Abnormal perception of pattern-induced flicker colors in subjects with glaucoma

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Pattern-induced flicker colors (PIFCs) are subjective colors that can be elicited with rotation of an achromatic stimulus such as the Benham disk. The perceptive mechanisms underlying PIFCs are not well-understood, but are thought to be generated primarily by retinal cell types which may be dysfunctional in glaucoma. Using a custom computer-based system, we tested PIFC perception across several Benham disk parameters, including the rates of acceleration and deceleration, rotational direction, and image contrast in both control and glaucoma subjects. We defined the Benham perception limit (BPL) during acceleration as the rotational speed at which PIFCs were first detected (Benham perception limit for acceleration) and the BPL during deceleration as the rotational speed at which PIFCs were extinguished (Benham perception limit for deceleration). In general, we found that glaucoma subjects perceived PIFCs less frequently than control subjects. For all subjects, we found that slower rates of acceleration and deceleration resulted in a lower Benham perception limit for acceleration and a higher Benham perception limit for deceleration, suggesting that PIFCs were both more easily detected and extinguished. Finally, subjects with glaucoma required increased rotational speeds during acceleration to detect PIFCs under certain conditions. Further study is needed to determine if these findings can be used to enhance clinical detection strategies.

Introduction

Glaucoma is a chronic and progressive disease of the optic nerve and retinal ganglion cells (RGCs), and a major cause of visual impairment and irreversible blindness (Congdon et al., 2004; Quigley & Broman, 2006). Multiple studies have shown that perhaps 50% of individuals with glaucoma have not yet been diagnosed (Dielemans et al., 1994; Leske, Connell, Schachat, & Hyman, 1994; Mitchell, Smith, Attebo, & Healey, 1996; Sommer et al., 1991; Varma et al., 2004). These difficulties in diagnosis occur in part because significant optic nerve loss and RGC loss may be present before detectable functional phenotypes (Kerrigan-Baumrind, Quigley, Pease, Kerrigan, & Mitchell, 2000; Quigley & Green, 1979). Intraocular pressure (IOP) remains the most important risk factor for glaucoma presence and progression and reduction of the IOP is the mainstay of all accepted treatments (Kass et al., 2002; Leske et al., 2003).

Animal models of experimental glaucoma provide evidence that RGC subtypes respond differently to elevated IOP and show a range of sensitivities and responses (Della Santina, Inman, Lupien, Horner, & Wong, 2013; El-Danaf & Huberman, 2015; Feng et al., 2013; Ou, Jo, Ullian, Wong, & Della Santina, 2016; Risner, Pasini, Cooper, Lambert, & Calkins, 2018; Sabharwal et al., 2017; Tao, Sabharwal, Seilheimer, Wu, & Frankfort, 2019). Similar experiments also show that some non-RGC cell types, especially amacrine cells, are also sensitive to IOP elevations (Akopian, Kumar, Ramakrishnan, Viswanathan, & Bloomfield, 2019; Frankfort et al., 2013; Pang, Frankfort, Gross, & Wu, 2015). Together, these results suggest a complex interplay among RGCs and interneurons, such as amacrine cells, in glaucoma. However, the functional assessment of neither amacrine cells nor their interactions with specific types of RGCs are a standard part of glaucoma care.

Pattern-induced flicker colors (PIFCs) are subjective colors that can be elicited when an achromatic
stimulus rotates. PIFCs are classically induced with the Benham disk stimulus, which consists of alternating achromatic arcs (von Campenhausen & Schramme, 1995). Although the perceptive mechanisms underlying PIFCs are unclear, they are thought to be generated primarily due to retinal, rather than cortical, processes and may involve the RGC blue–yellow opponent system, amacrine cells, and lateral inhibition systems (Adamczak, 1981; Festinger, Allyn, & White, 1971; Hess, 1952; Schramme, 1992; von Campenhausen, Hofstetter, Schramme, & Tritsch, 1992). Interestingly, the blue–yellow opponent system has also been implicated in human disease, and its dysfunction may be an early indicator of glaucoma (Johnson, Adams, Casson, & Brandt, 1993; Sample & Weinreb, 1990).

In this article, we probed PIFC perception with the Benham disk in both normal subjects and subjects with glaucoma and visual field deficits. We hypothesized that subjects with glaucoma would display abnormalities in PIFC detection, especially as related to the rotational speed at which PIFCs were perceived. To measure this, we defined a new term, the Benham perception limit (BPL), as the rotational speed at which PIFCs are initially detected during acceleration (Benham perception limit for acceleration [BPLa]) and the rotational speed at which PIFCs are initially extinguished during deceleration (Benham perception limit for deceleration [BPLd]), and recorded it for normal subjects and subjects with glaucoma. We found that subjects with glaucoma perceived PIFCs from the Benham disk less often, and, under some conditions, at different rotational speeds than normal subjects.

Methods

Subjects

All protocols were approved in advance, were reviewed annually by the Internal Review Board at Baylor College of Medicine, and are consistent with the Declaration of Helsinki. Glaucoma subjects were recruited from the faculty group practice at Baylor College of Medicine. Glaucoma subjects all had documented visual field abnormalities in both eyes on Humphrey 24-2 Visual Field testing (corresponding with moderate or severe stage glaucoma based on the International Classification of Diseases, 10th edition, classification) and visual acuity of 20/40 or better. IOP and lens status were extracted from the charts of glaucoma subjects. Control subjects were recruited by word of mouth and had visual acuity of 20/40 or better and no history of ocular disease. No additional clinical information was collected for control subjects. Glaucoma and control subjects with a known history of abnormal color vision, seizures, or neurological disorders were excluded.

Color vision was tested for all subjects using the Farnsworth D-15 test and subjects with abnormal color vision were excluded. For all subjects, both eyes were enrolled and tested. For each control subject, one eye at random was chosen for analysis. For each glaucoma subject, since the two eyes could not be considered to be independent, they were assigned according to Mean Deviation into two groups: glaucoma better and glaucoma worse. These groups were then compared independently with control subjects. All subject testing was performed as a contracted service by the Clinical Testing Division of the Baylor College of Medicine Department of Ophthalmology such that no members of the study team had any interaction with subjects during testing.

Software

The rotating Benham disk was presented through a password protected, encrypted, custom, web-based application running through the Salesforce platform. All subject data were automatically downloaded as an Excel workbook after completion of testing. No identifying data were entered or stored in the software application at any time.

Testing

Subjects were tested at ambient lighting conditions (approximately 300 lumens/m² at the position of the subject’s head) without adaptation. Subjects were seated in a cushioned chair and positioned 60 cm away from a laptop positioned on a 10-cm stand. The Benham disk image subtended 10° of arc and was presented centrally. The laptop monitor had a screen resolution of 1920 × 1080 and a refresh rate of 60 Hz. The computer was outfitted with an NVIDIA Quadro M500M video card and an Intel HD Graphics 520 adapter and was running in 32-bit true color mode. The luminance of the computer screen was measured with a Spectrophotometer (ThorLabs) and found to be approximately 125 cd/m² at the center of the Benham disk before the onset of rotation and approximately 50 cd/m² for the background adjacent to the Benham disk.

The testing procedure for this pilot study consisted of multiple presentations of a rotating Benham disk to each eye independently. All presentations began at a rotational speed of 30 rpm and accelerated gradually to 540 rpm. Once the maximum rotational speed was reached, it decelerated gradually back down to 30 rpm. The acceleration and deceleration phases of the individual presentation occurred according to either
Figure 1. Schematic of the Benham disk presentation and determination of the BPL. An achromatic Benham disk (right side, below the dotted line) was presented at a rotation speed of 30 revolutions per minute (rpm) and accelerated at a steady rate according to either a fast (26 seconds to peak rotation speed) or slow (39 seconds to peak rotation speed) paradigm. Upon reaching the maximum rotation speed (540 rpm), the Benham disk was decelerated at a steady rate according to the same paradigm. The speed at which PIFCs (right side, above the dotted line) were detected and extinguished is indicated by the dotted line. The speed at which PIFCs are detected is called the BPLa and the speed at which PIFCs are extinguished is called the BPLd.

a “slow” or fast paradigm lasting 39 or 26 seconds, respectively (Figure 1). During a presentation, the subject noted the moment when perception of PIFCs began during the acceleration phase by pressing the spacebar key and noted the moment when perception of PIFCs ended during the deceleration phase by again pressing the spacebar key. The rotational speed at the time the spacebar key was pressed was recorded as the BPL, defining the BPLa and BPLd. Thus, a higher number indicates that the Benham disk was rotating at a faster speed at the moment of PIFC perception (for BPLa) or loss of PIFC perception (for BPLd). The Benham disk rotated in either the clockwise or counterclockwise direction, and was presented at either 100% or 25% contrast as calculated according to the Michelson contrast. In all, the procedure consisted of a total of eight presentations, such that each potential combination of parameters was tested once. This series of eight presentations was considered to be one trial. The order of the eight presentations was randomized by the software at the start of each trial. Each eye was tested monocularly and independently, in sets of two trials consecutively, with the other eye covered. Trials were repeated a total of four times per eye (Figure 2).

Results

Twenty-eight subjects of both sexes were enrolled in the study (13 control and 15 glaucoma). Two control subjects and one glaucoma subject were unable to detect colors with Farnsworth D-15 screening and did not advance to BPL testing. Thus, the control group contained 11 subjects and the glaucoma group contained 14 subjects. The control group was younger than the glaucoma group, \( t \) test; \( p = 0.002 \). Both control and glaucoma groups contained approximately equal numbers of both males and females. Eyes from each glaucoma subject were subclassified into glaucoma better or glaucoma worse groups according to Mean Deviation. All groups had excellent visual acuity and glaucoma eyes had well controlled IOP (Table 1).

First, we assessed the presence of any BPL, an indication that PIFCs were perceived. This was done only during the acceleration phase (BPLa) because the loss of a BPL during deceleration could only occur if a BPLa was already present. Across four trials, each eye had 32 total opportunities to record a BPLa. In control eyes, a BPLa was recorded in nearly all cases, with a response rate of 98.9% (Table 2). In glaucoma better
Figure 2. Schematic of testing approach. The Benham disk was presented at either 100% or 25% contrast and rotated according to either a fast or slow acceleration/deceleration program in either the clockwise (CW) or counterclockwise (CCW) direction. These eight distinct Benham disk testing strategies were presented in a random order to create a trial. Each eye underwent four trials.

Control

| Subjects | 13 |
|---------|----|
| Male    | 7 (53.85) |
| Female  | 6 (46.15) |
| Age (years) | 62.36 ± 5.99 |
| Screen fail | 2 |

Glaucoma

| Subjects | 15 |
|---------|----|
| Male    | 4 (26.67) |
| Female  | 11 (73.33) |
| Age (years) | 72.64 ± 8.49 |
| Screen fail | 1 |

Table 1. Demographics and general clinical data. Subjects who failed screening procedures are not included in the calculations of visual acuity or age. Values are number (%) or mean ± standard deviation.

| Group           | Number of trials per eye | Number of responses | Frequency of responses |
|-----------------|--------------------------|---------------------|------------------------|
| Control         | 32                       | 31.55 ± 0.50        | 98.9 ± 0.02%           |
| Glaucoma better | 32                       | 26.85 ± 7.70        | 83.9 ± 24.1%**         |
| Glaucoma worse  | 32                       | 25.27 ± 7.21        | 79.0 ± 22.5%**         |

Table 2. Likelihood of any response to a rotating Benham disk during acceleration. The number and frequency of any response according to group. ** Fisher’s exact test comparing each glaucoma group with control, p < 0.01.
eyes, a BPLa was recorded less often, with a response rate of 83.9%, \( p < 0.01 \). In glaucoma worse eyes, a BPLa was recorded even less often, with a response rate of 79.0%, \( p < 0.01 \).

The mean ± SD, minimum, and maximum values of the BPL for all subject groups and conditions are presented in Tables 3 and 4. The BPLa and BPLd were first compared within each subject group, across each parameter (rotational direction, disk contrast, rate of acceleration and deceleration) (Table 5). Although some individual parameters (two values for disk contrast and two values for rotational direction among controls only) achieved statistical significance, the most consistent result in all groups came when comparing the impact of the rate of acceleration/deceleration (slow vs. fast). In general, for all groups, slower rates of acceleration and deceleration resulted in a lower BPLa and a higher BPLd. This finding suggests that PIFCs were both detected and extinguished more easily at slower rates of acceleration. There were no differences in BPL values in glaucoma subjects according to Mean Deviation; Pearson’s correlation, \( p > 0.05 \) for all values for both glaucoma better and glaucoma worse. Similarly, there were no differences in BPL values in glaucoma subjects according to lens status (phakic vs. pseudophakic); Mann–Whitney \( U \), \( p > 0.05 \) for all values for both glaucoma better and glaucoma worse.

Next, control eyes were compared independently to each group of glaucoma eyes to determine if glaucoma status impacted the BPL (Mann–Whitney \( U \) test; Tables 6 and 7). Interestingly, the BPLa and BPLd were consistently higher in both glaucoma groups compared with controls when the Benham disk was presented at 100% contrast (Tables 3 and 4). These differences between control and glaucoma worse were strongly significant for BPLa with either fast or slow acceleration in the clockwise direction at 100% contrast (Table 6). A similar difference was found between control and glaucoma better in the clockwise direction at 100% contrast but only with slow acceleration (Table 6). These results suggest that glaucoma eyes required higher rotational speeds to detect PIFCs under certain conditions.

Table 3. BPL for clockwise rotation of the Benham disk in control and glaucoma groups. Factors that were varied include rate of acceleration and deceleration (slow or fast) and disk contrast (100% or 25%). Values are mean ± standard deviation (min, max).

|          | Control          | Glaucoma better | Glaucoma worse |
|----------|------------------|-----------------|----------------|
| Slow     |                  |                 |                |
| 100%     | BPLa 172.17 ± 35.32 (125.81, 223.79) | 253.47 ± 74.93 (126.86, 369.74) | 237.86 ± 81.78 (122.18, 466.22) |
|          | BPLd 147.66 ± 44.29 (85.41, 214.95) | 182.25 ± 95.16 (59.31, 391.92) | 198.56 ± 102.31 (62.82, 422.93) |
| 25%      | BPLa 201.76 ± 67.26 (139.87, 365.78) | 249.60 ± 85.69 (143.41, 429.91) | 258.70 ± 100.73 (95.32, 426.20) |
|          | BPLd 150.39 ± 47.54 (90.69, 257.75) | 181.35 ± 75.71 (79.21, 361.16) | 190.22 ± 75.65 (51.57, 339.01) |
| Fast     |                  |                 |                |
| 100%     | BPLa 193.42 ± 48.62 (132.37, 284.81) | 257.63 ± 83.22 (128.28, 387.52) | 255.17 ± 67.20 (121.85, 377.95) |
|          | BPLd 110.34 ± 31.34 (57.31, 154.32) | 153.38 ± 77.63 (60.81, 336.45) | 144.74 ± 94.46 (37.24, 382.72) |
| 25%      | BPLa 234.97 ± 53.49 (162.08, 321.30) | 273.24 ± 96.03 (116.07, 414.90) | 272.79 ± 77.90 (176.43, 417.74) |
|          | BPLd 94.64 ± 34.32 (51.59, 159.04) | 152.81 ± 68.75 (63.64, 281.89) | 144.39 ± 105.64 (45.10, 391.83) |

Table 4. BPL for counterclockwise rotation of the Benham disk in control and glaucoma groups. Factors that were varied include rate of acceleration and deceleration (slow or fast) and disk contrast (100% or 25%). Values are mean ± standard deviation (min, max).

|          | Control          | Glaucoma better | Glaucoma worse |
|----------|------------------|-----------------|----------------|
| Slow     |                  |                 |                |
| 100%     | BPLa 207.87 ± 39.64 (168.87, 297.51) | 224.49 ± 47.34 (114.20, 282.41) | 227.89 ± 53.38 (110.60, 300.22) |
|          | BPLd 133.51 ± 34.33 (73.18, 188.84) | 155.69 ± 58.88 (58.69, 314.78) | 173.54 ± 70.30 (71.50, 338.76) |
| 25%      | BPLa 215.07 ± 48.87 (168.51, 331.49) | 229.56 ± 35.02 (194.79, 313.73) | 252.38 ± 78.68 (116.04, 408.44) |
|          | BPLd 142.08 ± 49.85 (73.32, 255.54) | 206.25 ± 95.62 (77.96, 355.28) | 171.99 ± 103.56 (68.69, 426.62) |
| Fast     |                  |                 |                |
| 100%     | BPLa 237.64 ± 43.67 (194.70, 344.39) | 254.10 ± 66.68 (129.06, 339.43) | 276.95 ± 67.44 (173.62, 396.45) |
|          | BPLd 127.60 ± 26.89 (87.75, 174.30) | 129.41 ± 47.13 (58.97, 244.30) | 136.80 ± 53.69 (50.11, 265.59) |
| 25%      | BPLa 265.58 ± 56.70 (198.60, 394.75) | 243.32 ± 70.20 (160.34, 396.34) | 260.56 ± 69.20 (126.65, 409.79) |
|          | BPLd 116.69 ± 33.89 (64.08, 195.33) | 134.09 ± 76.54 (62.19, 334.63) | 147.60 ± 117.60 (52.79, 477.44) |
In this study, we used the Benham disk to elicit PIFCs in both control subjects and subjects with glaucoma.

**Discussion**

We defined and recorded the BPL during acceleration of the Benham disk as the rotational speed at which PIFCs were first detected (BPLa) and the BPL during deceleration of the Benham disk as the rotational speed at which PIFCs were extinguished (BPLd). We found that control eyes perceived PIFCs more frequently than eyes with glaucoma. We also found that slower rates of acceleration and deceleration (slow vs. fast), in general, resulted in a lower BPLa and a higher BPLd, suggesting that PIFCs were both more easily detected and extinguished. We found only occasional effects of image contrast or rotational direction on PIFC detection. Finally, we found that eyes with glaucoma required increased rotational speeds during acceleration to detect PIFCs under certain conditions.

The reason why a lower BPLa and higher BPLd is seen with slower rates of acceleration and deceleration across all groups is unclear. However, because the temporal response properties of RGCs are diverse (Chichilnisky & Kalmar, 2002; Cowan, Sabharwal, & Wu, 2016; Pandarinath, Bomash, et al., 2010; Pandarinath, Victor, & Nirenberg, 2010; Sabharwal, Seilheimer, Cowan, & Wu, 2016) and the detection of PIFCs has already been linked to temporal systems in the retina (Becker & Elliott, 2006; Grunfeld & Spitzer, 1995; von Campenhausen, 1973), one possibility is that slower rates of acceleration optimize PIFC detection and extinction.

The Benham disk elicited PIFCs less often in subjects with glaucoma (Table 2). Furthermore, when PIFCs were detected during acceleration at 100% contrast and clockwise rotation, higher rotational speeds were often required (Tables 3, 4, and 6). What is the mechanism for this shift in rotational speed for PIFC detection in subjects with glaucoma? One possible explanation comes from rodent glaucoma models, in which an elevated IOP causes rapid effects on RGC temporal processing (Sabharwal et al., 2017; Tao et al., 2019; Tao, Sabharwal, Wu, & Frankfort, 2020), although...
these studies did not assess color perception. Rodent models also implicate amacrine cell abnormalities in IOP-induced RGC pathology (Akopian et al., 2019; Frankfort et al., 2013; Pang et al., 2015). In humans, amacrine cells are thought to underlie PIFC detection (Adamczak, 1981). Finally, PIFCs are thought to involve the blue–yellow opponent process (Schramme, 1992), which is also believed to be abnormal in glaucoma (Johnson et al., 1993; Sample & Weinreb, 1990). Thus, it is possible that the need for these faster rotational speeds is caused by a similar underlying biology impacting RGC–amacrine cell interactions, temporal tuning, and blue–yellow opponency. Additional studies are required to distinguish from among these possibilities.

Why are differences in PIFC detection in subjects with glaucoma only seen with clockwise rotation of the stimulus? Bias of directionality in rotational behavior and visuospatial function has been well-studied in humans as well as a variety of nonhuman animals. Most studies support a clockwise preference for rotational behavior and turning across a range of experimental and real-life situations (reviewed in Karim, Proulx, & Likova, 2016). Although this finding may suggest that preferential visual behavior is altered in subjects with glaucoma, additional research is needed to confirm this possibility.

This study contains several potential weaknesses. First, the study is a small pilot, which limits its ability to detect small effects. Second, control subjects were younger than subjects with glaucoma. This factor could suggest that the differences seen between control and glaucoma subjects are related to aging, rather than disease. However, if this is the case, then it occurred despite both equivalent visual acuities among the groups (Table 1), normal color vision, and no differences in BPL values based on lens status in glaucoma subjects. Third, we only tested the central 10° of vision, thereby ignoring potentially abnormal peripheral parts of the visual field in glaucoma subjects. Related to this factor, we did not use a gaze tracker, so it is possible that some subjects used slightly decentered areas of their central vision during testing. Fourth, we did not ask subjects about subjective color perception and therefore could not correlate measurements of the BPL to subjective findings.

There has been very limited study of PIFC detection in glaucoma (Tritsch & Pfeiffer, 1994) and neurological disease (Kaubrys, Bukina, Bingelyte, & Taluntis, 2016). Currently, the specificity of abnormal PIFC detection to glaucoma is unclear, and further studies of additional subjects with glaucoma and other ophthalmic diseases will be needed to make this determination. Although this study focused on incident glaucoma with visual field deficits, it is possible that glaucoma patients in the early (preperimetric) stage may also abnormally perceive PIFCs. If so, it may be possible to develop testing strategies to establish glaucoma risk based on abnormalities of PIFC perception, which can lead to the development of adjunctive clinical tests and potentially screening methods.

**Keywords:** glaucoma, pattern-induced flicker colors, PIFC, Benham disk

**Acknowledgments**

The authors thank Guofu Shen for assistance with the calculation of light intensity values.

Funded by a research award from the Clayton Foundation for Research (Houston, TX) to B.J.F. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the article.

Commercial relationships: none.

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