Pervasive Ocular Tremor in Patients With Parkinson Disease

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Objective: To further assess oculomotor control of patients with Parkinson disease (PD) during fixation and with movement.

Design: Case-control study.

Setting: A Parkinson disease research, education, and clinical center.

Patients: One hundred twelve patients with PD, including 18 de novo untreated patients, and 60 age-matched controls.

Intervention: Modern, precise eye tracking technology was used to assess oculomotor parameters. Oculomotor function was compared between groups during fixation and while tracking a randomly displaced target on a PC monitor.

Main Outcome Measures: Fixation stability and saccadic parameters.

Results: All patients with PD and 2 of 60 control subjects showed oscillatory fixation instability (ocular tremor), with an average fundamental frequency of 5.7 Hz and average magnitude of 0.27°. Saccadic parameters and occurrences of square wave jerks did not differ between subjects with PD and controls. The amplitude and frequency of fixation instability did not correlate with disease duration, clinical Unified Parkinson's Disease Rating Scale scores, or dopa-equivalent dosing. No differences in oculomotor parameters were found between medicated and unmedicated patients with PD.

Conclusions: All patients with PD exhibited persistent ocular tremor that prevented stability during fixation. The pervasiveness and specificity of this feature suggest that modern, precise oculomotor testing could provide a valuable early physiological biomarker for diagnosing PD.


Previous studies in patients with Parkinson disease (PD) have shown that the neurodegenerative changes in the brain affect the oculomotor control system, as well as the appendicular motor control. Although a number of studies describe various oculomotor abnormalities in subjects with PD, conflicts about the specific deficits remain. Some investigators have suggested that the principle abnormalities are reduced velocity and increased duration of saccades, while others have suggested that the frequency of square wave jerks (brief, conjugate, random movements away from the target that interrupt stable fixations) are increased. Deficits in ocular fixation, during which we critically fixate on objects to acquire information about the world around us, have been subjectively described in PD but have not been systematically quantified. In the present study, we used modern eye tracking equipment to further investigate oculomotor control in subjects with PD while fixating and during saccades to a randomly step-displaced target.

Methods

For this study, 112 patients with PD (mean age, 66.2 years; SD, 6.8 years) and 60 age-matched controls (mean age, 65.3 years; SD, 7.4 years) were recruited from the Southeast Parkinson’s Disease Research, Education, and Clinical Center at the Richmond Veterans Affairs Medical Center. All patients were screened by a movement disorder specialist (M.S.B.) and considered to have PD based on the criterion of having at least 2 of 3 cardinal signs (ie, rest tremor, rigidity, and akinesia/bradykinesia) without features suggestive of secondary forms of parkinsonism. Ninety-four of the patients had shown a clear therapeutic benefit to dopaminergic medications. 18 patients were de novo untreated. The mean duration of symptoms was...
Fixation stability

While fixing on a target, all 112 patients with PD showed persistent instability (Figure 1B-D) characterized by oscillatory behavior with a mean fundamental frequency of 5.7 Hz (SD, 1.5), ranging from 4.3 to 10.9 Hz. In contrast, 38 of the 60 control subjects (96.6%) showed highly stable fixations characterized by minimal drift of gaze and no oscillatory behavior (Figure 1A). Two control subjects (3.3%) exhibited oscillatory fixation instability similar to that in subjects with PD. The mean amplitude of the instability in subjects with PD was 0.27° (SD, 0.25) horizontally and 0.33° (SD, 0.28) vertically, ranging

Table. Subject Enrollment

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Medicated Patients with PD (n = 94)</th>
<th>Unmedicated Patients with PD (n = 18)</th>
<th>Controls (n = 60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean (SD)</td>
<td>62.6 (11.2)</td>
<td>65.8 (13.5)</td>
<td>65.3 (7.4)</td>
</tr>
<tr>
<td>Duration of symptoms, y, mean (SD)</td>
<td>6.1 (4.0)</td>
<td>1.4 (0.9)</td>
<td>NA</td>
</tr>
<tr>
<td>UPDRS part III examination score, mean (SD)</td>
<td>17.1 (7.2)</td>
<td>17.9 (4.8)</td>
<td>NA</td>
</tr>
<tr>
<td>UPDRS tremor subscore, mean (SD)</td>
<td>2.4 (1.4)</td>
<td>1.8 (1.4)</td>
<td>NA</td>
</tr>
<tr>
<td>Levodopa only, No.</td>
<td>77</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Levodopa and entacapone, No.</td>
<td>2</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Levodopa and ropinirole, No.</td>
<td>8</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Levodopa and amantadine, No.</td>
<td>7</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>RMS velocity (during fixation), mean (SD)</td>
<td>5.32 (2.14)</td>
<td>4.63 (1.11)</td>
<td>3.18 (0.46)</td>
</tr>
</tbody>
</table>

Abbreviations: NA, not applicable; PD, Parkinson disease; RMS, root mean square; UPDRS, Unified Parkinson’s Disease Rating Scale.

a Tested while taking their normally prescribed medications.
b Ropinirole hydrochloride.
c Amantadine hydrochloride.
d P < .001 compared with controls (with no significant differences between medicated and unmedicated patients with PD).

5.5 years (SD, 4.3) with a mean Unified Parkinson’s Disease Rating Scale part III examination score of 12.1 (SD, 9.6). The mean tremor subscore of the Unified Parkinson’s Disease Rating Scale was 2.2 (SD, 1.4). All medicated patients were tested while taking their normally prescribed medications, with a mean dopamine equivalent of 87.2.3 mg (SD, 10.1). Patients with superimposed neurologic or ophthalmic conditions (eg, glaucoma or macular degeneration) were excluded. Control subjects were recruited among spouses, relatives, and friends and were screened and similarly excluded if they had any significant neurological or ophthalmic conditions. The study summarized study subject characteristics. Both patients and control subjects were questioned as to whether they had any subjective visual complaints, such as blurred vision, double vision, or floaters. While subjects with ophthalmic conditions were excluded from the study, subjective visual complaints were not criteria for exclusion. The study was approved by the institutional review board at the McGuire Veterans Affairs Hospital and written informed consent was obtained from all subjects prior to testing.

Using a video-based binocular eye tracker (Eyelink II; SR Research Ltd), horizontal and vertical gaze data were collected from each eye at 500 Hz. The system uses infrared lights and cameras placed just below each eye, beyond the field of vision, to track the center of the dark pupils. The system rests on the subject’s head, allows free unrestricted head movement, is quick to set up and calibrate, and allows patients to wear their normal corrective prescription lenses. To exclude a potential contribution of head movements to the perceived ocular instability in subjects with PD, head position was simultaneously recorded in 62 subjects with PD and 31 control subjects by means of a 6−df magnetic tracking system (trakSTAR; Ascension Technology Corp). The magnetic tracking system was set to sample at 125 Hz and was integrated and synchronized with the eye tracker. The spatial resolution of the trakSTAR system is 0.5 mm in terms of position and 0.1° in terms of orientation.

RESULTS

Fixation stability

Stimuli were presented in a darkened room on a 26-in LCD monitor placed 75 cm from the subject’s eyes, covering ±20° horizontally and ±13° vertically. For each subject, the height of the display was adjusted so that the center of the screen corresponded to the center of the pupillary plane. Calibration and validation of the eye tracker was performed on a 9-point grid, immediately before recording commenced. Data were then collected while subjects followed approximately 100 random simple step changes in target position along the horizontal and vertical cardinal axes. The target stimulus was a white annulus sized to occupy 0.5° of visual angle, with a high-contrast center point of 0.1° presented on a black background. Both the timing and amplitude of step displacements were random and unpredictable. Subjects were encouraged to close their eyes and rest between each recording to prevent fatigue.

Data were analyzed offline by a researcher blinded to the patient’s diagnosis, using an interactive custom-written plotting program (P.A.W.). Fixations were analyzed for duration, number of square wave jerks, and stability. In cases of fixation instability, the data were subjected to a fast Fourier transform, and rhythmicity or tremor was assessed and a fundamental frequency was determined. To further quantify the fixation instability, the root mean square (RMS) of the velocity was computed during each fixation period. This measure accounts for the movement in all directions and permits quantification of the variability of the instability.

Saccades were analyzed for duration, peak velocity, acceleration, amplitude, and accuracy. Saccadic beginning and end points were determined by a velocity threshold set at 20°/s, and saccadic velocity was calculated by way of a 2-point central difference. Additionally, the main sequence, a well-established method originally described by Bahill and colleagues, was used to examine the relationship between the amplitude of a saccade and its duration or peak velocity. In the occasional more extreme cases of fixation instability, saccadic start and end points were judged subjectively by the investigator.

All statistical analyses was conducted using SPSS Statistics version 17.0 (IBM SPSS). For statistical analyses, a was set to .05. Data were assessed for normality using the Shapiro-Wilk test. Parameters that were not normally distributed (ie, Shapiro-Wilk P value <.05) were then log-transformed and confirmed to be log-normal distributions, and analyses were run on these values. Independent-sample, unpaired, 2-tailed t tests were conducted to assess for differences between medicated, unmedicated, and control sample groups. The Levene test for the equality of variances was calculated, and if the significance was found to be less than .05, equal variances were not assumed. In the later instance, a Welch t test was used to compare the means, which has the ability to compensate for samples of unequal variance.

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Figure 1. Normal oculomotor behavior contrasted with tremulous fixations in patients with Parkinson disease (PD). A, Recordings from a control subject demonstrate stable fixations. B-D, In distinction, in representative medicated (B and C) and unmedicated (D) patients with PD, fixations are unstable and dominated by ocular tremor. Black circles represent horizontal eye movements, with positive values indicating rightward eye movements, while red triangles indicate rotational head movement along the azimuth.
from 0.14° to 1.63°. The vertical component of the instability was of greater magnitude than the horizontal component in 92 of the 112 subjects (82.1%). In 71 subjects (63.3%), the maximum amplitude of the instability at times reached the 0.5° estimated threshold for obscuring foveal vision.1 The amplitude of instability regularly fluctuated and was not influenced by the gaze angle. In contrast to the amplitude, the fundamental frequency for each subject never varied by more than 1 Hz. All oscillatory eye movements were conjugate in nature, with the phase locked in both eyes. Additionally, the phase of the ocular tremor remained stable over the recordings, not resetting or shifting with saccades, blinks, or other eye movements. Magnetic head tracking in a subset of patients affirmed that head movements did not contribute to the ocular instability findings (Figure 1). Small, brief periods of translational head movements were observed when a patient shifted in the chair, but no tremulous head activity was found in any of the tested patients.

As a measure of the fixation instability, the mean RMS velocity during fixation was 3.11°/s (SD, 0.26) in the PD group compared with 1.80°/s (SD, 0.25) in the control group (P < .001) (Figure 2A). The absolute mean velocity (B) of the eye during fixation was 5.72°/s (SD, 3.01) in the PD group compared with 3.07°/s (SD, 0.41) in the control group. As another means of displaying the magnitude of the ocular instability,15 Figure 3 shows a 2-dimensional plot of fixation points at the origin, highlighting the comparatively much larger range of movements and variability during fixation in the medicated PD group. None of the measured fixation parameters correlated with Unified Parkinson’s Disease Rating Scale part III examination scores, tremor subscores, or disease duration. Additionally, there were no differences found between medicated vs nonmedicated patients in terms of fundamental frequency (P = .82), magnitude (P = .55), or RMS velocity (P = .71) of ocular tremor. The mean number of square wave jerks did not differ between the PD (11.2 per minute; SD, 9.4) and control (12.6 per minute; SD, 8.5) groups (P = .59).

**Saccadic Parameters**

Saccadic latency to step-displaced random targets did not differ between the PD (mean, 237.4 milliseconds; SD, 39.8) and control (mean, 232.5 milliseconds; SD, 33.2) groups (P = .78). Saccadic amplitude, velocity, and duration also did not differ between the PD and control groups. For each group, similar exponent values were found for the main sequence duration equation (n for subjects with PD = 0.31 and for controls = 0.33) and peak velocity (C for subjects with PD = 11.2 and for controls = 12.6). In each group, the main sequence equations showed a comparable exponential rise to a maximum value. Also, for both groups, the product of saccadic duration and peak velocity showed a comparable linear relationship. Figure 4 illustrates data on more than 14,000 saccades of controls and medicated subjects with PD and shows no statistical difference of the slope of regression lines for peak velocity times duration vs amplitude between the 2 groups (z = 0.554).16

**Comment**

The major finding of the present study was that using modern eye movement tracking, oscillatory fixation instability was universally seen in a large cohort of 112 patients with PD. Although fixation instability had been subjectively described in other studies,10,11 its pervasiveness had not been previously recognized nor had it been systematically quantified. Duval and Beuter1 previously described findings of ocular tremor in PD that did not correlate with appendicular rest tremor. However, they limited their investigation to 5 cases and did not study the ocular tremor in detail. Further, they reported monocular oscillations in 2 of the subjects, which we never observed in our large cohort. To the best of our knowledge, our study is the first to thoroughly describe fixation instability in a large cohort of patients with PD. In contrast to our study, prior investigators chiefly fo-
cused on the disruption of fixations by square wave jerks or saccadic intrusions in subjects with PD while reporting on the duration and mean displacement of the fixations. The fact that this behavior was universally observed in every tested patient with PD, including unmedicated patients, suggests that ocular tremor is a function of the disease process and not induced by medication. The lack of head instability in the subset of patients undergoing head monitoring affirms that perceived ocular instability is not attributable to head-related movements nor is it compensatory in nature.

The fixation instability in PD to an extent resembles that of pendular nystagmus but with notable differences. Although the fundamental frequency of the waveform and the consistency of the fundamental frequency in each patient are consistent with that of pendular nystagmus, the complexity and smaller magnitude of the waveforms in PD differ substantially from that generally characteristic of pendular nystagmus. Pendular nystagmus is most typically purely sinusoidal, whereas the instability in PD appears more chaotic with multiple sinusoidal frequency components. The amplitude of the waveform in pendular nystagmus is typically an order of magnitude larger than that in PD. Additionally, while the oscillations in pendular nystagmus are produced by a neural integrator that resets the phase with saccades, the phase of the oscillations in PD is not reset by a saccade. Largely on these bases, we feel that the oscillations in PD do not represent pendular nystagmus and instead propose that "ocular tremor" appropriately exemplifies the fixation instability in PD. Moreover, pendular nystagmus is typically associated with disorders of central myelin, spinocerebellar degeneration, and visual loss, none of which are associated with PD. Future studies will be required to determine whether the ocular and appendicular tremors in PD originate from similar or different pathological loci.

Among 60 control subjects, 58 (96.6%) showed very stable fixations. The 2 controls with abnormal fixations, corresponding with the 2 outliers in the RMS velocity box plot in Figure 2, exhibited oscillatory fixation instability indistinguishable from that in patients with PD. When their eye movements were initially recorded, neither of the 2 subjects noted parkinsonian symptoms or showed objective parkinsonian signs. However, both subjects have been followed up at least yearly and 1 began to manifest parkinsonian features, including unilateral rest tremor and abnormal finger tapping, at the 2-year follow-up examination.

In contradiction to prior reports, patients showed no differences in frequency of square wave jerks compared with control subjects. Although Rascol and colleagues suggested that 15% of their patients showed an increased frequency, their criterion of 10 square wave jerks per minute approximates the mean occurrence observed in both our control subjects and subjects with PD.

![Figure 3. Fixation variability for comparison between the control and Parkinson disease (PD) groups. The illustrated data consist of all sample points from 1 randomly selected fixation per subject (n = 94 fixations in medicated patients with PD and 45 control fixations), located at the origin, and with duration of at least 250 milliseconds. Note the major ocular fixation instability in patients with PD compared with the stable clustering of the controls.](image-url)
Hikosaka and Wurtz\textsuperscript{22} demonstrated changes in the firing pattern of the substantia nigra pars reticulata in response to internally driven, self-paced saccades vs externally driven reactionary saccades. Presently, all measured saccadic parameters, including latency, peak velocity, duration, and accuracy, did not differ between subjects with PD and controls for saccades made in response to randomly step-displaced targets. Additionally, saccadic measures were equivalent between the treated and untreated patient groups. Although we would expect to see saccadic abnormalities in self-paced or memory-guided saccades in PD,\textsuperscript{4,7,9,23,24} we did not expect to see differences in reflexive, externally driven saccades.\textsuperscript{5,21,22,25} Our data are consistent with these findings previously described by others.\textsuperscript{26,27}

We acknowledge limitations of the current study. First, because all treated patients were receiving levodopa therapy and a small proportion were taking additional parkinsonian medications, the extent to which individual medications may have influenced the present findings cannot be ascertained. Second, because we did not perform a formal objective test of visual acuity, we cannot directly correlate the extent of fixation instability with actual visual function. Additionally, although we investigated a saccadic task that cannot differentiate subjects with PD from controls, our findings from a large cohort of patients affirm that reflexive saccades remain universally normal in PD. Since reflexive saccades, as well as square wave jerks, are regularly abnormal in other movement disorders,\textsuperscript{1,2,7} these features could potentially serve as a valuable means to differentiate PD from other conditions.

In summary, we have established that fixation instability is a pervasive feature in patients with PD. During fixations, the eyes of patients with PD constantly rhythmically move at an average frequency of 5.7 Hz, in small-amplitude, complex oscillations. Because the fixation instability was present in all 112 tested patients (both medicated and de novo) and was evident in 1 subject with apparently presymptomatic PD and in only 1 other control subject, precise oculomotor testing could serve as a valuable physiological biomarker for diagnosing PD at an early stage.

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