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A case report on fixation instability in Parkinson's disease with bilateral deep brain stimulation implants

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Abstract

We report on fixation instabilities in a patient diagnosed with Parkinson's disease (PD). This patient underwent deep brain stimulation (DBS) surgery bilaterally in the vicinity of the subthalamic nuclei (STN). Examination of the eye movements of this patient revealed marked fixation instability compared with a healthy age matched control. The eye movements occurring during fixation differed from other reports of fixation instabilities in that they interrupted fixation for only brief durations. These interruptive saccades (IS) had saccade-like amplitude velocity relationships. The frequency of these IS was higher in the patient with PD than in the healthy age matched control. Furthermore, the frequency of the IS in the patient reduced toward control with application of bilateral DBS in the vicinity of the STN. From our observations we conclude that fixation ability may be altered in PD and improved with DBS.

Oculomotor abnormalities are well documented in Parkinson's disease (PD).[1-3] Oculomotor abnormalities include altered rapid eye movements, or saccades, as well as altered smooth pursuit tracking eye movements.[1 4] Whether patients with PD have deficits in the fixation system is less clear. For example, some report an increased number of square wave jerks (SWJ) in PD[1] whereas others demonstrate no difference between patients and healthy control subjects.[2 5] SWJ are random involuntary saccadic eye movements that move the eye horizontally away from a fixation point followed by a corrective saccade approximately 200-300 ms, a normal saccade latency, later.[6-8] SWJ occur with a frequency of less than 2/s.[6 8] Of course, involuntary eye movements are a normal aspect of fixation and these movements include (1) microsaccades, characterised by small amplitude and low frequency rapid eye movements away from fixation (0.1-0.2°, 1-2/s),[9 10] (2) saccadic intrusions which have amplitudes 3-4 times greater than microsaccades and occur in lower frequency (0.97 (±0.56)°, 7.0 (±11.4)/min)[11] and (3) saccadic oscillations, or opsoclonus, which are high frequency (10-15/s) involuntary disruptions of fixation that lack an intersaccadic interval and have variable amplitudes depending on the aetiology (0.1-20.0°).[8]

In light of the known disturbances in the oculomotor system of basal ganglia (BG) diseased patients, and the literature showing that the non-human primate BG plays a role in eye movements,[12 13] we describe here a fixation abnormality observed in a patient with PD that

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was minimised by deep brain stimulation (DBS) therapy. The present report describes high frequency and low amplitude interruptive eye movements measured with and without DBS in the vicinity of the subthalamic nuclei (STN) in a patient who was diagnosed with PD. We compared these data with fixation ability measured in a healthy age matched control during a 1000 ms fixation period.

MATERIALS AND METHODS

Subjects and behaviour

Fixation instabilities were measured in a 62-year-old patient diagnosed with PD (at age 54 years) who underwent DBS surgery ~6 months prior to this study. By history, and prior to DBS surgery, the patient responded well to levodopa therapy but experienced a marked wearing off effect. On neurological examination while on anti-Parkinson medications, the patient had no cogwheel muscle tone, was able to arise with difficulty, no involuntary movements, and a grade 4 resting tremor in the right upper extremity and grade 3 in the left upper extremity. There was a grade 2 postural tremor in the right upper extremity and no action tremor. The third, fourth and sixth cranial nerve examination showed full conjugate extraocular eye movements with good vertical gaze. There was mask-like facies. Finger-to-nose test was performed without ataxia or tremor. Finger tapping showed slowed rate, regular rhythm and diminished amplitude. Reflexes were 1+ and symmetrical at the biceps, triceps, knees and ankles. The plantar response was down-going bilaterally. The patient stood flexed. There was no retropulsion or loss of balance on the pull test. He initiated his gait slowly with short step lengths, without arm swing on the right but without ataxia. The patient met the UK Brain Bank Criteria for probable idiopathic PD.[14]

In 1999, the patient underwent a fluorodopa PET scan that demonstrated classic PD with decreased uptake greater in the putamen than in the caudate. The reduced uptake was greater in the right putamen consistent with his right-sided stage 1 disease. The patient suffered from resting tremor and rigidity in his right limbs. The patient's tremor responded well initially to levodopa, but by 2002 he had developed refractory dyskinesia and on/off symptoms. The patient did not suffer from cognitive impairment. In 2002, implants were placed bilaterally targeting the STN and stimulation parameters were set at contact 3(-)/case(+), 3.2 V, 145 Hz, 90 μs pulse width (right implant) and contact 3(-)/case(+), 3.5 V, 145 Hz, 90 μs pulse width (left implant). Postoperatively the optimal stimulation parameters were, on the left side, contact 0 (+), contact 1 (off), contact 2 (-) and contact 3 (-), case (off). Voltage was 3.5 V, pulse width was 90 μS and frequency was 130 Hz. For the right side, the settings were, contact 0 (off), contact 1 (off), contact 2 (off), contact 3 (-) and case (+). Voltage was 3.5 V, pulse width was 90 μS and frequency was 130 Hz.

After the implant surgery, the scores from part III of the Unified Parkinson Disease Rating Scale (UPDRS) for right hand tremor were 3, finger tapping 3 and hand opening 3, and muscle tone in the upper extremity was 3. In the DBS on (settings indicated above) and drug minimal state, the right hand tremor was 0.5, finger tapping 2 and hand opening 2, and muscle tone in the upper extremity was 1.5. The left hand tremor was 3.5, finger tapping 2.5 and hand opening 2.5, and the muscle tone in the upper extremity was 3.5. In the DBS on (settings indicated above) and drug minimal state, the left hand tremor was 0, finger tapping 1.5 and hand opening 1.5, and muscle tone in the upper extremity was 1.5.

Surgical methods were carried out as previously published.[15] Electrodes (model 3389; Medtronic, Inc, Minneapolis, USA) were placed bilaterally targeting the STN. As tobacco smoking increases oculomotor instabilities,[16] the patient and control subject selected for this study were both non-smokers. One hour before the study, the patient took his daily medications (Sinemet 50/200 CR tablets one orally three times a day; 10 mg Requip). Scores on part III of

the UPDRS were obtained after the surgical implants but not immediately prior to the data collection and a postoperative MRI was not available for this patient. A 58-year-old healthy control also participated in this study. This study was approved by the University of Wisconsin-Madison Institutional Review Board (IRB) and informed consent was obtained from both subjects.

The subjects sat in a chair with their heads stabilised using a Velcro head band and custom chin rest. Subjects performed a task in which a visual spot appeared in the centre of a monitor located 50 cm in front of the subject. Subjects remained fixating for a random interval (1000-1500 ms). Then, a second spot appeared in the periphery and after another delay the fixation point was removed indicating to the subject they should make a saccade to the peripherally located stimulus. The patient with PD performed this task under two separate conditions, first during bilateral DBS and second with both stimulators off.

Data acquisition and analysis

We used a real time experimental data acquisition and visual stimulus generation system (Tempo/VideoSync; Reflective Computing, St Louis, Missouri, USA), as described previously.[17] Vertical and horizontal eye movements were recorded using a non-invasive infrared camera and a computer-based image processing system (iViewX, SensoMotoric Instruments, Needham, MA). The infrared camera was a dedicated dark pupil system that created high contrast between the iris and the pupil allowing for a precise measurement of pupil location through iViewX image analysis software. Analogue signals corresponding to horizontal and vertical pupil position were filtered (eight pole Bessel 3 dB, 180 Hz) to prevent aliasing, digitised at 16 bit resolution, sampled at 1 kHz and stored for off-line analysis. The characteristics of eye movements were measured using an interactive computer program (Dex; NEI, Bethesda, Maryland, USA). Fixation instabilities were detected using velocity (20°/s), acceleration (10 000°/s^2) and amplitude (>0.4°) criteria. Fixation instabilities meeting the criteria were extracted from each trial during the 1000 ms fixation period prior to target onset. The accuracy of the algorithm was verified by the experimenter. Radial amplitude and radial velocity were calculated: $r = \sqrt{(v^2+h^2)}$, where r is the radial amplitude or velocity, v is the vertical amplitude or velocity and h is the horizontal amplitude or velocity. Statistical analysis was carried out and plots were generated using Matlab (MathWorks, Inc., Natick, Massachusetts, USA).

RESULTS

Horizontal and vertical position traces measured from a healthy control and a PD patient with and without stimulation in the vicinity of the STN during a saccade task are shown in fig 1. Initially the fixation point appeared and the subjects made saccades to acquire the fixation point, after which the subjects remained fixating until the fixation point turned off (fig 1A). To demonstrate fixation stability, pupil position traces are enlarged for the 1000 ms fixation period prior to target onset (fig 1B-D). Vertical and horizontal position traces of the healthy control exhibited normal fixation and had normal fixational eye movements which included microsaccades and slow wave drifts,[18] during the 1000 ms fixation period (fig 1B). In contrast, position traces from the patient with PD during no stimulation (Stim-off) showed periods of fixation disrupted by interruptive eye movements (fig 1C). Moreover, the movements appeared larger for vertical position (top trace) than the horizontal-position (bottom trace). To determine whether alterations in basal ganglia (BG) function were involved in these eye movement disturbances, we collected the same data while the DBS stimulators were active (Stim-on). In this condition, the frequency of interruptive eye movements was reduced (fig 1D).

To determine whether the interruptive eye movements in the patient with PD were saccade-like, we compared the amplitude-velocity relationship of the interruptive movements with the

amplitude-velocity relationship of saccades made by the healthy control (fig 2). To do this we generated a main sequence,[19 20] which shows the amplitude-velocity relationship of normal saccades, by computing the radial amplitude and radial velocity for saccades made by the healthy control (fig 2A; blue dots). The linear portion of the main sequence diagram, which corresponds to small amplitude saccades, was enlarged to compare the metrics of the interruptive eye movements measured in the patient with PD to normal saccade metrics (fig 2B, C). The amplitude-velocity relationship of the interruptive eye movements measured from the patient with PD (crosses) during both Stim-off (fig 2B) and Stim-on (fig 2C) conditions showed that these disruptive eye movements were indistinguishable from the control (fig 2B, C) and can therefore be characterised as saccades.

We also explored whether these interruptive eye movements, hereafter referred to as interruptive saccades (IS), differed from other small amplitude and high frequency fixation instabilities, such as saccadic oscillations and SWJ. For this, we calculated the duration of IS measured in the patient with PD. We measured the duration of IS—the time from movement onset to movement end, as distinguished from the inter-saccade interval. The mean duration of IS measured from the patient with PD was 20 (SD 23) ms. Duration of the IS reported here differed from other fixation instabilities in that the movement duration was longer than that measured for saccadic oscillations but shorter than that measured for SWJ (fig 3A). No significant difference was found between the movement duration of an IS measured from the control subject or the patient with PD during Stim-off ($p>0.01$; two sample t test). In addition, no significant difference was found in the movement duration of an IS measured during Stim-off or Stim-on conditions ($p>0.01$; two sample t test).

We quantified the frequency of IS during a 1000 ms fixation period and found that the mean number of IS per trial for the healthy control subject was 1.07 (SD 1.26) IS/trial ($n = 64$ total trials) (fig 3B). In contrast, during the Stim-off condition, the PD patient's mean number of IS per trial increased significantly from control levels ($p<0.001$; two sample t test) to 11.85 (SD 6.03) IS/trial ($n = 34$ total trials) (fig 3C). The number of IS measured for the patient with PD during bilateral stimulation in the vicinity of the STN decreased significantly ($p<0.001$; two sample t test) from Stim-off levels to 8.07 (SD 5.08) IS/trial ($n = 64$ total trials) (fig 3D). With DBS on, the frequency of IS was reduced. The frequency of IS in the patient, however, remained higher than that of the healthy subject ($p<0.001$).

Interestingly, we observed a difference in the number of vertical and horizontal IS in the patient with PD. The number of vertical IS measured during Stim-off was found to be significantly greater than the number of horizontal IS ($p<0.001$; two sample t test). We also found that the number of vertical IS measured during Stim-on was significantly greater than the number of horizontal IS ($p>0.01$; two sample t test); however, the difference between the number of vertical and horizontal IS was greater for the patient with PD during Stim-off compared with the difference seen during Stim-on.

The position trace data (fig 1) indicated that IS occurred sporadically during fixation rather than at fixed intervals like those observed for saccadic oscillations. To explore whether the IS had periodicity, fast Fourier transforms (FFT) on the eye position data were computed for the patient with PD and the control subject. The power spectra for position data were generated by plotting the discrete FFT (512 point transform) using the Cooley-Tukey algorithm, as implemented by Matlab. In agreement with our observations, the results of FFT showed no discernable power at any frequency, indicating a lack of periodicity for the IS (data not shown).

DISCUSSION

Characteristics of IS

In this study, we have reported a novel fixation instability in a patient with PD. The amplitude and velocity relationship for the interruptive eye movements described here was indistinguishable from that observed for saccades from a healthy control subject, indicating that these interruptive eye movements are saccadic. In contrast with previously published fixation instabilities (including SWJ, microsaccades, saccadic intrusions and saccadic oscillations), the IS we observed were of low amplitude (0.4-3.0°) fixation disturbances lacking an oscillating frequency and of short duration (20 (±23) ms). Although on the high end of the range, the frequency of IS measured in the patient with PD parallels reported frequencies of postural tremor in PD.[21,22] Unlike segmental tremor, however, the IS frequency was non-periodic.

We found that the frequency of vertical and horizontal IS in the patient with PD was greater than in the control. Furthermore, we found that the frequency of vertical IS was greater than the frequency of horizontal IS. This finding is consistent with other parkinsonian syndromes where vertical saccades are more affected than horizontal saccades.[2]

Effect of DBS on fixation stability

DBS has rapidly become a treatment option for patients with advanced stages of PD and those who are refractory to traditional medical therapies.[23] Several studies have demonstrated that stimulation within the vicinity of the STN in PD patients improves motor accuracy[24] and memory guided saccades.[25] However, the effect of bilateral DBS in the STN on fixation instabilities in PD patients was not reported. Unilateral pallidotomies performed on patients with PD significantly increase fixation instabilities, as measured by SWJ.[26,27] In this study, we found a novel form of fixation instability in a patient with PD, and further, we found that the fixation instability was reduced with DBS stimulation which was within the vicinity of the STN, although placement within the centre of the STN was not confirmed directly with an imaging procedure. Our observations combined with other work support the hypothesis that STN stimulation modulates the oculomotor circuit in the BG. In the non-human primate, electrophysiological reports indicate that structures of the BG, such as the substantia nigra pars reticulata,[28,29] STN[30] and the caudate nucleus[31] are involved in saccadic eye movement generation. Recent experiments show that stimulation of the substantia nigra pars reticulata influences the ability of monkeys to generate saccadic eye movements.[29] How BG circuits are involved in fixation behaviour is less well studied and represents an important area for future work. Although from our observations we conclude that fixation ability may be altered in PD and improved with DBS, future efforts should also be made to characterise IS among larger control and parkinsonian populations.

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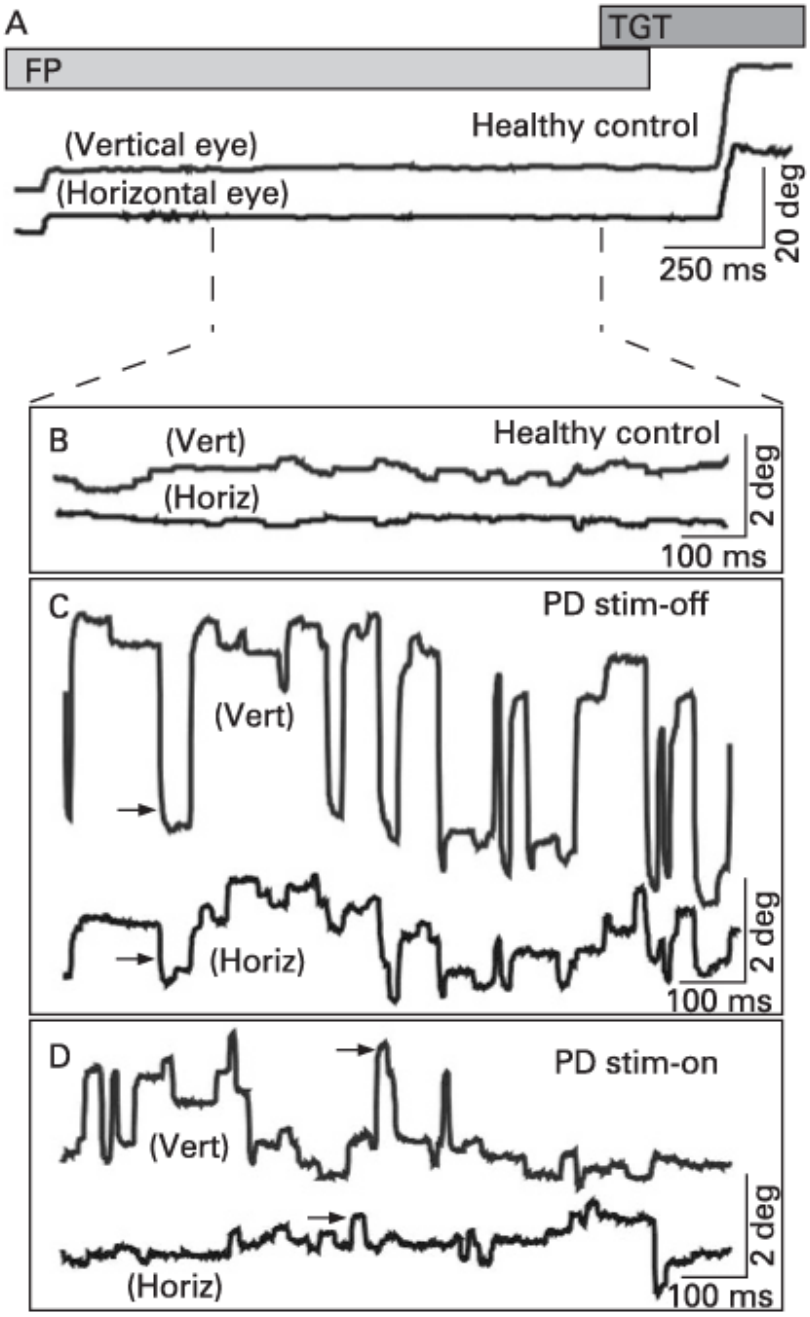

Figure 1.

Horizontal and vertical position traces measured during a saccade task. (A) Position traces for the healthy control subject during the task. (B) Expanded traces for the healthy control during the 1000 ms period of fixation prior to target onset. (C) Traces of a patient with Parkinson's disease (PD) measured during bilateral subthalamic nuclei (STN) Stim-off. (D) Position traces of the same subject in (C) during bilateral STN Stim-on. Vertical eye position traces are shown above horizontal eye position traces. Arrows point towards examples of fixation instability. FP, fixation point; Horiz, horizontal position; Stim-on, stimulation on; Stim-off, stimulation off; TGT, target point; Vert, vertical position.

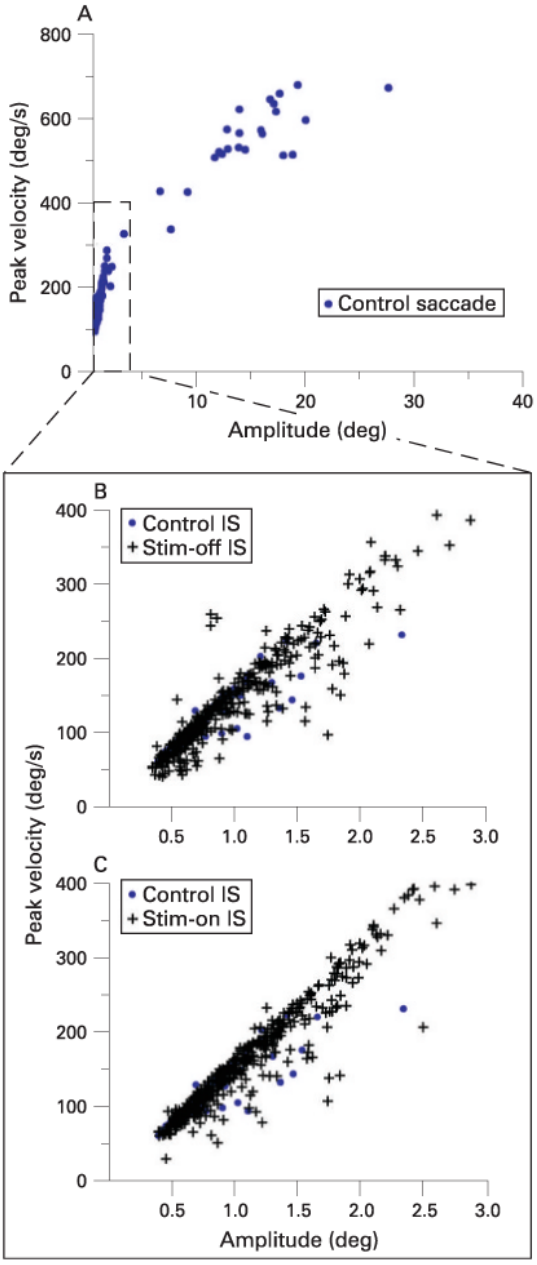

Figure 2.

Main sequence diagrams compare the characteristics of normal saccades to the fixation instabilities described in this report. (A) Radial amplitude and radial velocity of normal saccades made by the control subject from the fixation point to the target point (blue dots). The linear portion of the main sequence from (A), corresponding to small amplitudes and velocities, is enlarged to compare the radial amplitude and radial velocity of interruptive saccades (IS) made by the patient with Parkinson's disease (PD) during Stim-off (B; crosses) and during Stim-on (C; crosses) to the normal saccades made by the control (B, C; blue dots). Stim-on, stimulation on; Stim-off, stimulation off.

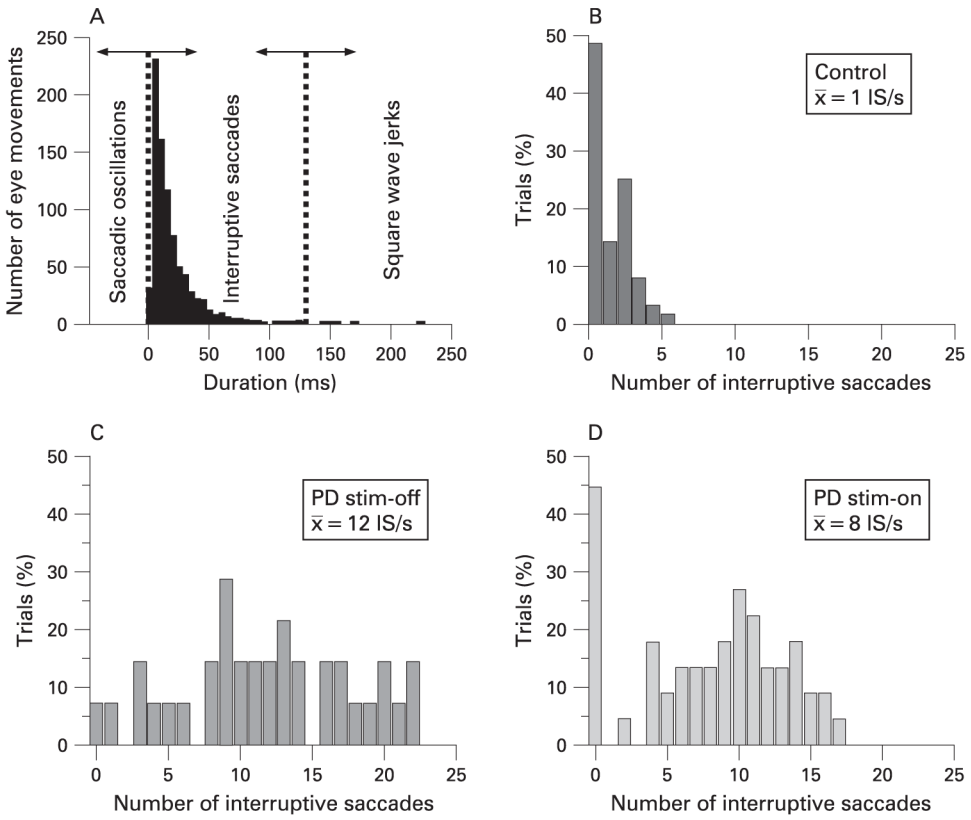

Figure 3.

Movement duration and frequency of interruptive saccades (IS) occurring during a 1000 ms period of fixation. (A) Movement duration of IS measured from the patient with PD. The duration of saccadic oscillations falls below the left vertical dotted line, the duration of SWJ falls above the right vertical dotted line and the movement duration of IS falls between the vertical dotted lines. (B) Distribution of IS measured from a healthy control (n = 64 trials). (C) Distribution of IS measured from a patient with Parkinson's disease (PD) during Stim-off (n = 34 trials). (D) Distribution of IS measured from the same patient with PD as in (C) during Stim-on (n = 64 trials). Arrows indicate intervals of duration for each type of eye movement. Stim-on, stimulation on; Stim-off, stimulation off.