Title

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Journal

Journal of Vision, 20(2)

ISSN

1534-7362

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Publication Date

2020-02-27

DOI

10.1167/jov.20.2.12

Peer reviewed

Exploration of the functional consequences of fixational eye movements in the absence of a fovea

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A recent theory posits that ocular drifts of fixational eye movements serve to reformat the visual input of natural images, so that the power of the input image is equalized across a range of spatial frequencies. This "spectral whitening" effect is postulated to improve the processing of high-spatial-frequency information and requires normal fixational eye movements. Given that people with macular disease exhibit abnormal fixational eye movements, do they also exhibit spectral whitening? To answer this question, we computed the power spectral density of movies of natural images translated in space and time according to the fixational eye movements (thus simulating the retinal input) of a group of observers with long-standing bilateral macular disease. Just as for people with normal vision, the power of the retinal input at low spatial frequencies was lower than that based on the $1/f^2$ relationship, demonstrating spectral whitening. However, the amount of whitening was much less for observers with macular disease when compared with age-matched controls with normal vision. A mediation analysis showed that the eccentricity of the preferred retinal locus adopted by these observers and the characteristics of ocular drifts are important factors limiting the amount of whitening. Finally, we did not find a normal aging effect on spectral whitening. Although these findings alone cannot form a causal link between macular disease and spectral properties of eye movements, they suggest novel potential means of modifying the characteristics of fixational eye movements, which may in turn improve functional vision for people with macular disease.

Introduction

Human eyes are almost never stationary, even when we try to maintain our gaze on an object of interest. Microscopic eye movements, specifically ocular drifts and microsaccades, cause frequent changes in the retinal stimulation, which in turn elicit strong neural responses (Greschner, Bongard, Rujan, & Ammermüller, 2002; Kagan, Gur, & Snodderly, 2008; Leopold & Logothetis, 1998; Martinez-Conde, Macknik, & Hubel, 2000; Snodderly, Kagan, & Gur, 2001). Ocular drifts have been shown to improve performance in the discrimination of fine spatial details (Ağaoğlu, Sheehy, Tiruveedhula, Roorda, & Chung, 2018; Ratnam, Harmening, & Roorda, 2017; Rucci, Iovin, Poletti, & Santini, 2007), whereas microsaccades and small saccades have been implicated in counteracting visual fading and relocating gaze with minute precision during visual tasks that involve fine spatial structure (Ağaoğlu et al., 2018; Costela, McCamy, Macknik, Otero-Millan, & Martinez-Conde, 2013; Havermann, Cherici, Rucci, & Lappe, 2014; Martinez-Conde, Macknik, Troncoso, & Dyar, 2006; Mostofi, Boi, & Rucci, 2015).

It is well known that the power spectra of natural scene images fall linearly in logarithmic axes with a slope of approximately –2 (Burton & Moorhead, 1987; Field, 1987; Ruderman & Bialek, 1994; van der Schaaf & van Hateren, 1996). The higher power contained within the lower spatial frequency bands means that adjacent points in the natural scenes are more correlated in terms of luminance (and other types of correlations, as well) than the higher spatial frequency bands. According to information theory (Shannon, 1948) and the efficient coding hypothesis (Barlow, 1961), the transmission of information representing natural scenes is most efficient when there is no redundancy in the transmitted signals. In normal vision, ocular drifts have been shown to reduce the redundancies in natural scenes by "whitening" or equalizing the spectral content of the retinal images within the spatial frequency bands to which retinal ganglion cells are most sensitive (Casile & Rucci, 2006; Kuang, Poletti, Victor, & Rucci, 2012), resulting in a slope of the power spectra close to zero. This flattening of the spatial power spectra (whitening) occurs while the power along the temporal frequency axis gets spread out from 0 Hz to nonzero frequencies, to which retinal ganglion cells are again more sensitive. The amount of power spilled over to nonzero temporal frequencies depends on the exact characteristics of

Citation: Ağaoğlu, M. N. & Chung, S. T. L. (2020). Exploration of the functional consequences of fixational eye movements in the absence of a fovea. *Journal of Vision*, *20*(2):12, 1–15, https://doi.org/10.1167/jov.20.2.12.

https://doi.org/10.1167/jov.20.2.12 Received July 4, 2019; published February 27, 2020 ISSN 1534-7362

fixational eye movements, and more power in nonzero temporal frequencies might be helpful for better visual performance.

Characteristics of fixational eye movements are affected by certain cortical and retinal disorders. For example, people with macular disease who do not have a functioning fovea are known to exhibit much higher fixation instability when compared with people with a normal fovea (Crossland, Culham, & Rubin, 2004; Kumar & Chung, 2014; White & Bedell, 1990). The increased fixation instability is attributed to larger amplitudes of ocular drifts and microsaccades[1] (Kumar & Chung, 2014). Poor fixation stability has been suggested as a major factor limiting visual performance for people with macular disease (Amore et al., 2013; Crossland et al., 2004; Reinhard et al., 2007; Rubin & Feely, 2009; Seiple, Rosen, & Garcia, 2013). Additionally, our recent finding suggests that, although natural fixational eye movements are beneficial to vision, excessive amount of retinal image motion causes a degradation in visual performance, at least in normal vision (Ağaoğlu et al., 2018). Therefore, potentially, poor fixation stability, associated with the larger amplitude of ocular drifts and microsaccades, is a factor contributing to the poor vision of people with macular disease. On the other hand, in the absence of a functioning fovea, people with bilateral macular disease often adopt a peripheral retinal location for visual tasks. This location, commonly referred to as the "preferred retinal locus" (PRL), often does not correspond to the retinal location with the highest visual acuity (Bernard & Chung, 2018). Because of its location in the peripheral retina, the photoreceptor spacing is larger and there is a higher convergence of photoreceptors onto a ganglion cell at the PRL when compared with the normal fovea. Hence, the increased fixation instability and the larger amplitude of ocular drifts and microsaccades may be necessary in order to sweep the visual input over different sampling units to avoid visual fading, thus improving visual perception. To date, the functional consequences of fixational eye movements of people with macular disease, which exhibit many abnormal characteristics when compared with "normal" fixational eye movements, remain unclear. This question is important from both a clinical and a basic science point of view. If the abnormal characteristics of fixational eye movements of people with macular disease are detrimental to visual perception, then one way to improve visual perception for these individuals could be via oculomotor training with the goal of training the characteristics of their fixational eye movements to fall within normal limits. From a basic science point of view, and based on our understanding of the functional consequences of normal fixational eye movements on visual perception, it would be important to determine and understand the conditions under which fixational eye movements cease to become beneficial to vision.

In the present study, we sought to determine whether the functional consequences of (abnormal) fixational eye movements of people with macular disease were qualitatively similar to those of people with normal vision. Specifically, we sought to determine whether or not (and how) abnormal fixational eye movements affect the power spectra of the retinal stimulation for a group of observers with long-standing macular disease and relatively stable PRLs. We hypothesized that if ocular drifts are tuned for spectral equalization based on the spatial-frequency tuning of the retinal ganglion cells at or around the PRL, then spectral whitening should be limited to lower spatial frequencies with increasing PRL eccentricity. For comparison, we included a control group of older adults with normal vision. The average age of this group matched that of the group of people with macular disease. As an auxiliary question, we also examined whether or not there is a normal aging effect in the amount of spectral whitening by including a group of normally sighted young adults as observers and comparing the amount of whitening exhibited by the young versus older adults with a normal fovea.

Methods

Code

All scripts for eye movement processing, power spectral analyses, and reproducing figures can be freely downloaded at https://github.com/mnagaoglu/whitening. All natural scene images used were downloaded from http://natural-scenes.cps.utexas.edu/db.shtml (Geisler & Perry, 2011).

Observers

A total of 36 observers participated in this study. These included 15 in the macular disease group, 14 in the older adults group comprised of individuals with normal vision and with an average age matching that of the macular disease group, and 7 young adults with normal vision. A summary of the visual characteristics of these three groups of observers is given in Table 1. All observers gave written informed consent before the commencement of data collection. This research adhered to the tenets of the Declaration of Helsinki and was approved by the institutional review board.

Measurements of fixational eye movements

Fixational eye movements were elicited by presenting a 1° cross (for observers with acuity better than or

Observer ID	Diagnosis	Age (y)	Gender	Years since onset	Acuity (logMAR)		PRL Eccentricity (Tested eye)
					Right eye	Left eye	
A	AMD	86	F	11	**1.12**	Hand motion	12.07°
B	AMD	77	F	5	1.12	**1.08**	10.33°
C	AMD	85	M	11	**0.70**	0.74	4.08°
D	AMD	79	F	8	**0.74**	0.92	1.66°
E	AMD	89	F	15	**1.00**	1.02	3.39°
F	AMD	78	M	9	**0.62**	0.86	3.57°
G	AMD	84	M	8	**0.56**	0.70	4.68°
H	AMD	74	F	6	**0.54**	1.12	1.39°
I	AMD	82	F	9	**0.5**	0.52	2.70°
J	AMD	84	M	19	0.44	**0.50**	1.77°
K	AMD	73	F	7	0.66	**0.48**	1.33°
L	AMD	78	F	3	0.40	**0.32**	2.01°
M	Stargardt disease	57	M	40	1.1	**1.1**	12.73°
N	Stargardt disease	56	M	38	**1.02**	1.04	8.41°
O	Stargardt disease	48	M	26	1.00	**0.98**	5.36°
Older adults	Normal vision	62–77	7 M, 7 F	—	0.1 or better	0.1 or better	—
Young adults	Normal vision	22–24	4 M, 3 F	—	0.0 or better	0.0 or better	—

Table 1. Demographics and visual characteristics of participants. Acuity values in bold type denote the tested eye. For the older and young adult groups, only the group characteristics are given. LogMAR acuity of 0.0 is equivalent to Snellen acuity of 20/20. AMD = age-related macular degeneration; M = male; F = female; PRL = preferred retinal locus.

equal to 0.7 logMAR) or a 2° cross (for observers with acuity worse than 0.7 logMAR) in the primary gaze of observers by using a Rodenstock 101 scanning laser ophthalmoscope (Rodenstock GmbH, Munich, Germany). Observers were asked to maintain steady fixation at the center of the cross for trials of 30 seconds each. Observers with macular disease were constantly reminded to keep the cross visible at all times to ensure that it did not fall within the scotoma area. Testing was monocular, with the non-tested eye remaining open throughout testing. Retinal images were digitally captured at 30 Hz and recorded as videos for the entire duration of each trial.

Retinal video processing

We extracted eye movements from recorded retinal videos offline by means of a brute-force cross-correlation algorithm described in detail elsewhere (e.g., Kumar & Chung, 2014; Stevenson & Roorda, 2005). Here we describe several details specific to the present study. Retinal videos were first preprocessed to improve sampling rate (de-interlacing) and to reduce the effects of non-uniform contrast and brightness as well as high-frequency noise in each frame. Specifically, de-interlaced videos went through gamma correction, mean removal, and bandpass filtering. Each processed frame was then divided into eight horizontal strips with 15 scan lines per strip. Because each strip was scanned at a different time, cross-correlating each strip with a reference frame allowed us to obtain changes in eye position as a function of time. This process essentially yielded a sampling rate of 480 Hz. Each pixel in a frame covered a 9-arcmin^2 retinal area (3 × 3).

Eye movement analysis

Horizontal and vertical eye movements were low-pass filtered with a passband frequency of 120 Hz and a stopband frequency of 150 Hz. The traces were further filtered with a bank of second-order band-stop filters (notch filters) to remove frame artifacts (30-Hz noise and its harmonics). The filtered traces were used to detect microsaccades in two-dimensional (2D) velocity space with a modified version of the method proposed by Engbert & Kliegl (2003). A velocity threshold of six times the median-based standard deviation of the eye velocity was used to detect microsaccadic regions in the eye movement traces. An additional criterion was used to ensure that post-saccadic ringing (low-pass filtering) did not contaminate microsaccade detection: If the onset of a microsaccade was within 10 ms of the offset of another microsaccade, these two were combined. Because individuals with macular disease tend to have more microsaccadic intrusions (Kumar & Chung, 2014), the duration of fixations (with just ocular drifts) were shorter compared with

controls with normal vision. This difference effectively limits across-group comparisons of the spectral content of retinal input. To overcome this, after detecting microsaccades and removing regions where observers blinked, we simply stitched epochs of ocular drift back-to-back as if observers never blinked or made a microsaccade. In the Supplementary Material, we show that this stitching method did not affect the power spectra of eye movements. Note that a similar approach was taken to reveal "micro-vergence" eye movements that would be obscured by interspersed microsaccades and blinks (Ivanchenko, Schaeffel, & Hafed, 2019). Considering that ocular drifts have usually been modeled as Brownian motion or random walks in normal vision, the exact shape of the power spectra of drifts should not depend on the size of the temporal window chosen. Previous studies reported almost identical findings for 128-ms and 512-ms time windows (Kuang et al., 2012). Nevertheless, this practice is further justified by means of additional simulations (see Supplementary Material). Power spectra of eye movement traces (both drifts-only and drifts + microsaccades) were computed with a sliding temporal window of 2048 samples (over a duration of 4.267 seconds) with 50% overlap. We also assessed how close Brownian motion can approximate ocular drifts by comparing the goodness of fit (e.g., root mean square error) between the actual drift traces and the best-fitting Brownian process.

Power spectra of retinal input

To determine if ocular drifts and microsaccades modulate the spectral content of retinal images similarly in the three observer groups, we used a subset of 87 images from a natural scene database that consists of images of outdoor scenes collected with a Nikon D700 camera (Nikon Corp., Tokyo, Japan) (Geisler & Perry, 2011). The horizontal field of view of the camera was reported as approximately 40°. Each 4284 × 2844 16-bit red, green, and blue image was converted to grayscale with 8-bit representation. We created movies of what the retinal stimulation would be by translating each of the images according to the eye movements extracted from the retinal videos (for drifts-only, and drifts + microsaccades separately), and calculated the power spectral density (PSD) of these movies.

The PSDs of our movies were computed using a 512 pixel × 512 pixel spatial window (~4.8° × 4.8°) and a temporal window of 128 samples (267 ms), with 50% temporal overlap across subsequent temporal windows. PSDs were computed for each observer separately (averaged across the 87 movies) and then averaged across all observers of the same group. To facilitate visualization, three-dimensional spectra were further averaged across all spatial orientations. The resultant 2D maps represent PSD as a function of spatial and temporal frequencies and are presented in decibel (dB) units (i.e., $10 \log_{10}[\mathrm{PSD}_{2D}]$).

Results

Before we examine whether or not the power spectra of "retinal input" are affected by abnormal fixational eye movements that often accompany macular disease and whether or not there is a normal aging effect on spectral whitening in normal vision, we first compare the power spectra of fixational eye movements across our three groups of observers. Figure 1 shows samples of eye movement traces from three observers, one from each of the three groups. Consistent with previous findings (Kumar & Chung, 2014), the eye movement traces from the observer with macular disease (blue) show larger amplitudes of microsaccades and ocular drifts when compared with the eye movement traces of the older adult (red) or the young adult (black). Observers with macular disease also generally exhibited a higher rate of microsaccades than the other two groups of observers. The exaggerated eye movements exhibited by observers with macular disease lead to more power in the power spectrum of the eye movements.

Fixational eye movements have more power in macular disease

Figure 2 plots the power spectra of eye movements averaged across all observers in a given observer group when we analyzed drifts-only (Figure 2A) or drifts + microsaccades (Figure 2B). Not surprisingly, including microsaccades in the analyses leads to more power in the power spectrum; that is, the vertical position of the power spectrum is higher in Figure 2B than in Figure 2A for the respective observer group. Regardless of whether or not microsaccades were included, fixational eye movements of the macular disease group contain more power than the other two groups of observers (shaded regions straddling each solid line represent ±1 standard error). We also observed an age effect in normal vision, in that there is more power for older adults (red) than young adults (black). Moreover, the age effect was more pronounced in the drifts-only power spectra. However, despite the vertical offsets (differences in the amount of power) among these power spectra, the slopes of these spectra are highly comparable.

After establishing that the slopes of the power spectra of fixational eye movements were

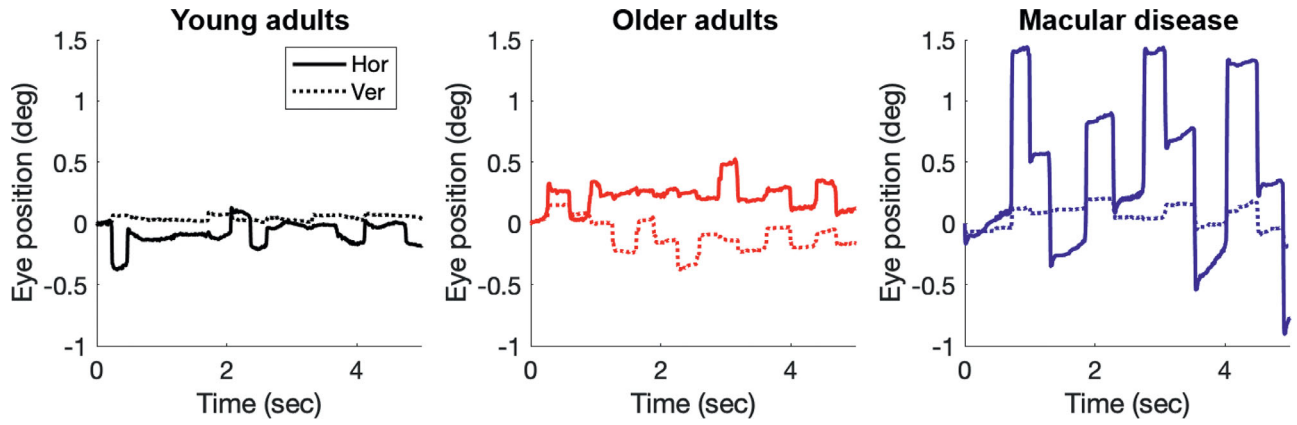

Figure 1. Sample eye movement traces from the three groups of observers: (black) young adults, (red) older adults, and (blue) macular disease groups. Solid and dashed lines represent horizontal and vertical eye positions, respectively.

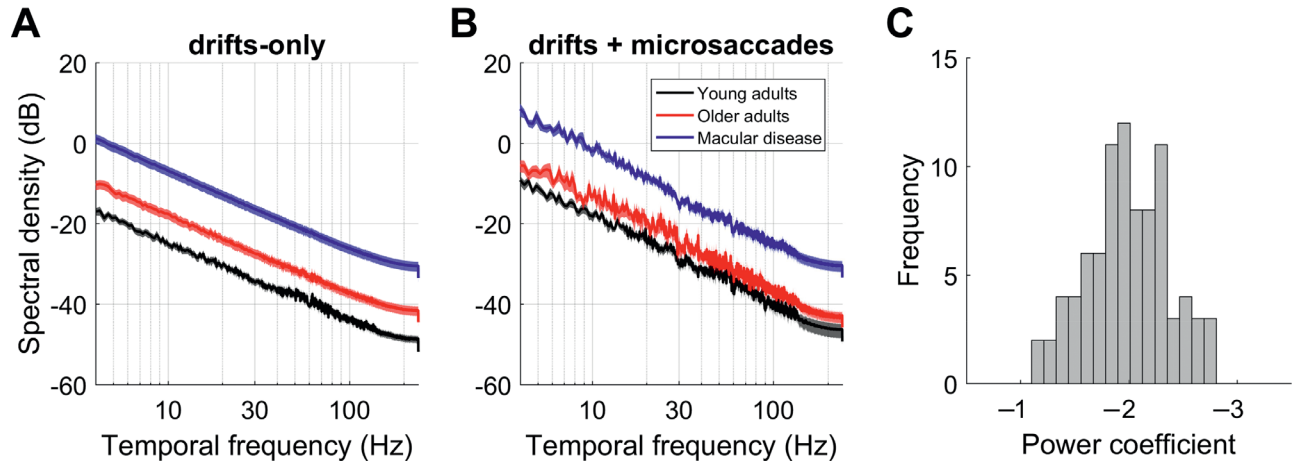

Figure 2. Power spectra of (A) drifts-only and (B) drifts + microsaccades for different observer groups. Each power spectrum represents the average across all observers of a given group. Black color represents young adults, red color represents older adults, and blue color represents the macular disease group. Shaded regions represent ±1 standard error. (C) Histogram of the slope of power spectra of the natural scene images ($N = 87$) used in this study.

highly comparable across our three groups of observers, we proceeded to creating movies using each observer's fixational eye movements and our set of natural scene images. Figure 2C shows the distribution of the coefficients describing how power contained within our set of natural scene images falls with spatial frequencies. The mean of the power coefficients for our set of images was –1.98 ± 0.38 SD, consistent with the value of –2 reported in the literature (Burton & Moorhead, 1987; Field, 1987; Ruderman & Bialek, 1994; van der Schaaf & van Hateren, 1996).

Spectral whitening is reduced in macular disease

Figure 3 shows the spatiotemporal power density spectra of the "retinal input" (movies created by translating a natural scene image according to recorded fixational eye movements). Each plot was obtained by averaging the power density spectra of 87 movies per observer and then across all observers of a given group. The top panels represent the power density spectra obtained when the natural scene images were

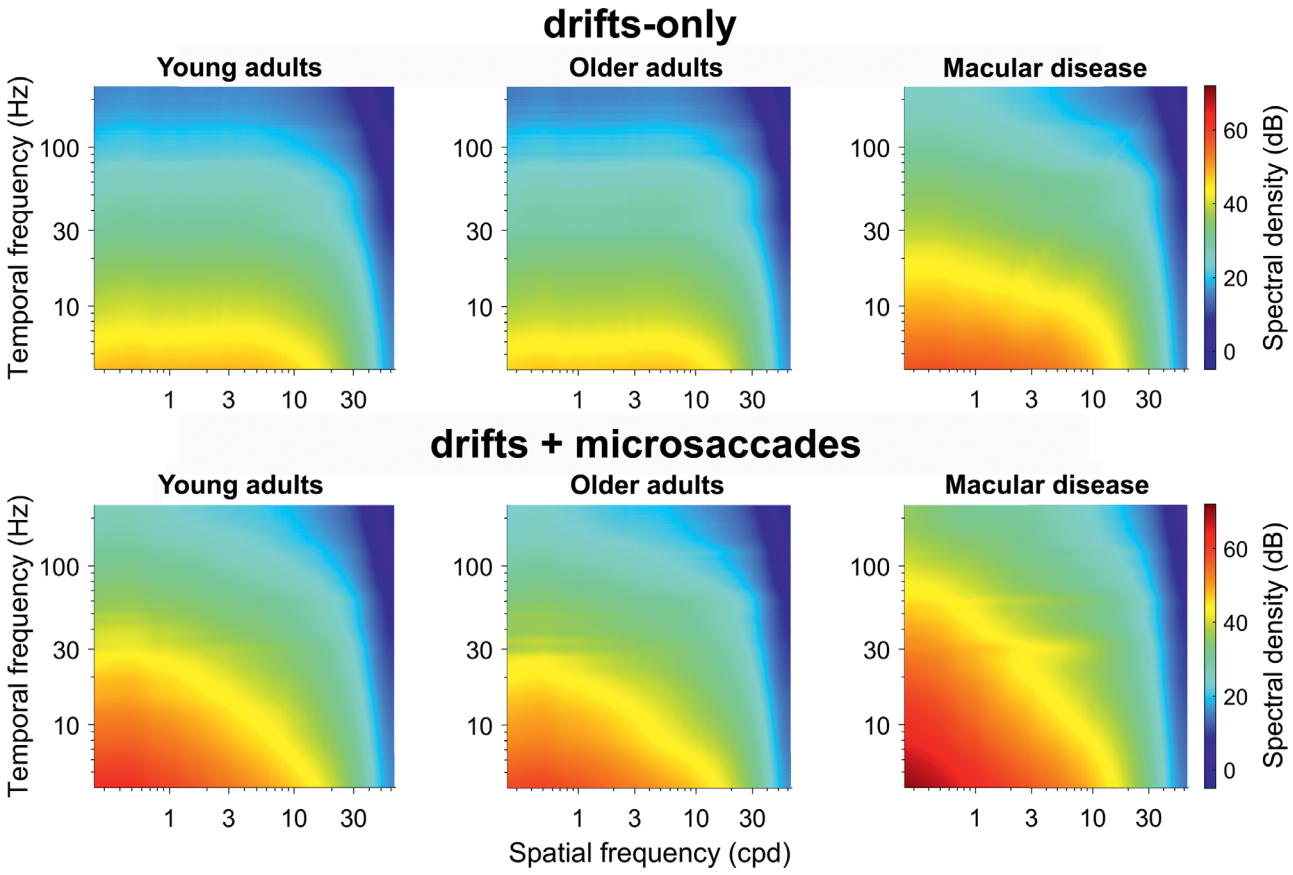

Figure 3. Two-dimensional average power spectra for all observer groups for (top) drifts-only and (bottom) drifts + microsaccades. Note that the power distributions in nonzero temporal frequencies are highly similar in the young and older adults with normal vision and that the power spectra are more spread out along the temporal frequency axis in the macular disease group.

translated in space according to ocular drifts only, and the bottom panels represent the counterparts when the images were translated according to both ocular drifts and microsaccades. Note that the power distribution in nonzero temporal frequencies are highly similar in the young and older adult groups, implying that there is a very little age effect; however, the power spectra are more spread out along the temporal frequency axis in the macular disease group.

The changes in the power density with spatial or temporal frequencies may be more clearly illustrated in Figure 4, where we plot how power density changes with only one of these dimensions. The top panels show how power density changes with spatial frequency, with the values averaged across all nonzero temporal frequencies. Dashed lines in the panels depict how power falls off with spatial frequency for our set of natural scene images. Consistent with the finding reported by Kuang et al. (2012), normal fixational eye movements in young adults cause a substantial reduction in power contained within the retinal input, at least for spatial frequencies up to approximately 10 cycles per degree (cpd; black traces), such that the power is virtually identical for this range of spatial frequencies. Here, we show that a highly similar spectral whitening effect is observed in older adults with normal vision (red traces), implying that there is very little normal age effect in fixational eye movements. Most importantly, the macular disease group also demonstrates the whitening effect (blue traces), albeit the reduction in the slope is less, and the range of spatial frequencies over which the slope is reduced is also smaller, when compared with those of the young (black) and older (red) adults.

To quantify the magnitude of spectral whitening, we fitted a line to the power density spectrum for each observer, for spatial frequencies ranging from 0.3 to 10 cpd, and used the slope of this line to compute the "whitening factor" as follows:

$$\textit{Whitening factor} = \frac{s_0 - s}{s_0},$$

where s_0 represents the average slope of the power spectra of natural images, and s is the slope of the spatial PSD for each observer. Figure 5 summarizes

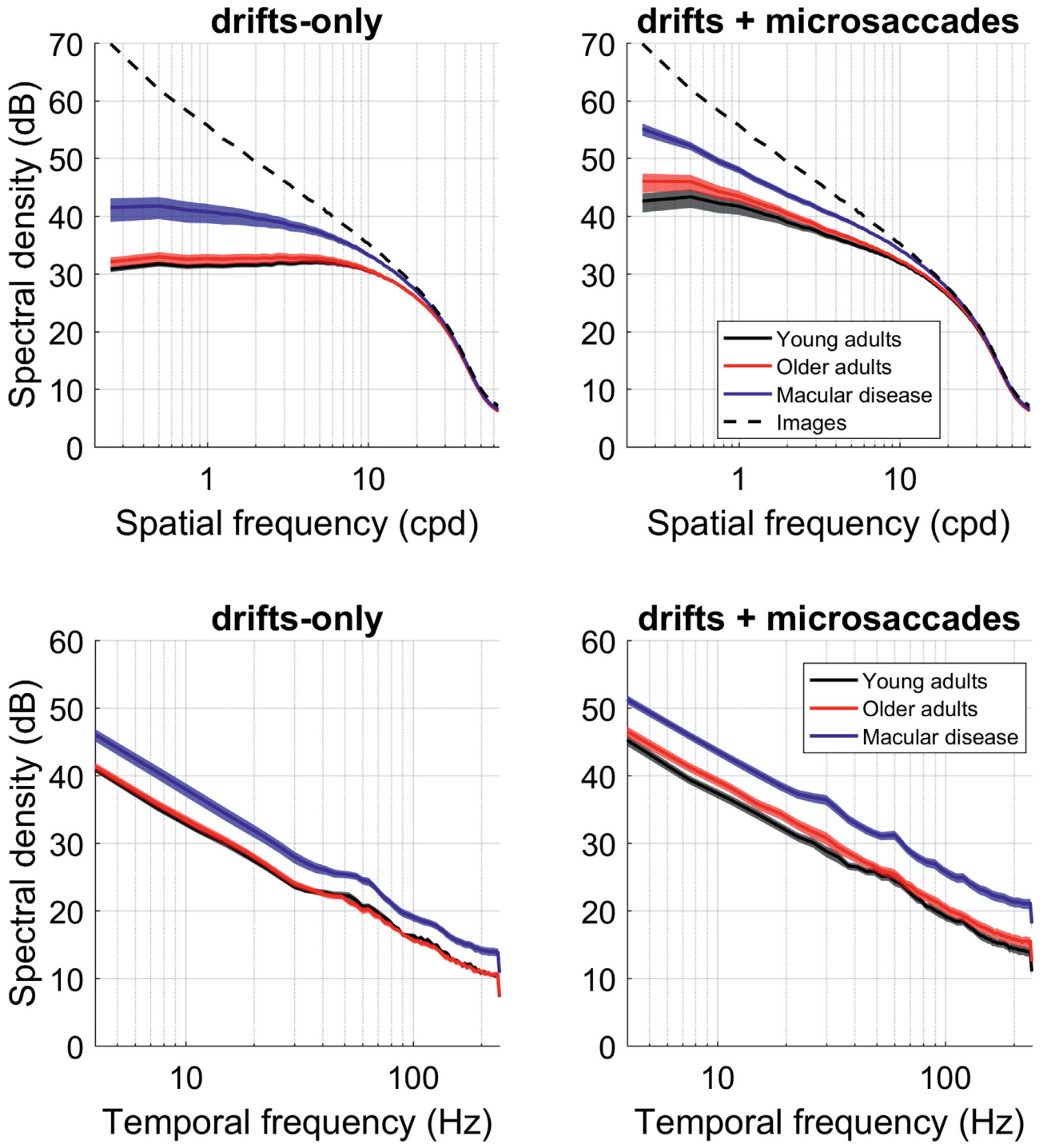

Figure 4. Average (top) spatial and (bottom) temporal power spectra for drifts-only (left) and drifts + microsaccades (right). Shaded regions represent ±1 standard error. Dashed lines in the top panels represent the average spatial frequency content of all images in the natural scene database that we used. This also corresponds to the hypothetical power spectra of retinal images had there not been any fixational eye movements. Note that whitening occurs only along the spatial axis and that it is more complete when microsaccades are excluded. Most importantly, observers with macular disease also demonstrated whitening, although the effect is smaller when compared with the whitening demonstrated by the other two observer groups.

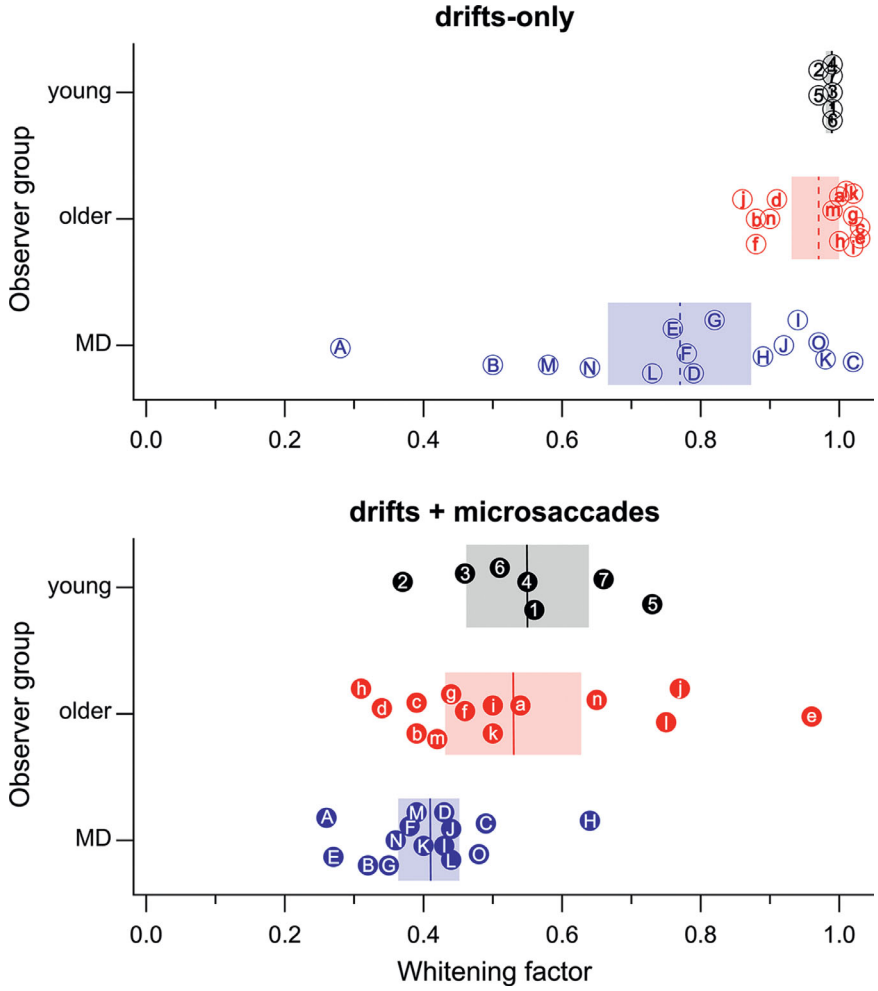

Figure 5. Whitening factors are plotted for individual observers for the three observer groups. Each observer is represented by a number (young adults), a lowercase letter (older adults), or an uppercase letter. Unfilled symbols represent the drifts-only condition (top panel), and filled symbols represent the drifts + microsaccades condition (bottom panel). Vertical lines (dashed lines for drifts-only condition and solid lines for drifts + microsaccade condition) represent the mean of the respective group, with the shaded regions representing the 95% confidence intervals. MD = macular disease.

the magnitudes of spectral whitening for individual observers, plotted separately for the three observer groups (different colors) and for the two conditions (drifts-only, unfilled symbols; drifts + microsaccades, filled symbols). Vertical lines represent the mean whitening factors of the respective group and condition (drifts-only, dashed lines; drifts + microsaccades, solid lines), with the shaded regions representing the 95% confidence intervals. Overlaps of confidence intervals from two different observer groups mean that the two groups are not significantly different from each other. Consistent across all three groups of observers, there is less whitening (smaller whitening factors) when microsaccades are included in the analysis. With respect to observer groups, the confidence intervals for the young and older adult groups overlap with one another, for both the drifts-only and drifts + microsaccades conditions, further supporting our finding that there is no significant aging effect on spectral whitening in normal vision. Not surprisingly, the macular disease group shows significantly less whitening than for the other two observer groups. This is especially so for the drifts-only condition.

Diffusion constant and PRL eccentricity account for the degree of spectral whitening

What could explain the smaller whitening factors exhibited by observers with macular disease? Recall that the power spectra of fixational eye movements are higher for observers with macular disease than for their age-matched normally sighted counterparts

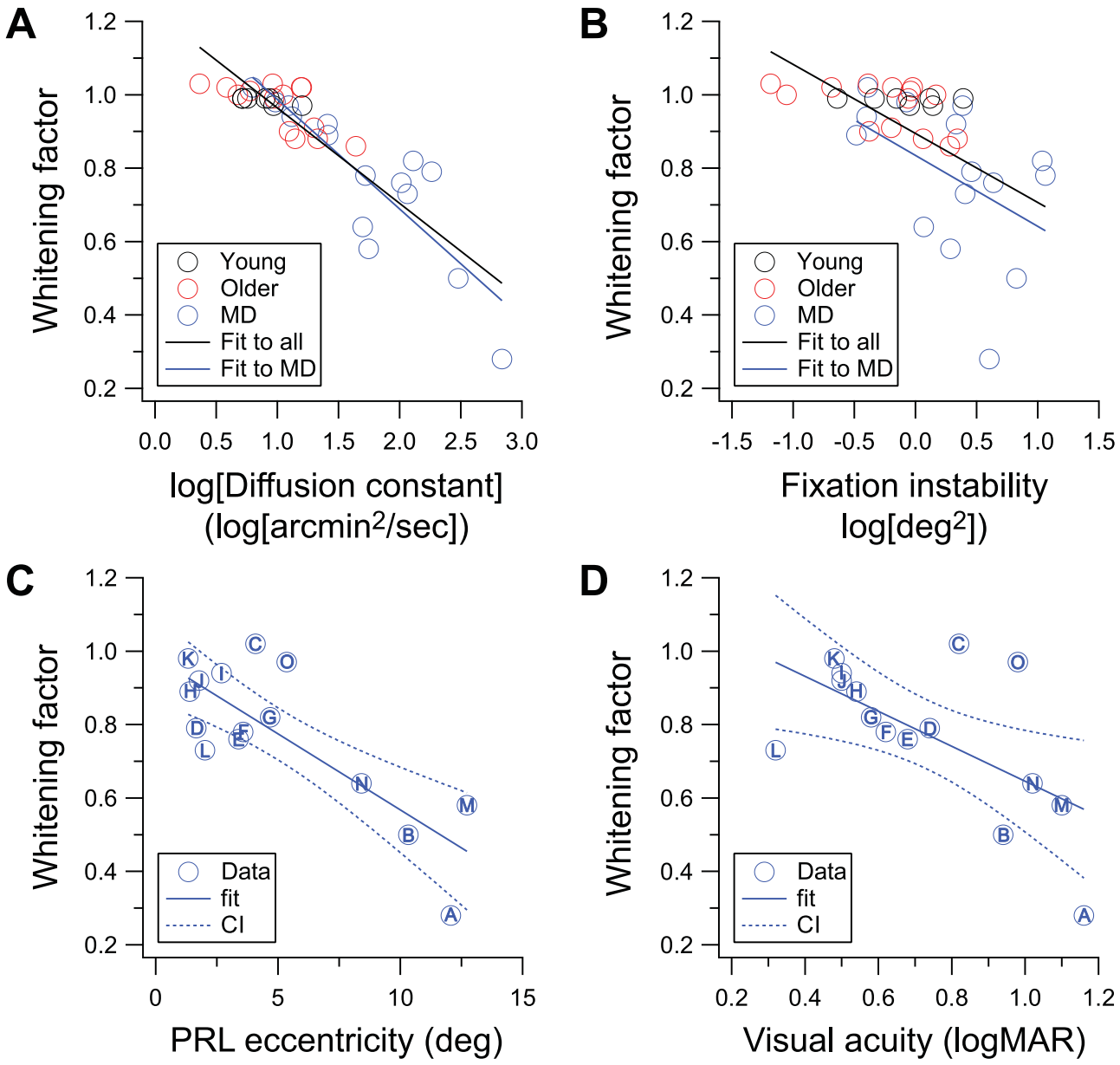

Figure 6. Whitening factors are plotted as a function of (A) estimated diffusion constant of ocular drifts, (B) fixation instability (computed using the 68% isoline area; see Castet & Crossland, 2012), (C) PRL eccentricity, and (D) visual acuity. Only observers with macular disease are plotted in (C) and (D). Letter codes representing individual observers in (C) and (D) are the same as those plotted in Figure 5.

and the young adults (Figure 2); clearly, one potential contributor to the smaller whitening factor is the higher power contained in the fixational eye movements for these observers. The higher power could be due to the known abnormal characteristics of fixational eye movements exhibited by people with macular disease (Kumar & Chung, 2014). In an exploratory[2] correlation analysis that follows, we will examine the relationship between whitening factor and a couple of characteristics of fixational eye movements (diffusion constant and fixation stability). Besides oculomotor differences, people with macular disease rely on their PRL for seeing; thus, the reduced spectral whitening could also be due to properties associated with the use of the PRL.

Kuang et al. (2012) showed that, besides normal ocular drifts, Brownian motion also leads to spectral whitening. In fact, the whitening effects exhibited by normal ocular drifts and Brownian motion are very similar, consistent with the widely accepted notion that normal ocular drifts can be approximated by Brownian motion (Pitkow, Sompolinsky, & Meister, 2007; Kuang et al., 2012). In Figure 6A, we examine the relationship between whitening factor and diffusion

constant (log-transformed) for our observers. Diffusion constant represents how fast the underlying motion is, assuming that the motion is governed by a Wiener process. The calculation of the diffusion constant is given in the Supplementary Material. As shown in Supplementary Figure A3, although the diffusion constants for observers with macular disease are much higher than those with normal vision, the diffusion constants for all our observers appear to follow a continuum, thus justifying the use of the diffusion constant to represent an oculomotor property even for people with macular disease. Figure 6A shows that regardless of whether we excluded observers with normal vision (young and older adults), there is a significant relationship between whitening factor and diffusion constant (all groups: $F(1, 34) = 116.0$, $p < 0.0001$; only macular disease group: $F(1, 13) = 36.0$, $p < 0.0001$). Specifically, whitening factor increases with decreasing values of the diffusion constant.

Another important property of fixational eye movements is fixation stability, which is usually quantified by the area that encloses a certain percentage (most conventionally, 68%) of the fixation locations on the retina. Using the isoline area method (Castet & Crossland, 2012) that does not assume that the fixation positions follow a normal distribution, we found a significant relationship between whitening factor and isoline area (log transformed, see Figure 6B) when all data were included ($F(1, 34) = 16.8$, $p < 0.001$), implying that increased fixation instability (larger isoline area) is associated with less whitening, but not when we considered only the macular disease group ($F(1, 13) = 3.67$, $p = 0.078$). Besides oculomotor properties, we also examined an important factor that limits vision in people with macular disease: the distance between the PRL from the fovea (eccentricity). As shown in Figure 6C, whitening factors show a significant correlation with the eccentricity of the PRL ($F(1, 13) = 23.1$, $p < 0.001$). Given that supposedly, the purpose of whitening is to reformat the visual input to better match the spatiotemporal tuning of retinal ganglion cells, we wonder whether or not more whitening indeed correlates with better vision. In Figure 6D, we examined the relationship between whitening factor and acuity and found a significant correlation between the two ($F(1, 13) = 7.49$, $p = 0.017$).

In sum, individuals with macular disease who have a PRL at a further distance from the fovea, which usually is associated with poorer acuity, exhibit less whitening. However, is it possible that the three factors that show significant relationships with whitening factors—diffusion constant, PRL eccentricity, and acuity—are all related and that the amount of whitening is essentially limited by only one factor? To examine this possibility, we performed a mediation analysis to examine whether there is a mediator variable; in other words, whether the direct effect of a factor can be explained completely by the indirect effect of another factor (the mediator). Details of the procedures of the mediation analysis follow those described in Chung, Kumar, Li, and Levi (2015) and are given in the Supplementary Material. The mediation analysis showed that (1) the effect of acuity on the whitening factor can be completely explained by the PRL eccentricity (the ratio of the indirect effect to the total effect is 1.032), and (2) the effect of PRL eccentricity on the whitening factor can be partially explained by the effect of the diffusion constant on the whitening factor (the ratio of the indirect effect to the total effect is 0.454). These findings suggest that the diffusion constant and PRL eccentricity are the main factors that govern the amount of whitening. Details of the procedures of the mediation analysis and tables showing the results of the analysis are given in the Supplementary Material.

Discussion

Most natural scenes have a power spectrum that can be best captured by a $1/f^2$ trend, where f represents spatial frequency. With normal fixational eye movements, the power spectrum of the retinal input below ~10 cpd becomes flattened (i.e., spectral whitening) due to the attenuation of power in low spatial frequencies (Casile & Rucci, 2006; Rucci et al., 2007). Attenuation of low spatial frequencies gives rise to a *relative* increase in the power in high spatial frequencies, thus facilitating fine discrimination (Ratnam et al., 2017; Rucci et al., 2007). Here, we showed that in the absence of a fovea, individuals with macular disease who must use a peripheral retinal location for fixation also demonstrate whitening, although to a lesser extent. Figure 4 shows that averaged across observers in the macular disease group, the smaller whitening effect manifests itself as a slope relating power with spatial frequencies (up to 10 cpd) that is greater than zero (the slopes were close to 0 for the other two observer groups). Another way to look at the data is that the range of spatial frequencies that are equated in power is smaller and is limited to spatial frequencies lower than 10 cpd. Based on results in normal vision that the function of ocular drifts is to equalize the spectral content of the retinal images within the spatial frequency bands to which retinal ganglion cells are most sensitive (Kuang et al., 2012), if spectral whitening were to be observed in people with macular disease who must use their peripheral retina for seeing, then it should match the spatial-frequency tuning of the retinal ganglion cells at or around the PRL. In other words, spectral whitening should be

negatively correlated with PRL eccentricity. This is exactly what we observed (Figure 6C).

Casile and Rucci (2006) and Kuang et al. (2012) argued that whitening of the retinal input originates from the interaction between the statistics of natural scene images and the spatiotemporal structure of fixational eye movements. According to these authors, how retinal ganglion cells process visual input across various locations in the visual field is not taken into account and is not required for whitening to happen. To demonstrate their argument, Kuang et al. (2012) showed that whitening did not occur when the input images were replaced by those with power spectra that declined with spatial frequencies according to relationships of $1/f^3$, $1/f^4$, or $1/f^5$. Even for images with power spectra that obeyed the $1/f^2$ relationship, when eye movements were artificially amplified, less whitening was observed. Specifically, the slope relating power spectra with spatial frequency became less flat, and the range of spatial frequencies over which there was a reduction in slope shifted toward lower spatial frequencies—effects that were not unlike the empirical findings we observed in the present paper for observers with macular disease.

This raises an interesting question: Is the smaller whitening effect a mere consequence of the larger amplitude of eye movements? People with macular disease exhibit abnormalities of fixational eye movements that are not restricted to simply larger amplitude of ocular drifts and microsaccades, but also include an increased tendency for microsaccade intrusions and faster microsaccades (Kumar & Chung, 2014). In addition, our current understanding of the neuronal mechanisms for controlling fixation in the normal visual system is that there is a strong foveal involvement, at least for the control of microsaccades (the neuronal mechanism for ocular drifts is much less understood; for a review, please see Krauzlis, Goffart, & Hafed, 2017). The superior colliculus, a sensorimotor structure that is responsible for saccadic eye movements, contains a retinotopic representation of the visual world where its rostral end corresponds to the foveal region of the retina, and increasing distance from this end corresponds to retinal locations with increasing eccentricity from the fovea. Stimulation of neurons at any given location in the superior colliculus would always initiate a saccade with an amplitude and a direction that bring that location to the fovea.

It is widely accepted that the superior colliculus is also responsible for microsaccade generation, with most of the neuronal activities clustered around the rostral end (Hafed, Goffart, & Krauzlis, 2009; Hafed & Krauzlis, 2012). In addition to just a motor map for saccades and fixation, the superior colliculus also contains a map of behaviorally oriented goal locations (Hafed & Krauzlis, 2008; Hafed, Goffart, & Krauzlis, 2008) in the deeper layers. For example, Hafed and Krauzlis (2008) trained monkeys to track the midpoint of a pair of moving bars so that the visual stimuli were in peripheral locations while the goal/targeted position was a central one. Recordings in the superior colliculus showed that there were still neuronal activities in the deeper layers of the rostral end of the superior colliculus. In the presence of macular disease, there is no visual input from the fovea, hence there will be a lack of neuronal activities in the visual layers of the rostral end, but, given that activities in the deeper layers of the rostral end can represent goal and movement endpoints, potentially microsaccade generation may not be affected. However, considering the empirical evidence that the characteristics of microsaccades for people with macular disease are different from those with normal fovea (Kumar & Chung, 2014), future studies using animal models of macular disease (and allowing the animals to develop a PRL) might allow us to better understand the time course of how the properties of microsaccades change in response to an absence of a direct foveal visual input to the visual layers of the superior colliculus.

Given that whitening is supposed to benefit our ability to see fine details, from a clinical point of view, it is reassuring to learn that people with macular disease who exhibit abnormal fixational eye movements would also be able to benefit from whitening, even if the benefit is smaller than that observed in people with a normal fovea. Two interesting and practical questions are (1) could we improve the whitening factor for people with macular disease, and, more importantly, (2) would there be any associated benefits? The present study cannot offer a convincing answer to the latter, as a causal link between spectral whitening (and/or other oculomotor behavior) and visual function has yet to be established. Such a link would be very important because the analysis we performed here, as well as the analyses performed by Kuang et al. (2012), only took into account the fixational eye movements and the spectral density of the visual input. In other words, how the information impinging on the retina is subsequently processed is not considered. Studies that include some kind of performance measurement (especially one that could relate to how retinal ganglion cells process information, such as contrast sensitivity) while observers view natural scene images would be very helpful for us to better understand the relationship among spectral whitening, fixational eye movements, and vision. There is ongoing work in our laboratory to address this issue. Regarding the first question, results of our mediation analysis show that the diffusion constant and the PRL eccentricity are important factors in limiting the whitening factor. Therefore, one way to improve the whitening factor would be to train people with macular disease to use another PRL that is closer to the fovea. However, currently very little is known about how a retinal location evolves to become

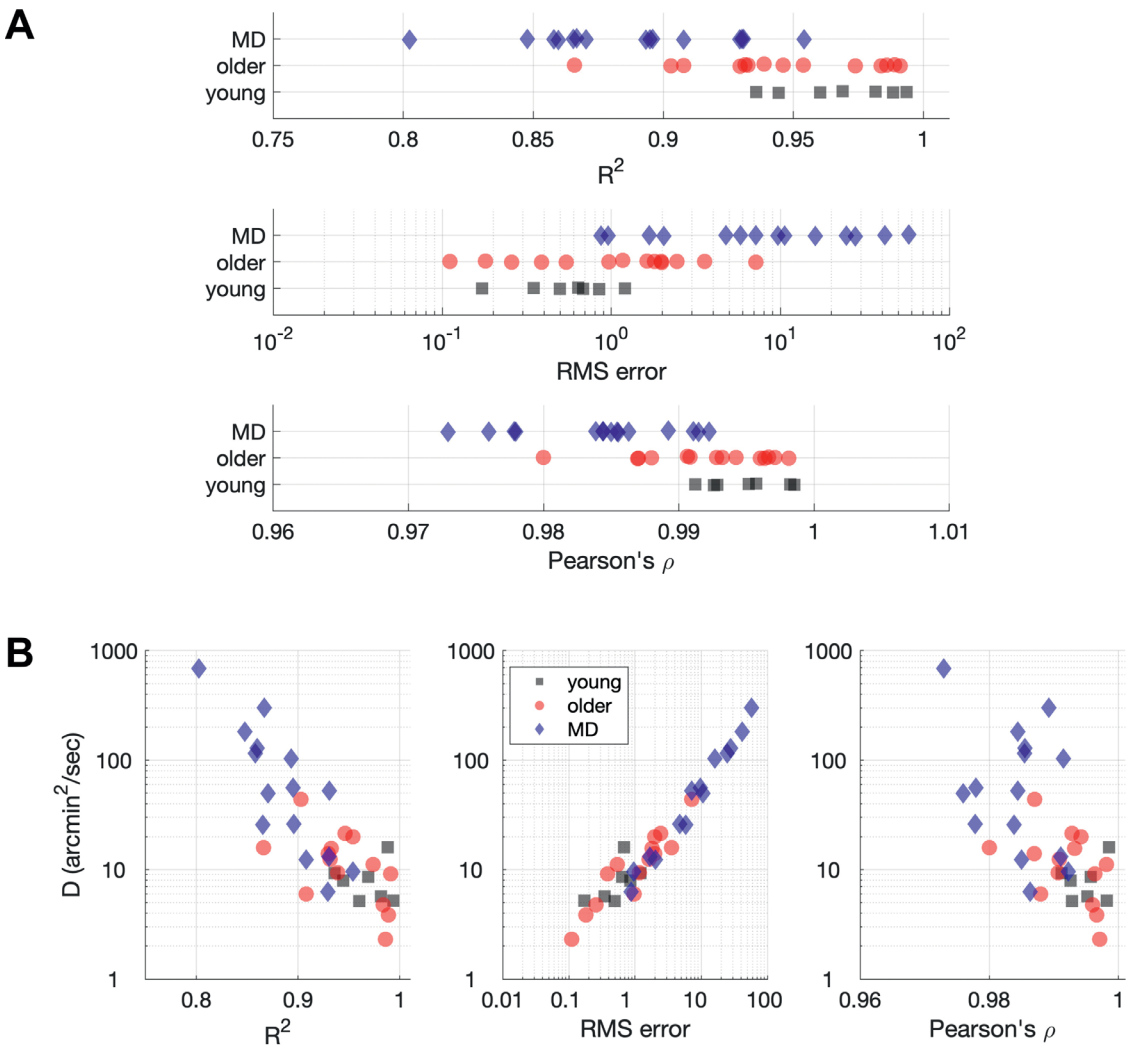

Figure 7. (A) Three goodness-of-fit metrics (R^2, Pearson's ρ, and root mean square error) for approximating ocular drifts with Brownian motion. (B) Scatterplots showing how estimated diffusion constants co-vary with the goodness-of-fit metrics.

a PRL for an individual with macular disease, although the visual capability and integrity of the region are likely to be important determinants. Therefore, potentially, training an individual to abandon his/her naturally developed PRL and to adopt another retinal location as his/her PRL might have some unforeseen negative consequences. Another means of improving the whitening factor could be through oculomotor training to reduce the diffusion constant. Whether these two methods can indeed improve the whitening factor would have to be tested in future studies.

How Brownian are ocular drifts in macular disease?

A major limitation of this study is that we made an important assumption that ocular drifts follow a Wiener process even after changes in fixational eye movements due to macular disease occur. In other words, we assumed that Brownian motion can approximate the fixational eye movements of all three groups of observers here. To test this, we computed several goodness-of-fit metrics (R^2, Pearson's ρ, and root mean square error) when we estimated the diffusion constants and assessed how they change across different groups of observers, and whether or not they co-vary with the magnitude of the diffusion coefficient. Figure 7 summarizes the results. Compared with the young- and older adults groups, the macular disease group had lower goodness-of-fit values. Moreover, across all observers, larger diffusion constants were associated with worse goodness-of-fit values. Because diffusion constants in macular disease are significantly elevated, our previous analyses concluded that spectral whitening might be a result of larger diffusion constants. This point is supported by early simulations of Kuang

et al. (2012). However, given that the resemblance of eye movements to Brownian motion also decreases with increasing diffusion constants, it is difficult to tease apart whether the root cause of the reduced spectral whitening in macular disease is attributed to the elevated diffusion constant of ocular drifts alone (assuming that ocular drifts remain perfectly Brownian) or the fact that ocular drifts do not follow a Wiener process. Future studies providing causal evidence to link certain characteristics of drifts to spectral whitening are necessary to fully answer these questions.

Conclusions

Despite their abnormal characteristics, fixational eye movements exhibited by people with macular disease also demonstrate spectral whitening, although the magnitude of whitening is less (and is limited to lower spatial frequencies) than that observed in people with normal vision. The less-than-normal whitening should not be interpreted as indicating that the benefits of fixational eye movements, especially those due to ocular drifts, are smaller for people with macular disease. Rather, it just means that spectral whitening occurs for a range of spatial frequencies lower than that for normal vision, which is reasonable given that people with macular disease must rely on their peripheral retina for vision. Using a mediation analysis, we found that the eccentricity of the PRL adopted by these observers and the diffusion constant of ocular drifts are the important factors limiting the amount of whitening. These findings offer novel potential means of improving the characteristics of fixational eye movements, which may, in turn, improve functional vision for people with macular disease. Finally, we did not find a normal aging effect on spectral whitening.

Keywords: fixational eye movements, macular disease, spectral whitening, aging

Acknowledgments

This study was supported by research grant R01-EY012810 from the National Institutes of Health. We thank Girish Kumar for his help in the initial stage of this study.

Commercial relationships: none.
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Footnotes

[1] Here, we use the term "microsaccades" to refer to the saccades made during fixation, although for people with macular disease, the amplitude of these microsaccades during fixation often exceeds the conventional numerical definition of a microsaccade (10–30′).
[2] We acknowledge that stronger conclusions could only be drawn with larger number of observers, as well as across a wider range of ages for the normal aging effect. The goal of this study was to explore if such effort of testing larger samples of observers would be warranted by demonstrating the potential correlations between whitening factors and several properties related to the PRL.

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