Visual Contrast Sensitivity in Early-Stage Parkinson's Disease

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Purpose. Visual impairments are frequent in Parkinson's disease (PD) and impact normal functioning in daily activities. Visual contrast sensitivity is a powerful nonmotor sign for discriminating PD patients from controls. However, it is usually assessed with static visual stimuli. Here we examined the interaction between perception and eye movements in static and dynamic contrast sensitivity tasks in a cohort of mildly impaired, early-stage PD patients.

Methods. Patients (n = 13) and healthy age-matched controls (n = 12) viewed stimuli of various spatial frequencies (0–8 cyc/deg) and speeds (0°/s, 10°/s, 30°/s) on a computer monitor. Detection thresholds were determined by asking participants to adjust luminance contrast until they could just barely see the stimulus. Eye position was recorded with a video-based eye tracker.

Results. Patients' static contrast sensitivity was impaired in the intermediate spatial-frequency range and this impairment correlated with fixational instability. However, dynamic contrast sensitivity and patients' smooth pursuit were relatively normal. An independent component analysis revealed contrast sensitivity profiles differentiating patients and controls.

Conclusions. Our study simultaneously assesses perceptual contrast sensitivity and eye movements in PD, revealing a possible link between fixational instability and perceptual deficits. Spatiotemporal contrast sensitivity profiles may represent an easily measurable metric as a component of a broader combined biometric for nonmotor features observed in PD.

Keywords: visual psychophysics, eye movements, smooth pursuit, microsaccades, contrast sensitivity

Visual contrast sensitivity is the capability to distinguish a visual object from its background. It is critical for many daily activities[1] and is impaired in patients with neurodegenerative diseases such as Parkinson's disease.[2–5] Conventionally, contrast sensitivity has been measured in the laboratory as a function of an object's richness in texture, its spatial frequency. We define spatial contrast sensitivity as the ability to distinguish static stimuli, and spatiotemporal contrast sensitivity as the ability to detect moving stimuli while tracking them with smooth pursuit eye movements. Healthy adults are most sensitive to objects in the medium spatial-frequency range; that is, they can see these objects even at low contrast. Contrast sensitivity is lower when objects are almost uniformly gray (low spatial frequency) or highly textured (high spatial frequency).

Contrast sensitivity is affected by several factors, including age and disease status. Higher thresholds across spatial frequencies have been observed in infants and children; maturity is reached in early adolescence.[6] Sensitivity in the high spatial-frequency range decreases in mid-adulthood while functioning at low spatial frequencies is relatively preserved in the elderly.[7] Robust impairments in spatial contrast sensitivity have been observed across a variety of pathologies,[4,8] including Parkinson's disease (PD). However, results for contrast sensitivity in this group of patients are highly variable: Whereas some studies observed impairments across the entire spatial-frequency range,[5] others report loss of sensitivity in the medium- to high-frequency range.[3,4] Together, these findings indicate that PD might result in a loss in sensitivity as well as a shift of the contrast sensitivity function toward lower spatial frequencies as compared to controls,[4] implying selective impairment of a subset of spatial-frequency channels. Contrast sensitivity decreases with disease progression,[5] although deficits in the low spatial-frequency range can be ameliorated with L-dopa treatment.[3,9] In general, the prevalence of early visual function impairment and the importance of assessing these functions in patients with PD have been widely recognized.[1,10,11] Contrast sensitivity contributes to successful performance in many tasks of daily living. For instance, it is a strong predictor of poor motor vehicle driving outcome in patients with PD, especially under low-contrast visibility conditions.[12]

Despite the importance of this capability for everyday life, most studies on contrast sensitivity in healthy, aging, and clinical populations have been conducted with static visual stimuli. However, our natural environment is highly dynamic, and most visual objects produce retinal image motion due to the motion of the object itself or due to self-motion. Deficits in

motion processing[1,10,13] are prevalent in PD and may result in relatively larger impairments in spatiotemporal (dynamic) versus spatial (static) contrast sensitivity.[14]

An additional factor to consider in all perceptual tasks is the contribution of eye movements. Eye movements are critical for our ability to perceive fine spatial detail and to recognize and react appropriately to visual objects and events. The close interaction between perception and eye movements in general[15,16] implies that impairments in one capability will affect the other. Assessing spatial contrast sensitivity requires an observer to fixate the eyes on a visual object; evaluating spatiotemporal contrast sensitivity requires the observer to track a moving object with smooth pursuit eye movements to keep it close to the fovea. Smooth pursuit, saccades, and fixational eye movements are severely impacted in PD or other Parkinsonian disorders.[17–20] Smooth pursuit and saccades have longer latencies and lower velocity in PD patients versus healthy age-matched controls.[17–23] Generally, lower pursuit eye velocity gain produces higher retinal image motion (motion blur), impairing perception of moving images. Fixational eye movements are characteristically unstable in PD, with more frequent small saccadic intrusions and tremor than in healthy controls.[24,25] Larger-amplitude square-wave jerks—saccades of similar magnitude, going into opposite directions, separated by a brief time interval—have particularly been found in patients with progressive supranuclear palsy (PSP) and other Parkinsonian movement disorders,[24,26,27] but also in PD patients.[28]

Despite well-documented eye movement abnormalities in PD, the direct impact of eye movement deficits on perception has not been assessed in these patients. Here we investigated spatial and spatiotemporal contrast sensitivity in PD patients and age-matched, healthy adults across a range of spatial frequencies and velocities. We simultaneously recorded eye movements with a high-accuracy eye tracker to assess potential effects of known oculomotor deficits—fixational instability and slowed smooth pursuit eye movements—on contrast sensitivity.

Methods

Observers

Participants were 13 patients with idiopathic mild to moderate PD and 12 healthy, age-matched controls (Table). Observers were included in the study if they had normal or corrected-to-normal visual acuity, no history of ocular motility abnormality (e.g., no strabismus or amblyopia), and no history of any neurologic or psychiatric condition. All observers were screened to confirm normal visual acuity. Monocular and binocular visual acuities were determined using the Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity chart at 4-m test distance (Original Series Chart "R"; Precision Vision, La Salle, IL, USA); all observers had normal ($n = 12$) or corrected-to-normal visual acuity ($n = 13$) with binocular acuity 20/20 or better in $n = 15$, 20/30 or 20/25 in $n = 7$, and 20/40 in $n = 2$. Those with refractive errors wore their regular glasses or contact lenses during the study. All PD patients were on L-dopa or equivalent medication (see Table) and were tested within 2 hours of taking their last regular dose of medication. All procedures were in alignment with the Declaration of Helsinki and were approved by the University of British Columbia Clinical Research Ethics board; subjects participated after giving written informed consent.

Setup and Stimuli

Participants were seated in a dimly lit room facing an 18-inch CRT monitor (ViewSonic Corporation, Walnut, CA, USA) with a refresh rate of 75 Hz controlled by an NVIDIA GeForce GT 430 graphics card (Nvidia Corporation, Santa Clara, CA, USA) and set to a resolution of 1280 × 1024 pixels. This resulted in a visible range of 35.5 × 25.5 cm (36° × 26° of visual angle at a 55-cm viewing distance). The gamma nonlinearity of the screen was measured using a LS-100 luminance meter (Konica Minolta, Inc., Chiyoda, Tokyo, Japan) and corrected using a lookup table.

Stimuli were Gabor patches, that is, patterns with alternating black and white stripes of vertical orientation (sinusoidal gratings) and spatial frequency 0.5, 1, 2, 4, or 8 cycles per degree (cyc/deg), windowed by a Gaussian function (Fig. 1). The perceived size of a Gabor with a fixed standard deviation depends on contrast.[31] We thus determined the Gaussian standard deviation σ at each contrast level following procedures outlined in the literature[31] to maintain a constant perceived radius, $P_r = 1°$ (apparent size: 2° diameter). The stimulus in our study was sufficiently large to be easily visible even for subjects with visual acuity 20/40. Gabor patches were shown either inside a stationary aperture in the center of the screen or inside an aperture moving across the screen at a constant velocity of 10°/s or 30°/s. Gabor contrast was varied relative to the neutral gray background (mean luminance 25 cd/m^2).

Table. Subject Demographic Data

Parameters	Control Subjects, $n = 12$	Parkinson's Subjects, $n = 13$
Age, y	66.8 (6.8)	67.0 (9.3)
Age range	55–79 y	46–81 y
Sex	7 female	5 female
Handedness	12 right-handed	12 right-handed
ETDRS*	20/22	20/24
MoCA†	27.2 (2.1)	27.1 (3.1)
UPDRS score‡	–	22.4 (11.5)
HY staging§	–	1.5 (0.66)
Levodopa dose‖	–	758.2 (639.7)

Means (SD) are shown. None of the differences between controls and patients were significant (all $P > 0.05$).

* Early Treatment of Diabetic Retinopathy (ETDRS) visual acuity chart "R" (Precision Vision).

† Montreal Cognitive Assessment,[29] a test rating cognitive ability on a scale from 0 to 30.

‡ Unified Parkinson's Disease Rating Scale (Movement Disorder Society Task Force, 2003).

§ Hoehn and Yahr scale[30] for symptom severity, ranging from 1 (unilateral involvement only) to 5 (confinement to bed or wheelchair unless aided).

‖ Effective levodopa dose (mg/d).

Design and Procedure

We determined contrast detection thresholds for static and moving stimuli in separate blocks of trials using the method of adjustment.[32] In this method, observers adjust the luminance value of a stimulus until they can just barely see it. On one hand, this method may be considered subjective and prone to differences in interpreting the meaning of "barely visible." On the other hand, it is fast and well tolerated by subjects; it is less prone to floor effects and widely used in contrast sensitivity testing.[33,34] Each trial started with central fixation on a small black circle (diameter 0.5°), followed by the Gabor patch. In blocks with static stimuli, the Gabor was presented in the center of the screen and participants were instructed to fixate on it. In blocks with moving stimuli (Fig. 1A), the Gabor moved at a constant speed of 10°/s or 30°/s across the screen (19° ± 1°), pausing for 500 ± 100 ms at each end, and participants

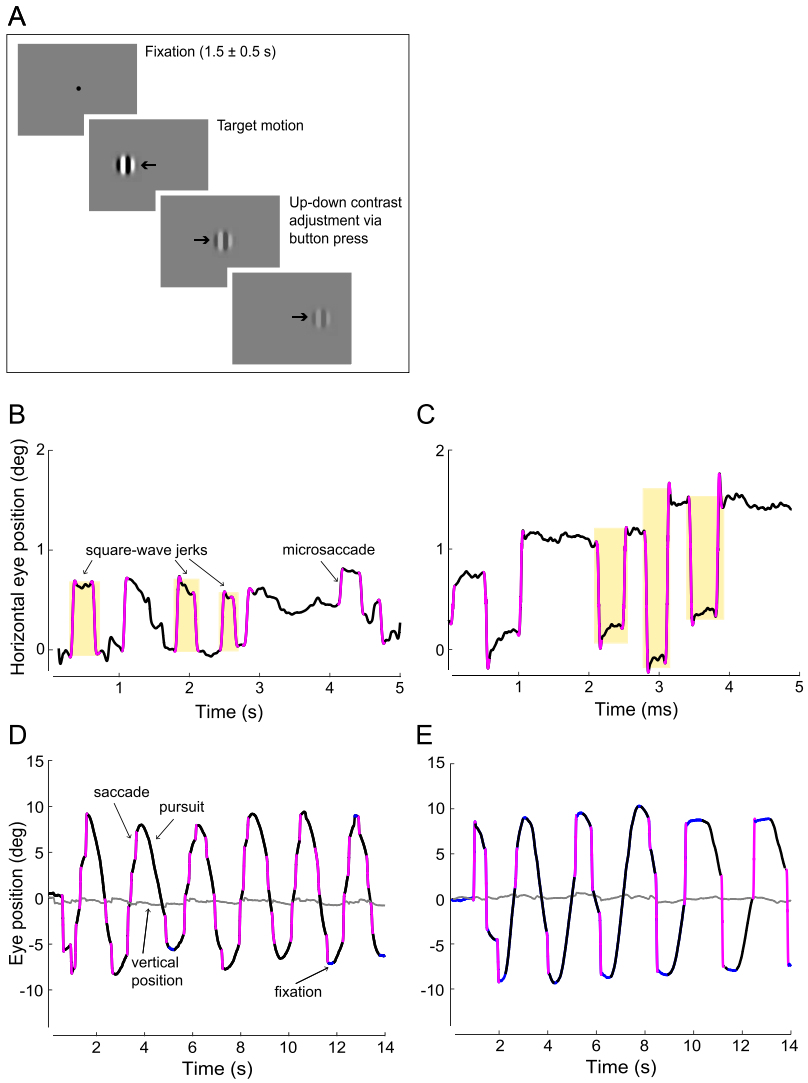

Figure 1. **(A)** Trial timeline for dynamic stimuli. Each trial starts with central fixation, followed by target presentation, either stationary in the center or moving left and right. Observer presses up/down buttons on keyboard to adjust contrast. **(B, C)** Horizontal eye position traces in static trials for two representative observers, patient 12 **(B)** and control 13 **(C)**. Saccades and microsaccades are marked in *magenta*; SWJ are indicated by *yellow rectangles*. Vertical position not shown for clarity. **(D, E)** Horizontal and vertical eye position traces in dynamic trials for two observers, patient 14 **(D)** and control 2 **(E)**. Pursuit indicated in *black*, catch-up saccades in *magenta*, fixation in *blue*. Thin *gray line* is vertical eye position.

were instructed to track the stimulus with their eyes. Initial stimulus contrast was 3% of maximum contrast for the first trial, and decreased by 0.6% per trial for the subsequent four trials to prevent habituation. Participants had to adjust the Gabor's luminance contrast using the up and down arrow keys on the keyboard until they could just barely see the stimulus (criterion). To ensure that all observers followed this instruction we asked them to initially adjust the luminance down until the stimulus disappeared, and then slowly adjust luminance up until the stimulus became visible again across the entire tracking range (in dynamic trials); observers received five practice trials at the beginning of the experiment to experience this procedure and to ensure that they adjusted the luminance to a value below threshold. All observers confirmed verbally that they fully understood the instruction and specified criterion. Each spatial frequency × velocity combination (5 × 3 conditions) was repeated five times, resulting in 25 static and 50 dynamic trials, split into blocks of 10 trials. Observers were encouraged to take breaks between blocks of trials, every 5 minutes on average, to prevent effects of fatigue. Observers also initiated and ended each trial, giving them full control over the pace of the experiment, and could take as long as needed to give their manual responses, thus further preventing fatigue.

Eye Movement Recording and Analysis

Binocular eye position signals were recorded with a tower-mounted, video-based eye tracker (EyeLink 1000; SR Research, Kanata, ON, Canada) and sampled at 1000 images per second (1 kHz); the apparatus was calibrated before each block of trials. The eye tracker chosen for the present study is a noninvasive, remote, video-based system that requires use of a chin rest to stabilize head position, but it can track the eye with a high sampling rate. This eye tracker has been used extensively for the investigation of the spatiotemporal dynamics of eye movements, including microsaccades,[26,27] and is sufficiently accurate and precise (instrument noise around 0.01° root mean square) for the fine spatiotemporal analysis of smooth pursuit and fixation. The system reliably tracks

observers with glasses or soft contact lenses and is therefore highly suitable for use in our cohort of patients, of whom many have corrected visual acuity. Stimulus display and data collection were controlled by a PC running Matlab version 2009a (The MathWorks, Inc., Natick, MA, USA) with Psychtoolbox Version 3.0.10.[35]

Trials in which subjects did not have at least one judgment reversal (e.g., increasing and then decreasing the contrast value) and trials with less than 2 seconds of usable data due to prolonged eye blinks or lost signals were excluded from analyses of perceptual and eye movement data (20.2% of static and 26.8% of dynamic trials). We also did not analyze saccades that were within 100 ms of detected signal loss due to blinks. For correlational analyses, we flagged trials as outliers where contrast threshold or saccade frequency exceeded 3 standard deviations of the mean (1.1% trials excluded for contrast threshold, 2% for saccade frequency, respectively). Subjects for whom we were unable to obtain clear cornea reflection, due to reflections off their eye glasses, and with calibration errors $>$ 0.35°, were not included in the study (control no. 12). We were also unable to run dynamic blocks in patient 6 despite successful completion of static blocks, and static blocks in control 11; hence, only static/dynamic data, respectively, were included for these subjects. This results in a total of 23 sets of usable eye movement data per static and moving conditions.

Eye position data and button presses were analyzed offline using custom-made routines in Matlab. Eye velocity profiles were derived from digital differentiation of eye position data over time; both were filtered using a low-pass, second-order Butterworth filter with cutoff frequencies of 15 Hz (position) and 30 Hz (velocity).

Eye Movements in Static Trials. Saccades were detected based on a fixed velocity criterion: Three consecutive frames had to exceed a velocity of 10°/s; saccade on- and offsets were then determined as the nearest sign changes in the acceleration profile before and after the samples exceeding the velocity criterion (Figs. 1B, 1C). This algorithm is sufficiently sensitive to detect even the smallest saccades, as confirmed by visual inspection of each individual position and velocity trace. Microsaccades were defined as saccades of $<$0.5° amplitude (see Figs. 1B, 1C). In static trials, we computed the rate of saccades and microsaccades per second as well as the mean saccade amplitude. Next, we classified saccades into square-wave jerks (SWJ), defined as pairs of saccades of equal magnitude, that is, one saccade followed in quick succession by another saccade in the opposite direction[26,27] (marked by yellow rectangles in Figs. 1B, 1C). For each pair of saccades, we calculated the directional dissimilarity, the amplitude similarity, and the temporal proximity and classified pairs as either SWJ or non-SWJ using software described in the literature[26] (freely available for download at http://smc.neuralcorrelate.com/sw/swj/). We report the proportion of saccades and microsaccades that were classified as SWJ.

Dynamic Trials. Smooth pursuit was interspersed with fixation (marked in blue in Figs. 1D, 1E) and saccade intervals (magenta in Figs. 1D, 1E). For the analysis of pursuit velocity, saccades (a minimum of three consecutive samples exceeding a fixed velocity criterion of 30°/s) were removed from eye position and velocity profiles. We then segmented the remaining eye movement traces into fixation and pursuit based on the eye trajectory's angular dispersion using directional statistics to determine whether the eye moves in a consistent direction, indicating smooth pursuit.[36,37] We computed the mean velocity of the eye during pursuit segments, as well as the amplitude density of catch-up saccades (cumulative saccade amplitude per trial divided by trial duration).

Statistical Data Analysis

Contrast sensitivity is defined as the reciprocal of the contrast sensitivity threshold. The contrast sensitivity threshold was determined by taking the mean of the final threshold (luminance value) for each included trial per subject and spatial frequency. To examine effects of stimulus condition and differences between groups we conducted repeated-measures ANOVAs with between-subjects factor disease and within-subjects factors speed and spatial frequency. For each ANOVA, we confirmed the normality of the data and the equality of variances using Mauchly's test for sphericity. All post hoc *t*-tests were Bonferroni corrected for multiple comparisons. Correlational analyses were conducted to reveal relations between contrast sensitivity and disease severity, medication, and cognitive ability. All statistical analyses were done in IBM SPSS Statistics Version 23 (Armonk, NY, USA).

Rather than just examining each spatial frequency independently for differences between groups, we also investigated whether entire contrast sensitivity profiles (sensitivity across spatial frequencies) might differ between groups and target speeds. This was done with independent component analysis (ICA) and bootstrapping methods—multivariate analyses methods that allow us to look at systematic changes across spatial frequencies. First, all contrast profiles from all subjects and trials were assembled. Each profile was then assumed to be derived from the summation of fundamental "building blocks"; these were the same for all observed profiles, but the relative amounts of each fundamental building block differed across profiles. Independent component analysis computes what these fundamental profiles are. Crucially, these profiles can be similar to one another (e.g., are not required to be orthogonal)—just that for a specific observed profile, the relative contribution of one fundamental profile does not imply a higher/lower contribution from another fundamental profile. We then investigated whether or not any of the fundamental profiles were more/less likely to contribute to the observed profile, depending upon target speed and group. Specifically, we took the final contrast from each trial at the slower target speed of each of the five spatial frequencies to obtain a vector, t, (5×1). This was repeated for each trial at each speed to make a matrix T. The matrices from all subjects were then concatenated to create an all-subjects matrix, X. We then performed ICA using the ICASSO software package under Matlab (ICASSO 1.21)[38]:

$$X = A \times s,$$

where A is 5×5 and the rows of s are the statistically independent components. The columns of A can be considered as fundamental spatial-frequency profiles that are independently added to provide the observed profiles.

To examine if the observed spatial-frequency profiles were significantly affected by disease status and/or velocity, we performed a bootstrapping procedure to estimate the null distribution. For example, for the first spatial profile (first column of A), we took the first row of s and randomly permuted the order of the elements. We then took the mean of the elements that corresponded to the original trials that were designated, for example, "PD patients, slow." This was repeated 1000 times, and a histogram of the means was plotted. We then took the mean of the same trials using the nonpermuted data. This value was plotted as a vertical line in the histograms. A vertical line far from the mean of the null distribution would suggest that the corresponding spatial profile was strongly represented in the "PD patients, slow" category.

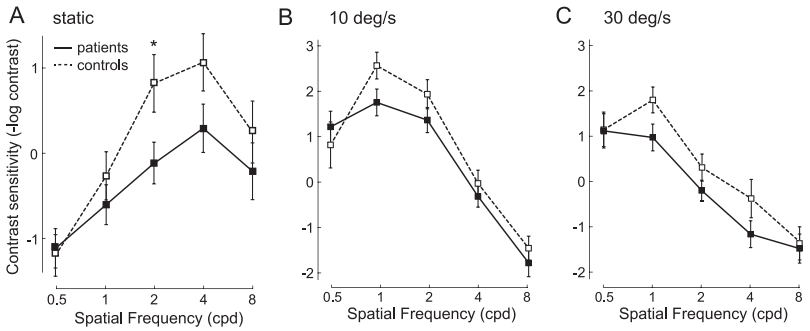

Figure 2. (**A**) Static contrast sensitivity performance for patients ($n = 13$) versus healthy controls ($n = 12$) for five spatial frequencies. (**B**) Dynamic contrast sensitivity performance for patients ($n = 13$) versus healthy controls ($n = 12$) for slower speed (10°/s). (**C**) Dynamic contrast sensitivity for faster speed (30°/s). *Error bars* denote standard errors of the mean; *asterisk* indicates significant result in 2-tailed *t*-test (*$P < .05$).

Results

Spatial Sensitivity

Compared with healthy age-matched controls, patients' spatial (static) contrast sensitivity was normal in the low and high spatial-frequency range, but decreased in the medium spatial-frequency range (Fig. 2A). These findings were confirmed in a repeated-measures ANOVA yielding a significant disease × spatial-frequency interaction, $F(4,84) = 2.51$, $P = .04$, and main effect of spatial frequency, $F(4,88) = 24.7$, $P < .001$. The main effect of disease was not significant, $F(1,22) = 3.41$, $P = .08$, indicating that patients' performance is overall comparable to contrast sensitivity in healthy controls, despite significant impairments at medium spatial frequencies at 2 cyc/deg (2-tailed *t*-test, $t(22) = 2.46$, $P = .02$, $d = 1.1$; 4 cyc/deg: $t(22) = 1.74$, $P = .09$, $d = .53$; see Fig. 2A).

We next assessed whether the observed differences in contrast sensitivity between groups might be related to impairments in fixational stability in patients. Across all spatial frequencies, patients showed a higher number (53% frequency increase) of small microsaccades (<0.5° amplitude), even though the main effect of disease on microsaccade rate did not reach significance $F(1,22) = 3.15$, $P = .09$ (Fig. 3A, left). Of these microsaccades, 9.9% were classified as SWJ. This number did not differ between patients (10.3%) and controls (9.5%; $F < 1$, not significant [n.s.]), indicating similarities in the occurrence of SWJ across groups (Fig. 3B). Patients also showed a higher rate of saccades (>0.5° amplitude) across all spatial frequencies (9% increase, but $F < 1$, n.s.; Fig. 3A, right); of these, 23.7% were SWJ, 27% in patients and 20.5% in controls, with no significant differences found between groups ($F(1,22) = 1.74$, $P = .20$; Fig. 3B). We next assessed trial-by-trial correlations between microsaccade rate and contrast sensitivity, because group differences were largest for microsaccades. Figure 4 shows individual observers' trial-by-trial results for each spatial frequency and reveals the strongest relation between fixational stability and perceptual performance at 2 cyc/deg (Fig. 4C), where the difference between patients' and controls' contrast sensitivity was largest.

Spatiotemporal Sensitivity

Results for spatiotemporal contrast sensitivity show expected main effects of velocity, $F(1,22) = 25.1$, $P < .001$, and spatial frequency, $F(4,88) = 64.1$, $P < .001$: Sensitivity decreases with increasing stimulus speed, and the peak of the contrast sensitivity function shifts from 4 cyc/deg for stationary stimuli (Fig. 2A) to 1 cyc/deg for dynamic stimuli (Figs. 2B, 2C), confirmed by a significant velocity × frequency interaction, $F(4,88) = 8.35$, $P < .001$. Patients' sensitivity was generally lower as compared to controls, especially for intermediate spatial frequencies, but this was not significant $F(1,22) = 2.38$, $P = .15$. These findings indicate comparable contrast sensitivity for patients and controls for dynamic stimuli.

Consistent with these results, smooth pursuit velocity did not differ significantly between patients and controls ($F(1,22) = 1.63$, $P = .23$), even though controls consistently had higher pursuit velocity than patients across stimulus speeds (Fig. 3C). Controls and patients also showed similar saccade amplitude densities ($F < 1$, n.s.) and similar expected main effects of

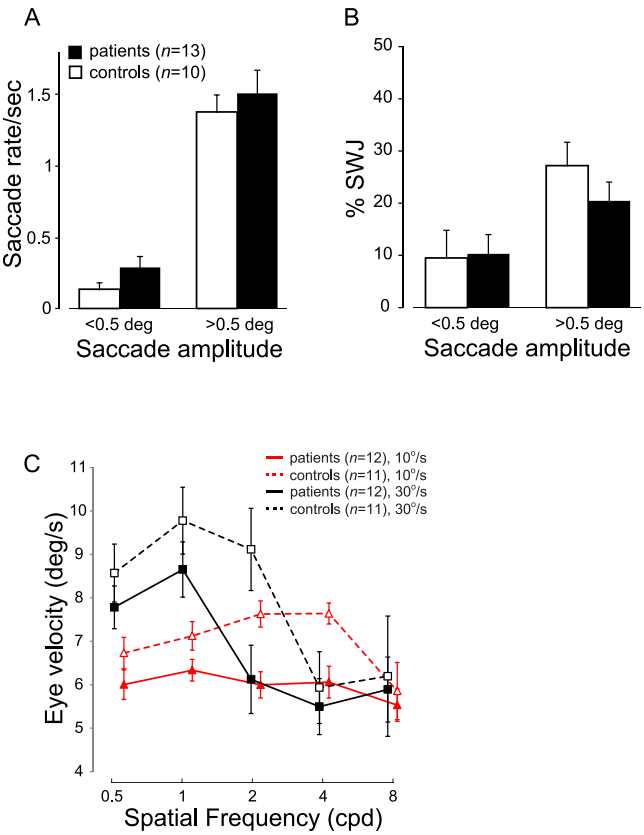

Figure 3. Eye movement stability and accuracy in static and dynamic conditions. (**A**) Saccade frequency (rate/second) for small microsaccades (<0.5° amplitude) and saccades with amplitudes > 0.5° in static trials. (**B**) Percentage of microsaccades/saccades classified as SWJ in static trials. (**C**) Mean eye velocity (°/s) across spatial frequencies for slower (*red*) and faster (*black*) stimulus speeds in dynamic trials; symbols are offset for clarity. All *errors bars* are standard errors of the mean.

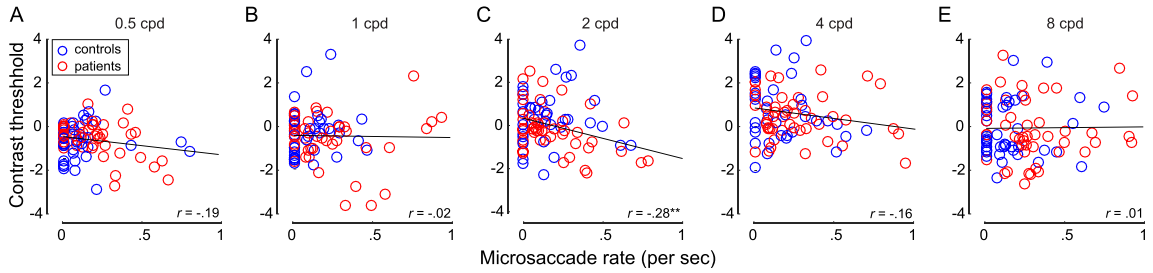

Figure 4. Trial-by-trial correlations between contrast sensitivity (threshold) and microsaccade rate across spatial frequencies. Each data point is one trial for each patient (*red*) and control (*blue*); lines are regression lines and results of correlational analyses for controls and patients (**$P < .01$). (**A**) 0.5 cyc/deg. (**B**) 1 cyc/deg. (**C**) 2 cyc/deg. (**D**) 4 cyc/deg. (**E**) 8 cyc/deg.

speed: Pursuit velocity was significantly higher ($F(1,22) = 5.0$, $P = .04$) and saccade amplitude density increased ($F(1,22) = 119.5$, $P < .001$) in response to fast as compared to slower stimuli. These differences were most pronounced in the mid spatial-frequency range, as indicated by a speed × frequency interaction (e.g., for pursuit velocity: $F(4,88) = 20.33$, $P < .001$; Fig. 3C). Taken together, these findings indicate relatively normal decoding of stimulus speed for the control of smooth pursuit eye movements in our cohort of patients.

Motion Gain

When compared to spatial contrast sensitivity, spatiotemporal contrast sensitivity was higher for low spatial frequencies and lower for high spatial frequencies. These motion gains and losses, expressed as the difference between spatiotemporal and spatial contrast sensitivities, were significantly different from zero at each spatial frequency (all $P < .001$ in Bonferroni-corrected *t*-tests) for low and high speed (Figs. 5A, 5B), with the exception of medium spatial frequencies (2 cyc/deg) at high speed for patients (Fig. 5B; $P = .82$). Importantly, similar motion gains and losses in contrast sensitivity were observed for both groups of subjects (no main effect of disease, and no significant interactions with disease, all $F < 1$), indicating that patients' ability to process visual motion information in this task is relatively unimpaired.

Contrast Sensitivity and Clinical Features

All patients were receiving L-dopa treatment at the time of testing. There was no correlation between medication dose and perceptual performance in spatial or spatiotemporal conditions, indicating that medication did not constrain contrast sensitivity. We further ruled out the potentially limiting factors age, cognitive ability (Montreal Cognitive Assessment), and disease severity (Hoehn and Yahr stage, Unified Parkinson's Disease Rating Scale score), indicating a relatively homogenous sample of mildly impaired patients.

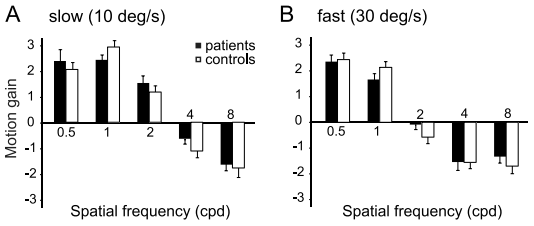

Figure 5. (**A**) Motion gain at slower speed (10°/s) across spatial frequencies. (**B**) Motion gain at faster speed (30°/s). *Errors bars* denote standard error of the mean.

Rather than considering contrast sensitivity at each spatial frequency independently, we next used ICA to see if contrast sensitivity profile components differed with respect to disease and/or velocity (Fig. 6). Figure 6A shows a spatial profile component peaking at 1 cyc/deg that is sensitive to stimulus velocity (compare left, 10°/s, and right, 30°/s) but relatively invariant to disease status (note the similarity between controls and PD patients). The mean values (blue vertical lines; see Methods) are significantly different from (located to the left or right of) the null distribution obtained from bootstrapping, implying that this profile is seen more than expected by chance at slow speeds and less than expected at fast speeds. By contrast, Figure 6B shows a spatial profile component measuring the difference between sensitivity at 8 and 4 cyc/deg (and to a lesser extent 1 cyc/deg). This component is particularly prominent for PD patients and fast stimulus speed, indicating that the performance difference between spatial frequencies at 8 and 4 cyc/deg appears to be particularly prominent in PD patients at higher stimulus velocities.

Discussion

We examined the sensitivity to stationary and moving stimuli at low contrast in early-stage PD patients and age-matched healthy controls and report three key findings. (1) Patients show reduced spatial contrast sensitivity in the intermediate spatial-frequency range. (2) Patients' and controls' spatiotemporal contrast sensitivity, as compared to spatial sensitivity, is similarly boosted at low spatial frequencies and impaired at high spatial frequencies, indicating that patients' ability to process visual motion information is relatively unimpaired in this task. (3) We observed a possible link between perceptual performance and fixational eye movement accuracy: Fixational instability—the rate of small microsaccades—is larger in patients than in controls in trials with static stimuli. Even though pursuit is overall slower in patients than in controls, this difference was not significant, consistent with preserved spatiotemporal sensitivity and motion gain in patients. The observed possible relation between eye movements and contrast sensitivity is in line with previous reports in the literature on healthy adults.[21,22] However, our study was not specifically designed to assess the dynamic interaction between perception and eye movements in response to luminance contrast. Previous studies have shown effects of luminance contrast on the quality of smooth pursuit[39] and perception of visual motion.[40] Fluctuations in luminance contrast within each trial of our study will likely have affected the quality of eye movements—both fixation and pursuit—and future studies should implement procedures to systematically vary stimulus contrast on a trial-by-trial basis to establish a causal link between contrast sensitivity and eye movements. Our study provides data on the kinematics of eye movements

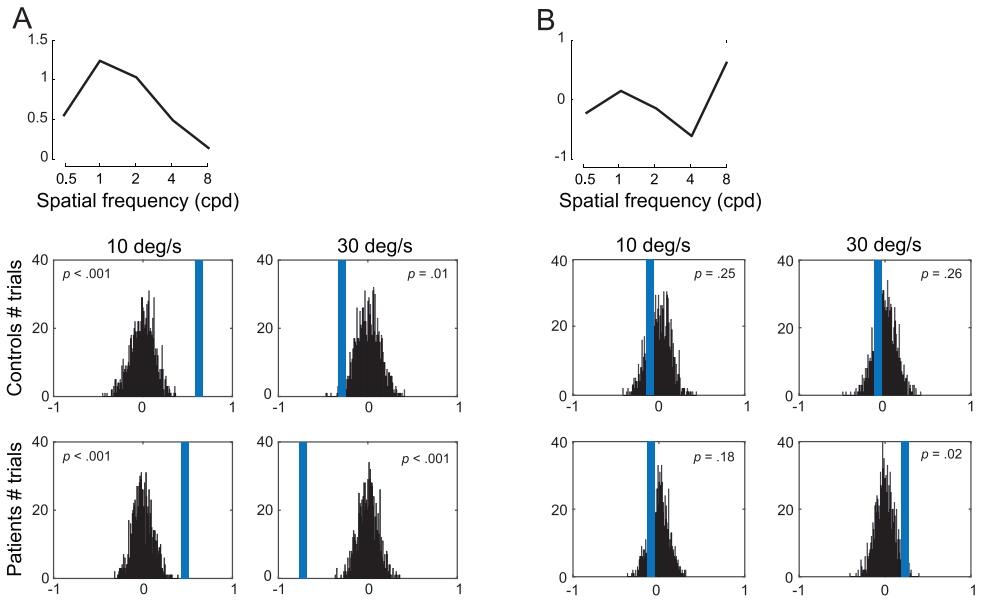

Figure 6. ICA components. (**A**) *Top*: the weighting across different levels of spatial frequency with a peak at 1 cyc/deg. *Bottom*: results of bootstrapping for slow and fast speeds and controls versus patients. Note the similarity between controls and patients. (**B**) Same as (**A**) but for a different component. Note the difference between controls and patients at fast speed.

in the context of a contrast sensitivity assessment in patients with PD and indicates a possible relation between perception and eye movements.

Previous reports on contrast sensitivity deficits in PD patients produced highly variable results, with some studies finding selective spatial contrast sensitivity impairments in the medium to high spatial frequencies,[3,4] or across a wide range of frequencies.[5,23] Heterogeneity between patient populations in terms of age, symptom severity, and medication likely contributes to the variability in results. In our study, the largest deficits were observed at spatial frequencies of 2 and 4 cyc/deg, where all subjects performed best (note the similar shape of the contrast sensitivity function in patients and controls; Fig. 2). We acknowledge that our sample sizes were small, potentially preventing us from seeing effects across the entire spatial-frequency range and from seeing differences between groups for spatiotemporal sensitivity (dynamic stimuli). However, our findings are in alignment with previous studies reporting impairments in the midfrequency range in PD patients compared with age-matched controls.[4,41] They are also congruent with results in mildly impaired patients (stages 1–2) in a study assessing contrast sensitivity across all stages of symptom severity.[5] Moreover, the finding of reduced contrast sensitivity in the midfrequency range in PD bears similarity to findings obtained in patients with autism spectrum disorder (ASD): Reduced midfrequency range static contrast sensitivity has been reported in children and adolescents[42,43] as well as adults.[44]

Many parts of the visual system have been implicated as the cause for visual deficits, such as the retina, where thinning of the inner retinal nerve fiber layer and decreased dopamine concentration seem to mirror the loss of dopaminergic neurons in the basal ganglia.[2,45,46] Pattern electroretinogram studies in PD subjects have shown significant loss at midspatial frequencies of 4 cyc/deg, corroborating our findings.[47]

With the addition of motion, both PD and control subjects improved their contrast sensitivity at low spatial frequencies. This "motion gain" was previously demonstrated in healthy subjects, who exhibited selectively increased contrast sensitivity at a spatial frequency of 1 cyc/deg with moving stimuli of up to 4.3°/s.[7] In PD subjects, one study found motion gain with stimuli between 0.8 and 12.8 cyc/deg modulated at 10 Hz (equivalent to velocities of 0.78–12.5°/s) compared to static stimuli,[48] in partial agreement with our study, where motion gain was found between 0.5 and 2 cyc/deg with velocities 10°/s and 30°/s (5–60 Hz). However, we found motion loss at spatial frequencies greater than 2 cyc/deg. This may be attributable to the much higher frequencies used in our study; for example, with spatial frequencies of 4 to 8 cyc/deg and a velocity of 10°/s and 30°/s, the stimuli were modulated at 40 to 240 Hz. Comparing PD subjects to controls, Mestre et al.[49] found that overall motion gain was significantly reduced in patients at 1 cyc/deg and 2 to 4 Hz (equivalent to 2–4°/s). These findings are not in line with our study, which showed preserved motion gains in Parkinson's subjects over the same spatial frequencies and velocities. Some of these inconsistencies may be explained by the ICA results (Fig. 6). The performance difference between spatial frequencies at 8 and 4 cyc/deg (and to a lesser extent 1 cyc/deg) appears to be particularly prominent in PD subjects at higher stimulus velocities. Relatively intact spatiotemporal contrast sensitivity and preserved ability to benefit from motion information and to decode stimulus speed for pursuit eye movements point to intact processing in brain areas along the magnocellular pathway, most notably the mediotemporal cortical area (MT), responsible for visual motion processing.[50]

In the context of interpreting our motion gain results, it should be mentioned that the adjustment method in general might lead to an overestimation of contrast thresholds, especially with moving stimuli. Because our observers were instructed to maintain smooth pursuit tracking, they might not have reduced the contrast to the same extent as they did in fixation trials, where there is no uncertainty about the target's position. However, smooth pursuit eye movements can be maintained, for brief periods, even in the absence of a visual stimulus; they can be driven by velocity memory and cognitive expectation.[51,52] Given that our target motion was predictable, and that predictive eye movement control has been found to be relatively preserved in patients with PD,[53] we assume that

our method allowed observers to adjust contrast below threshold and still maintain tracking.

When comparing our findings to the literature, it is important to note that we tested a small and relatively high-functioning cohort of patients with no cognitive impairment and mild to moderate motor symptoms (Hoehn and Yahr stage between 1 and 2); all patients were on dopaminergic medications. Whereas eye movement deficits are highly characteristic of PD and other Parkinsonian disorders[17,19,21–28] and neurodegenerative disorders in general,[18,20] we observed impairments in fixational stability only, and these were limited to the rate of small microsaccades. We did not observe a significant increase in the proportion of saccades classified as SWJ. Notably, more severe deficits in contrast sensitivity and eye movement control are usually found with more advanced disease.[5] Decreased contrast sensitivity at 6 and 12 cyc/deg—that is, in the high-frequency range that is found to be spared in may studies, including ours—has been observed with symptom progression, when patients' performance in static tasks was retested 20 months after the first testing.[54] Sensitive longitudinal eye movement assessments, concurrent with perceptual testing, could reveal the time course of oculomotor impairments in PD and clarify the role of microsaccades and saccadic intrusions such as SWJ in known perceptual impairments in these patients. Our findings indicate that frequent small-amplitude microsaccades occur even at the earliest stage of the disease, while smooth pursuit is still relatively unimpaired.[53] Dopaminergic medications have been found to have little effect on contrast sensitivity with moving stimuli.[49] They have, however, been found to improve ocular motility, which may explain preserved pursuit in our patients.[22] To conclude, our results suggest that specific spatiotemporal contrast sensitivity profiles may represent an easily measurable metric as a component of a broader combined biometric[55] for nonmotor features observed in PD. The simultaneous assessment of eye movements and perceptual contrast sensitivity in PD patients can enhance our understanding of the mechanisms underlying sensorimotor deficits in these patients.

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