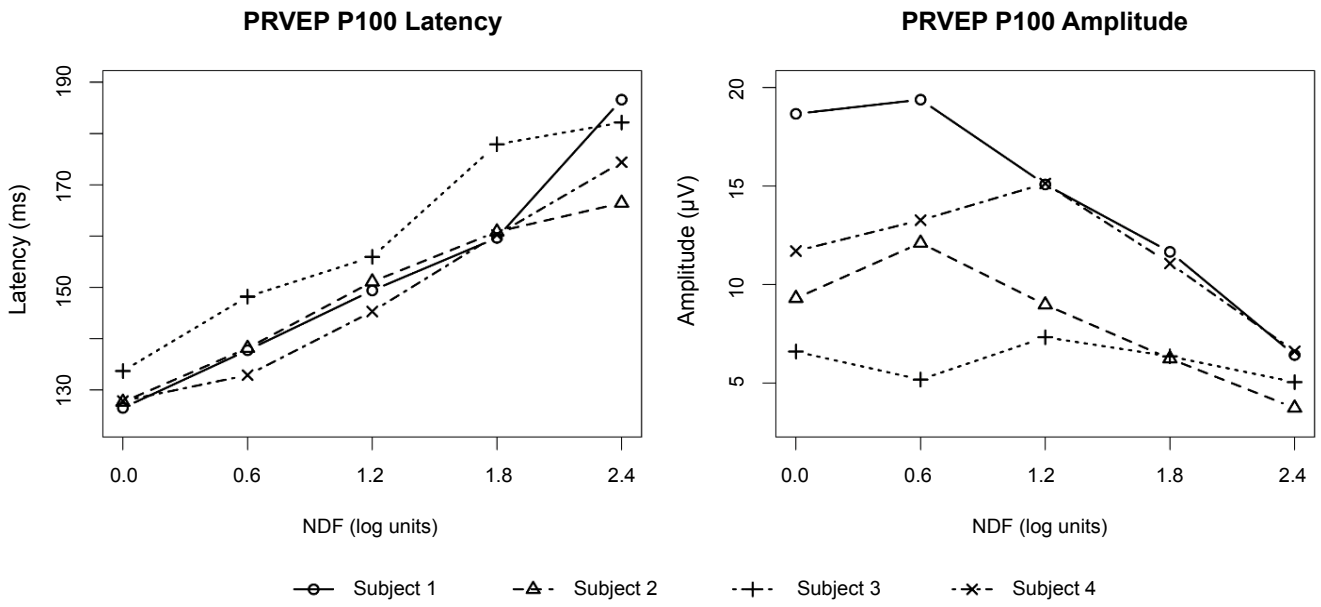

Figure 3: Plots of PRVEP P100 latency and amplitude as function of log stimulus luminance (NDF) for four subjects. The PRVEP were recorded in the right eye for each subject with two repeats. The averages of the repeats are shown here. Data for 3.0 log NDF are excluded. The PRVEP P100 latency vs. NDF function demonstrated a linear correlation, with increasing NDF associated with increasing P100 latency ($p < 0.001$) (left). Similarly, a decrease in P100 amplitude was associated with increasing NDF ($p < 0.001$), although individual subjects had markedly different trajectories (right).

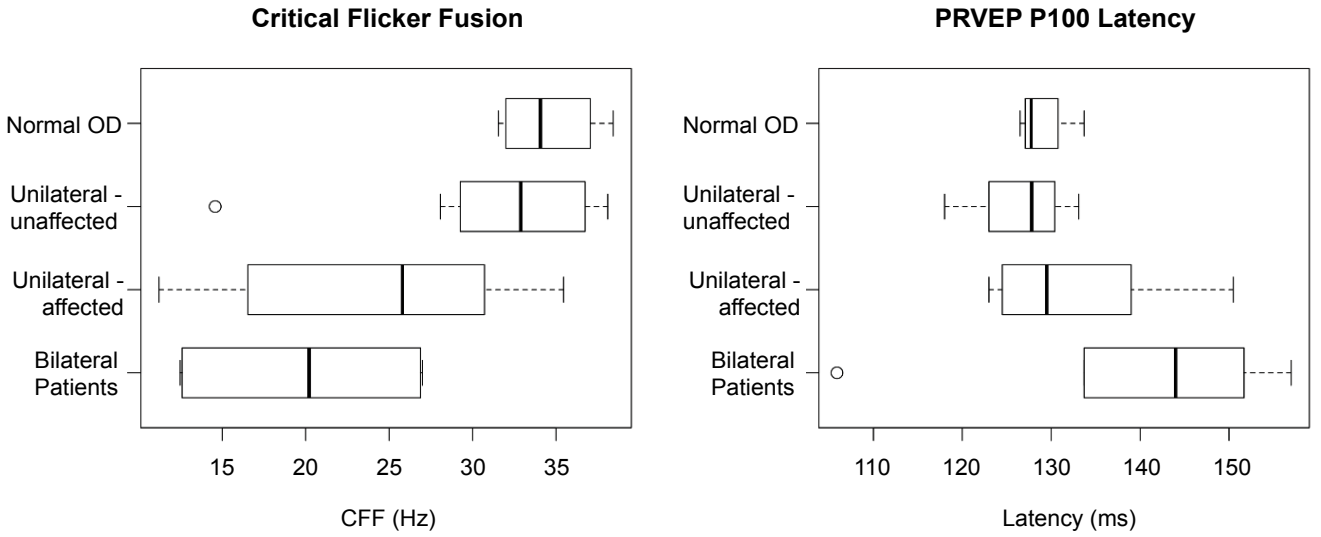

Figure 4: Box-and-Whisker plot of CFF (left) and P100 latency (right) in normal subjects, unaffected eyes of unilaterally affected patients, and affected eyes in unilaterally and bilaterally affected patients, all assessed at NDF = 0. The median value, 1st and 3rd quartiles of the CFF and P100 latency are shown in box and the ranges are shown in Whisker plot. The extreme values are shown in open circles. There was no significant difference in CFF ($p = 0.33$) or PRVEP P100 latency ($p = 0.38$) between eyes of healthy subjects and *unaffected* eyes of (unilaterally affected) patients. Patients' affected eyes had significantly lower CFF than healthy eyes ($p = 0.002$), but there was no observed P100 latency difference ($p = 0.17$).

onset of acute optic neuritis and none of the patients was diagnosed in later follow-up. Testing to rule out other systemic inflammatory and infectious etiology that may cause optic neuritis, such as neuromyelitis optica (NMO) antibody, antinuclear antibody (ANA), rheumatoid factor (RF), angiotensin converting enzyme (ACE), rapid plasma reagin (RPR), Lyme disease antibodies, as well as cerebrospinal fluid analysis, were pursued at the discretion of neurologists based on clinical suspicions. NMO antibody was tested in 6 of 11 patients, all negative. One patient had a known diagnosis of follicular lymphoma but with no cancer cells were found in the spinal fluid analysis. All patients were treated with systemic steroids due to moderate to severe visual decline based on visual acuity, color vision, or visual field assessment. At the presentation of acute optic neuritis, the Snellen visual acuity ranged from 20/20 to light perception with median of 20/60. At the time of the study, the Snellen visual acuity ranged from 20/20 to 20/800 with median of 20/20. The mean interval between the initial presentation and the

time of the study is 34.2 months (3 to 204 months). The patients also underwent automated perimetry testings (Humphrey Field Analyzer using the SITA-standard 24-2 or 30-2 protocol [Humphrey visual field (HVF)], Carl Zeiss Meditec, Dublin, CA) at the time of presentation and within one year of the study as part of their clinical assessment. The mean deviation (MD) ranged from -33.86 to -9.71 dB (mean ± SD: -24.47 ± 8.21) at presentation and from -20.68 to -0.79 dB (mean ± SD: -7.60 ± 6.50) at the time of the study.

Figure 4 shows CFF (left) and PRVEP P100 latency (right) for normal right eyes for the four healthy subjects, unaffected eyes from the unilaterally affected patients, and affected eyes from the unilaterally and bilaterally affected patients, all assessed at NDF = 0. There was no significant difference in CFF ($p = 0.33$) or PRVEP P100 latency ($p = 0.38$) between eyes of healthy subjects and *unaffected* eyes of (unilaterally affected) patients. Patients' affected eyes had significantly lower CFF than healthy eyes ($p = 0.002$), but there was no observed P100 latency difference ($p = 0.17$). Within unilaterally affected patients, the affected eye had CFF an average 7.2 Hz lower (95% CI [0.1, 14.3]) than the unaffected eye ($p = 0.05$) but with no evidence of difference in P100 latency ($p = 0.14$).

Figure 5 shows a plot of CFF versus P100 latency for normal subjects (black squares) at varying NDF levels from 0 to 2.4, together with affected patient eyes (crosses for non-MS patients, triangles for MS patients) assessed at NDF = 0. A multivariable regression line (of both dependent variables against NDF) and associated 95% and 99% profile prediction bands calculated using data from normal subjects only (n = 20 eyes) show the expected relationship between CFF and P100 latency for normal eyes. Note that, in normal eyes, CFF is inversely correlated with P100 latency due to modulation by NDF, with the area of high CFF and low P100 latency corresponding to 0 NDF. In contrast, five of fourteen affected patient eyes exhibit a combination of low CFF with relatively low latency that falls outside the 99% profile prediction bands of normal eyes at varying NDF levels. These five affected patient eyes exhibit a pattern that is significantly different from that exhibited by normal eyes ($p < 0.001$ for each of the five eyes, tested against a Bonferroni $\alpha = 0.05/22 = 0.002$ adjusted for n = 22 patient eyes including both affected and unaffected

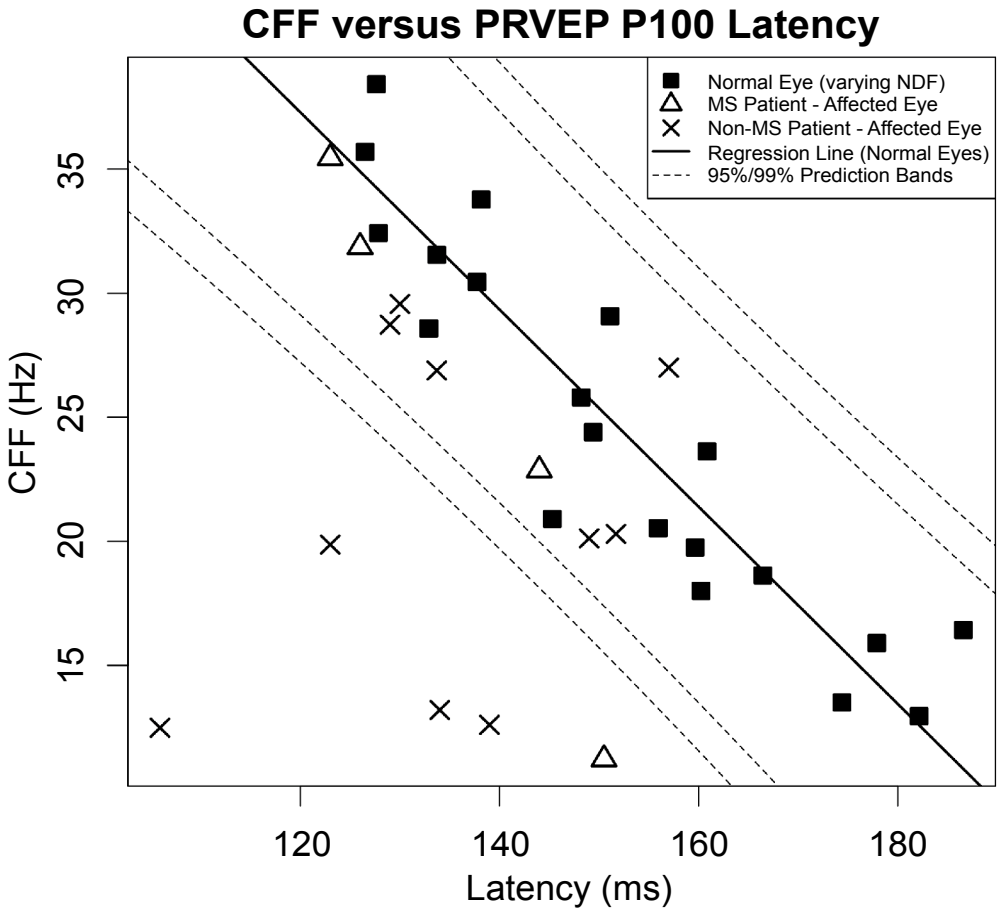

Figure 5: Distribution of CFF vs. PRVEP P100 latency in normal subjects and affected patient eyes. For normal subjects, the CFF and PRVEP P100 latency for the right eye (average of two repeats) are plotted for all NDF. A regression line and 95% and 99% prediction bands are shown, based on a multivariable regression of both dependent variables against NDF using data from normal subjects only. For patients, CFF and latency for affected eyes (average of two repeats) are shown using different symbols for MS and non-MS patients. Five of the fourteen affected patient eyes exhibit a pattern that is significantly different ($p < 0.001$) than the prediction band fit to normal eyes.

eyes to be maximally conservative).

Discussion

In this study, we measured CFF in normal subjects and patients who recovered from acute optic neuritis, and compared CFF with PRVEP to explore the relation between the two measurements. To our knowledge, this is the first study to directly compare CFF and PRVEP in such a clinical setting. The study revealed several findings:

First, both CFF and PRVEP P100 latency are linearly correlated with log stimulus luminance in normal subjects (Figure 1, left and Figure 3, left). In contrast, logMAR acuity and Ishihara color test are less affected by reduction of log stimulus luminance, evidenced by the findings that the NDF of less than 1.2 log had minimal influence on logMAR acuity, and Ishihara color function only declined at high NDF level (Figure 1, middle and right), suggesting its greatest resistance to reduction in stimulus luminance. CFF uses high intensity white light stimuli oscillating at a high temporal frequency which recruits exclusively cone response and foveal projection to the occipital cortex [24]. Similarly, the stimulus used for PRVEP in this study likely also activates cone response given high stimulus intensity and a high luminance background which suppresses rod contribution to the VEP response. Studies have shown that reduced retinal illumination causes delay in the cone ERG response. It is therefore possible that the linear correlation of CFF and PRVEP P100 latency with stimulus luminance is a result of a common dependence on the cone response in the retina [25,26]. In this study, we found a significant correlation between both the latency and amplitude of the PRVEP P100 response with log stimulus luminance, although the response vs. stimulus intensity function appears more homogeneous for P100 latency than amplitude. The finding supports the results from other studies that PRVEP P100 latency is a more sensitive measure than amplitude for optic nerve dysfunction in optic neuritis [27,28].

Second, CFF appears to linearly correlate with PRVEP P100 latency in normal subjects exposed to varied stimulus luminance (Figure 5). The CFF is a psychophysiological measurement of temporal property of perception at which a flickering spot of light appears steady, whereas PRVEP is an electrophysiological measurement of the latency of a cortical electrical field. As mentioned before, the possible mechanism for the correlation between these two fundamentally different measurements likely relies on the shared anatomical substrate for CFF and PRVEP pathway, the cones. However, the response-stimulus intensity curve for CFF and PRVEP P100 latency should also receive contribution from the visual pathway beyond the level of cones, otherwise one would expect similar slope between the CFF, P100 latency and the cone response-stimulus intensity curve. The exact mechanism underlying the stimulus-intensity function for CFF requires further investigation. Nevertheless, the strong linear correlation between CFF and log stimulus luminance as well as CFF and PRVEP P100 latency supports the role of CFF, as a supplement for VEP, in the assessment of optic nerve function.

Furthermore, when CFF and VEP are recorded with zero NDF, i.e., no diminish in stimulus luminance, the CFF vs. PRVEP P100 latency distribution in at least some affected eyes of patients appears to follow the linear CFF-PRVEP P100 latency curve observed in normal subjects, whereas others deviate from that of normal subjects (Figure 5). The inhomogeneity of the CFF vs. PRVEP P100 latency distribution among the study patients could potentially be due to varying pathophysiologic process underlying their visual loss (e.g., demyelinating vs. axonal injury), even though they seemed to follow a similar clinical course. Further research is needed to show how CFF vs. P100 latency changes in different types of optic neuropathy to elucidate such a speculation. One would further speculate that an optic nerve that recovered from previous optic neuritis may have more impaired ability to differentiate temporal than spatial property of the light stimulation embedded in the CFF and VEP stimulus, given that the majority of the affected eyes of patients demonstrated relatively good Snellen acuity and visual field function, and yet significantly decreased CFF and prolonged PRVEP P100 latency at the time of the study (Table 1).

Lastly, CFF appears to be more sensitive in identifying previous optic nerve injury in this group of patients who recovered from acute optic neuritis. The CFF is significant lower in the affected eyes than the unaffected eyes of patients and normal subjects (Figure 4, left), even though the visual acuity recovered to near normal in most patients. It is somewhat unexpected that the PRVEP P100 latency was not significantly different in the affected eyes of patients from that in the unaffected eyes of patients or normal subjects (Figure 4, right), since VEP is generally regarded as a sensitive neurophysiologic testing for optic nerve function [29]. These findings suggest that CFF may add to low-contrast visual acuity testing as a valuable tool to measure persistent optic nerve dysfunction after recovery of acute optic neuritis [30]. Compared to PRVEP, CFF is faster to administer, less demanding on testing environment and technical support, and more cost-effective.

One must be aware that, unlike the PRVEP, CFF is a subjective test and could thus be influenced by subject's attention and cognition. However, CFF change contributed by age, fatigue, sleep deprivation, drug use (antidepressants or sedatives), and cognition (Alzheimer's, Parkinson's or hepatic encephalopathy) [31-37] appears small and is usually on a scale of several Hz [31,32,35,38-48], compared to a much greater change of CFF observed in diseases of the optic nerve [49,50] and to the large drop of CFF (7.8 Hz) per log unit decrement

in stimulus intensity demonstrated in this study. Furthermore, one would expect that CFF change from attention and cognition should be more symmetrical between the two eyes; the attention and cognitive factor should thus have little impact on CFF especially when unilateral optic nerve dysfunction is concerned.

We acknowledge several limitations of the study. (1) In this retrospective study, the patients underwent a varying collection of clinical testing for systemic inflammatory and infectious etiologies contributing to optic neuritis, resulting in a heterogeneous group contained in "idiopathic optic neuropathy". However, the differentiation between MS and "idiopathic" optic neuritis is felt to be fairly distinct as the diagnosis of MS was established by MS neurologists using a standard criterion, (2) The normal control group only included four subjects. However, the visual function testing (visual acuity, color vision, CFF, and VEP) among the four normal subjects demonstrated a strong consistency (Figure 1, Figure 3 and Figure 4), and (3) the longitudinal measurements of CFF among patients during their recovery of visual function are not available. Such information will help assess the value of CFF in monitoring optic nerve function and should be evaluated in future study.

Conclusion

Both CFF and PRVEP P100 latency are linearly correlated with log luminance. CFF is significantly decreased in the affected eyes of the patients who recovered from acute optic neuritis. CFF may complement the existing technology for the evaluation of optic nerve dysfunction. The clinical utility of CFF in assessing optic nerve function will be explored in future studies comparing the sensitivity of CFF and PRVEP P100 in patients with different types of optic nerve disease.

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Conflict of Interest Statement

No interest to disclose.

Ethical Statement

The procedures conformed to the tenets of the Declaration of Helsinki.

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