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Multiple step pattern as a biomarker in Parkinson disease

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Abstract

Objective—To evaluate quantitative measures of saccades as possible biomarkers in early stages of Parkinson disease (PD) and in a population at-risk for PD.

Methods—The study sample ($n = 68$) included mildly to moderately affected PD patients, their unaffected siblings, and control individuals. All participants completed a clinical evaluation by a movement disorder neurologist. Genotyping of the G2019S mutation in the *LRKK2* gene was performed in the PD patients and their unaffected siblings. A high resolution, video-based eye tracking system was employed to record eye positions during a battery of visually guided, anti-saccadic (AS), and two memory-guided (MG) tasks. Saccade measures (latency, velocity, gain, error rate, and multiple step pattern) were quantified.

Results—PD patients and a subgroup of their unaffected siblings had an abnormally high incidence of multiple step patterns (MSP) and reduced gain of saccades as compared with controls. The abnormalities were most pronounced in the more challenging version of the MG task. For this task, the MSP measure demonstrated good sensitivity (87%) and excellent specificity (96%) in the ability to discriminate PD patients from controls. PD patients and their siblings also made more errors in the AS task.

Conclusions—Abnormalities in eye movement measures appear to be sensitive and specific measures in PD patients as well as a subset of those at-risk for PD. The inclusion of quantitative laboratory testing of saccadic movements may increase the sensitivity of the neurological examination to identify individuals who are at greater risk for PD.

Keywords

Parkinson disease; Saccade; Multiple step pattern

1. Introduction

Parkinson disease (PD) is a progressive, neurodegenerative disorder with clinical manifestations that include akinesia, resting tremor, muscular rigidity, and postural instability.

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Five genes have been identified which, when mutated, can result in PD [1]; however, mutations in four of these genes (*SNCA*, *PRKN*, *PINK1*, *DJ-1*) are relatively rare. One particular mutation in the fifth gene, the G2019S substitution in *LRRK2*, has been found in 5% of familial PD and 1% of sporadic PD [2,3].

Based on the hypothesis that there is a genetic predisposition for PD, several biomarker studies have examined unaffected family members of PD patients and suggested that some unaffected members were at increased risk for PD. Imaging studies have evaluated dopaminergic deficits as a possible biomarker in the unaffected twins of PD patients [4–6]. Olfactory [7,8] and cognitive [4,9] deficits have also been detected in unaffected relatives of PD patients. A recent study [10] reported that blink amplitude was increased in carriers of *PRKN* mutations. There is currently no clear understanding of the mechanisms underlying the observed deficits in asymptomatic relatives of PD patients. Several studies suggested that the deficits point to a preclinical stage of PD [5–7]. Nevertheless, the results of longitudinal studies of the asymptomatic relatives of PD patients were not conclusive, with some studies reporting an increased risk of developing PD [5,7], while others did not find a correlation between specific deficits, such as smell identification, and the subsequent onset of PD [8]. Other possible explanations for the observed deficits in asymptomatic relatives of PD patients include an asymptomatic carrier state or a currently unknown environmental exposure [9,10].

Saccades are rapid eye movements that redirect the fovea from one object to another. Studies of saccades in PD patients have reported a deficit of volitional saccades elicited in response to a command [11,12]. The most consistent findings were associated with a special type of saccadic hypometria [13–16]. Analysis of eye movement records demonstrated that PD patients typically reach a target eye position through a series of discrete short saccades. The latency and velocity of the series of saccades were in the normal range, while the amplitude was reduced. This deficit is often referred to as a multiple step pattern (MSP). MSP is a relatively consistent eye movement characteristic of PD patients, particularly in memory-guided tasks, and is only observed occasionally in normal individuals [17]. Several studies also noted an elevated number of errors in anti-saccade and memory-guided tasks, suggesting that PD patients have difficulty inhibiting reflexive saccades [12,18,19].

The primary goal of our study was to investigate saccadic eye movements as a possible biomarker in PD. We hypothesized that saccadic abnormalities may reflect clinical/subclinical PD and/or may be a trait that identifies individuals at elevated risk for PD. Based on this hypothesis, we speculated that normal, healthy individuals would perform saccadic tasks better than both PD patients and their asymptomatic relatives. To determine whether this was correct, we compared the performance of mildly to moderately affected PD patients, their asymptomatic relatives, and a control group on a series of saccadic tasks.

2. Methods

2.1. Subjects

PD patients, their siblings and control participants were recruited through an ongoing research study to identify PD susceptibility genes. The sample included: 1) patients diagnosed with idiopathic PD ($n = 24$); 2) reportedly healthy siblings of the PD patients ($n = 21$); and 3) reportedly healthy individuals without a family history of PD (controls, $n = 10$). An experienced movement disorder neurologist (JW) completed the Unified Parkinson Disease Rating Scale (UPDRS) [20] including the Hoehn and Yahr Scale (H&Y) and the Geriatric Depression Scale Score (GDS). The Mini Mental State Examination (MMSE) was administered to assess cognitive impairment and dementia.

Following the neurological evaluation, the neurologist selected a confidence rating to define the likelihood that the individual had PD. The rating took into account the degree to which the subject's history was suggestive of classical PD (rather than the other parkinsonisms such as multiple system atrophy, progressive supranuclear palsy, Lewy body disease, corticobasal degeneration, essential tremor, etc.). The ratings were defined as: (1) highly likely that the individual has PD (definite PD); (2) likely that the individual has PD (possible signs of PD); (3) less likely that the individual has PD (non-specific abnormalities); and (4) unlikely that the individual has PD (no abnormalities).

All PD patients received a rating of 1 (definite PD). Ten of the siblings of the PD patients received a rating of 4 (no abnormalities), ten of the siblings received a rating of 3 (non-specific abnormalities), and one sibling received a rating of 2 (possible signs of PD). All control individuals had a normal neurological examination (rating of 4). All individuals from the PD families were tested for the G2019S mutation in *LRRK2* [3].

Additionally, 13 control participants were recruited through an ongoing study of Huntington disease (HD) onset and progression. The participants recruited from the HD protocol were also examined by a movement disorder neurologist who completed the Unified Huntington Disease Rating Scale (UHDRS) [21]. All subjects were rated as having none or non-specific abnormalities (UHDRS = 0 or 1). Molecular testing of these participants was performed to confirm a normal number of CAG repeats in the huntingtin gene (both alleles ≤ 31 CAG repeats) [22]. There were no significant age or male/female ratio differences between the control participants recruited through the two different studies. Importantly, the controls in both studies were felt not to have any neurological abnormalities. Thus, the controls in both groups were classified as neurologically normal participants.

Demographic and clinical characteristics for the PD subjects, their siblings, and the controls are shown in Table 1. The PD participants were mildly to moderately affected with a mean H&Y of 2.3 ± 0.6 (range 1–3). None of the participants had additional, concurrent neurological illness, severe psychiatric disease (i.e. bipolar, schizophrenia) or a history of alcohol or drug abuse. All participants had normal or corrected visual acuity, did not have a history of eye surgery, and did not report significant eye-related complaints. 75% of the PD patients were taking medication to treat their neurological disorder; they were instructed to continue taking their medications. After explanation of the protocol, which has been approved by the IUPUI Institutional Review Board, all study participants provided written informed consent.

2.2. Ocular motor assessment

Ocular motor testing was completed during a 30-min session. The vertical and horizontal positions of the participant's eye pupils were recorded binocularly with two ultra-miniature, high-speed video cameras attached to a headband and digitized at 250 Hz for later analysis (EyelinkII, SR Research Ltd, spatial resolution <0.1 degree).

2.3. Testing procedure

The participant was seated in a darkened room, 1 m from a large white screen with a cross of target lights (light-emitting diodes, LED). The target lights were located at 0° (central LED), 10° and 20° to the right and left horizontally, and 10° up and down vertically from the central LED. The headband with video cameras was adjusted on the participant's head and the participant's head movements were restricted by a neck support. Four saccadic tasks were performed in a fixed order. Before each task, the examiner instructed the participant verbally and performed a practice demonstration to ensure that the participant understood the oral instructions correctly. Each of the four saccadic tasks consisted of 24 trials.

1. *Visually guided (VG) trial.* The participant was instructed to fix his/her gaze on the central illuminated LED (0°). The central LED was extinguished simultaneously with illumination of a peripheral LED. Timing (2–3 s) and position of the peripheral LED were randomized. The participant was instructed to visually track the target light as rapidly as possible.
2. *Anti-saccade (AS) trial.* The participant was instructed to fix their gaze on the central illuminated LED (0°). The central LED was extinguished simultaneously with illumination of a horizontal peripheral LED. The participant was instructed to look in the opposite direction of the light at an equal distance from the central LED.
3. *Single memory-guided trial (MG1).* The participant was instructed to fix their gaze on the central illuminated LED while a horizontal peripheral LED flashed for 50 ms. The participant was asked to continue to fixate on the central LED until it was switched off, which was after an additional delay of 1–2 s. Then, the participant was asked to look at the remembered position of the peripheral flash.
4. *Memory-guided saccade sequence (MG2).* This trial was similar to *MG1* except that the flashes (50 ms) occurred sequentially on three peripheral LEDs, both vertical and horizontal, and always alternated in direction. The timing of the flashes was randomized. The participant was asked to continue to fixate on the central LED until it was switched off, which was after an additional delay of 1–2 s. Then the participant was instructed to look sequentially at the three remembered positions of the flashes.

2.4. Quantitative measures of saccades

After the participant completed the testing procedure, an interactive computerized analysis [23] was carried out to quantify primary saccade measures for each task. An illustration of saccadic performance and quantified measures are shown in Fig. 1. Initially, the latency (i.e. reaction time), peak velocity (dynamic), and gain (i.e. ratio of saccade amplitude to LED amplitude) were quantified for the first saccade in each correct trial (made according to the task instruction, Fig. 1A). Then, for each participant, these measures (latency, peak velocity of the idealized 15-degree saccade by using main sequence, and gain) were averaged across similar trials. For the *VG* task, the horizontal and vertical saccades were analyzed separately. All participants made timing and directional errors in some of the *AS*, *MG1*, and *MG2* trials. Particularly in the *AS* task, the participants in some trials made the first saccade in the incorrect direction (toward the stimulus) and then looked in the opposite (correct) direction (Fig. 1B). In the *MG1* trial, a common error was for the participant to initiate the first saccade before the central light was extinguished (timing error). The other possible error in the *MG* tasks was a missed peripheral flash, i.e. the participant did not perform a saccade to the remembered position of the flash (or a sequence of saccades for the *MG2* task). The percentage of trials with errors was computed for each task as the percentage of the number of trials performed with mistakes to the total number of trials completed in the task. Latency, velocity, and gain were not calculated for subjects who made errors in more than 75% of the trials.

In the more complex *MG2* task, the percentage of trials with at least one gaze shift consisting of 3 or more saccades made in the same direction (classical “multiple step pattern”, MSP) was computed.

2.5. Statistical analysis

Analysis of covariance (ANCOVA) was employed to test for significant group (PD, sibling and control) effects on the primary study measures (latency, velocity, gain, percentage of errors, and percentage of trials with MSP); age and gender were employed as covariates. The alpha level was set to 0.05. For the measures with a significant group effect, post-hoc testing was

performed to evaluate the pair-wise differences between groups using the one-sided Dunnett test for multiple comparisons. We hypothesized that the control group would perform better than the other two groups. Specifically, we postulated that the saccades of the control group would be more accurate (higher gain and fewer errors) than the saccades of either the PD or sibling groups.

To further interpret results, Pearson correlation was computed between pairs of study measures. Logistic regression was employed to test the ability to discriminate PD patients from controls using the saccade measures providing the most significant group effects.

3. Results

3.1. Gain and percentage of trials with MSP

Analysis of covariance detected a significant group (PD, sibling, control) effect for gain and percentage of trials with MSP (%MSP) in the *MG2* task (Table 2). Post-hoc comparisons demonstrated that controls made more accurate saccades and had fewer trials with MSP than either the PD patients ($p < 0.0001$ for both measures) or siblings ($p = 0.08$ and $p = 0.02$ for % gain and %MSP, respectively). A typical record of an *MG2* trial is presented in Fig. 2. During the trial, a PD patient, sibling, and control looked sequentially at the remembered positions of the flashes. The PD patient and their sibling made several discrete saccades before reaching the memorized locations of the flashes (Fig. 2). In contrast, the control individual moved their eyes between the remembered locations in a nearly one-saccade pattern. Significant group effects were also observed for the gain of saccades in the vertical *VG*, horizontal *VG*, and in the *MG* tasks (Table 2). Post-hoc comparisons found that PD patients made less accurate saccades in both the vertical and horizontal *VG* and *MG* tasks than the controls ($p \leq 0.002$).

The %MSP and the gain of saccades were two quantitative measures of saccadic hypometria. As demonstrated by Kimmig et al. [17], the %MSP and gain were highly correlated in memory-guided tasks. In our study, we also found that the %MSP and gain were highly correlated in the *MG2* task ($r = -0.54$, $p < 0.0001$). Furthermore, gain was correlated across different tasks. That is, gain in the *MG2* task was significantly correlated with the gain in the *VG*, *AS* and *MG1* tasks across all study participants, (*VG*: $r = 0.40$, $p < 0.001$; *AS*: $r = 0.32$, $p = 0.01$; *MG1*: $r = 0.62$, $p < 0.0001$). When the correlation was examined within each study group, the PD and controls groups had significant correlation between the gain in the *MG1* and *MG2* tasks (PD: $r = 0.48$, $p = 0.02$; and Control: $r = 0.58$, $p = 0.01$). The siblings of the PD participants had marginally significant correlation between the gain in the two *MG* tasks ($r = 0.46$, $p = 0.06$).

3.2. Percentage of errors

A significant group effect was also observed for the percentage of trials in which there was an error (%errors) in the *AS*, *MG1* and *MG2* tasks (Table 2). Post-hoc comparisons demonstrated that controls made fewer errors than either the siblings or PD patients in the *AS* task (siblings vs. control, $p = 0.02$; PD vs. control, $p = 0.0001$). PD patients also made more errors in the *MG1* and *MG2* tasks as compared with controls ($p \leq 0.005$). Overall, the %error and %MSP (and gains) showed significant group effect. Contrary to the %errors and %MSP, the latency and velocity of saccades did not show significant group effects.

3.3. Discrimination between the PD and control group

Logistic regression analysis was performed to evaluate the sensitivity and specificity of the two saccadic measures (%errors in the *AS* task and %MSP in the *MG2* task) to discriminate the PD patients from controls. While %errors in the *AS* task yielded only modest sensitivity

(71%) and specificity (78%), the %MSP showed good sensitivity (87%) and excellent specificity (96%) in discriminating the PD patients from controls.

Fig. 3 illustrates the distribution of the %MSP in the three study groups. We referred to the 0–35% range as the “normal range of %MSP” because 95% of the control individuals fell within this range. Among the siblings of the PD patients, 8 showed high %MSP, outside the normal range.

3.4. Correlations between saccadic measures and UPDRS motor scores

The gain in *MG1* and *MG2* tasks correlated significantly with disease severity in the PD group, as measured by the total UPDRS motor scores ($r = -0.41$, $p < 0.05$ and $r = -0.56$, $p < 0.01$, respectively). More detailed analysis showed that the correlations were driven by three more advanced PD patients ($H\&Y = 3$). The correlation was not significant in the subgroup of mildly affected PD patients ($H\&Y = 1-2$). The correlation with the total UPDRS score was also not significant for %MSP and for % errors in the AS and MG tasks for the PD group.

3.5. LRRK2 G2019S molecular testing

Molecular testing of the PD subjects and their siblings identified the *LRRK2* G2019S mutation in three PD families (Table 3). In these three *LRRK2* G2019S mutation positive families, seven individuals completed the study; five carried the mutation and two did not. Although the number of subjects with this mutation was too small for statistical analyses of the eye movement measures, we noted that four of the 5 *LRRK2* mutation positive individuals had significant abnormalities of MSP.

4. Discussion

As described in Michell et al. [24], there is a clear clinical need for PD biomarkers to help stratify this heterogeneous disease; however, all potential biomarkers identified to date have significant limitations. Saccadic eye movements have been one of the attractive candidates for use as a potential PD biomarker since saccades show high test–retest reliability in control population, are abnormal in PD patients, and are under genetic influence [25]. A recent study investigated saccadic latency distributions as a potential biomarker of PD [26].

In our study, we used several saccadic tasks including visually guided and more complex memory-guided (*MG1* and *MG2*) and anti-saccade (*AS*) tasks. We found two kinds of saccadic deficits in PD patients: hypometria of saccades and an increased percentage of errors in volitional saccades. Saccadic hypometria was quantified as saccadic gain or as the percentage of trials with MSP (%MSP) and has been previously reported to be abnormal in both PD patients and MPTP-induced parkinsonism [27,28]. These deficits were more pronounced in *MG* tasks. In our study population, hypometria of *MG* saccades was observed in a majority of the PD patients, but was seen only rarely in controls. In particular, the %MSP showed good sensitivity (87%) and excellent specificity (96%) in discriminating PD patients from controls. The %error in the *AS* task showed only modest sensitivity (71%) and specificity (78%) in discriminating PD patients from controls. Overall, the saccadic deficits of the PD patients found in this study were in a good agreement with the results reported previously.

We report herein for the first time that similar saccadic abnormalities are also observed in some of the unaffected siblings of PD patients when they were completing the *AS* tasks and the more challenging version of the memory-guided task (*MG2*). We found abnormally high rates of MSP (and a decrease in gain of saccades) in the sample of unaffected siblings. Eight of the 21 siblings of the PD patients showed an abnormally high incidence of MSP while performing the *MG2* task. Among these 8 siblings, four had a normal neurological examination and four

had non-specific neurological abnormalities. We also observed that the asymptomatic siblings made more errors in the AS task than did the control participants.

According to a current model of neural mechanisms, the pathway from frontal cortex to the superior colliculus via the basal ganglia is involved in the control of volitional saccades, which are significantly more impaired in PD patients than controls. The dysfunction of this pathway is considered to be responsible for the increased number of errors in the AS and MG tasks. Currently there is no consensus regarding which pathways (or brain areas) are responsible for hypometria of MG saccades, although some studies have suggested the involvement of the subthalamic nucleus. Rivaud-Pechoux et al. [29] reported an improvement in the accuracy of MG saccades in eight PD patients treated by bilateral electrical stimulation of the subthalamic nucleus.

Although our current results point to the hypometria of MG saccades as a sensitive and specific measure for discriminating PD patients from controls, the potential use of this measure as a diagnostic biomarker for PD or as a biomarker for PD progression may be limited. The hypometria did not correlate with motor symptoms of early PD as measured by UPDRS motor scores and did not improve with levodopa [30]. Since the hypometria presents at higher level in apparently unaffected siblings of the PD patient, it may reflect subclinical changes or at-risk (genetic or environmental) factors. Only a longitudinal study will be able to address whether a subgroup of the unaffected siblings with this deficit will eventually develop PD. Because a high proportion of asymptomatic siblings were classified as abnormal by the measure, it appears unlikely that this deficit suggests an imminent PD diagnosis. However, it is likely that the deficit identifies a subgroup of the siblings at increased risk for PD.

Overall, our results suggest that saccadic measures may be sensitive and specific biomarkers in individuals at-risk for PD. Recent developments in eye movement recording techniques allow for accurate and non-invasive measures of oculomotor control. The results of quantitative laboratory testing may be warranted as part of the neurological evaluation to increase the sensitivity of the clinical exam and to identify a subgroup of individuals at-risk for PD.

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Fig. 1.

A and B. Records of anti-saccade trials (60-years-old male, control). Solid line showed the position of the right eye (in degrees). Dotted line showed the direction and timing of the target LED. At the beginning of the trial, the participant fixed his gaze on the central illuminated LED (0°). Square showed timing when the peripheral LED (20 degree to the right horizontally) was illuminated. Solid dot showed the beginning and star showed the end of saccade. A. The participant looked at the direction opposite to the target. The latency (time interval between peripheral LED onset and beginning of saccade), velocity (max velocity during saccade execution), and gain (ratio of saccade amplitude to the 20 degree target amplitude) were

quantified. B. The participant looked first to the target and then looked at the opposite direction, i.e. performed the trial incorrectly.

Fig. 2.

The record of a memory-guided trial (*MG2* task) for a 60-year-old female PD patient, her 59-year-old sister and an unrelated 57-year-old female control. During the trial, the participants were instructed to fixate on the central LED while three eccentric flashes (duration of each flash was 50 ms) occurred sequentially on the horizontal peripheral LEDs. The dashed lines show timing, direction and amplitude of flashes (10 degrees right, 20 degree left, and 10 degree left). Participants were instructed to continue to fixate on the central LED until it was switched off. They were then told to look sequentially at the remembered positions of the flashes. Squares mark the time when the central LED was switched off. The PD patient and the sibling made several short saccades to reach the remembered positions of the flashes. Their gaze shifts showed the characteristic multiple step patterns. In contrast, the control individual shifted their gaze in a nearly one-saccade pattern.

Fig. 3.

The histograms show the distribution of %MSP in the control, sibling, and PD groups. The *X* coordinate is %MSP; the *Y* coordinate is the proportion of participants within a given interval of %MSP. Grey bars show the proportion of participants who made less than 35% of trials with MSP. The range 0–35% was considered as the normal range of %MSP since 95% of the controls fell within this range. In contrast, most PD patients showed a higher percentage of MSP trials. Eight siblings made more than 35% of trials with MSP.

Table 1

Demographic and clinical characteristics of the three study groups.

	PD (<i>n</i> = 24)	Sibling (<i>n</i> = 21)	Control^a (<i>n</i> = 23)
Age (years) ^b	58 ± 8	53 ± 7	59 ± 9
Male-female ratio	13/11	8/13	8/15
UPDRS summed motor score ^b	28 ± 14	4 ± 3	2 ± 3
Mini-Mental Status Exam ^b	29 ± 1	29 ± 1	30 ± 0.7
Geriatric depression scale score ^b	13 ± 3	10 ± 2	12 ± 2

^aThe sum of the motor assessment scores (14–27) of the UPDRS and Geriatric Depression Scale Score were evaluated for only the 11 control subjects recruited from the PD study.

^bMean ± SD.

Table 2

Gain, %MSP, and %errors.

	Control	Sibling	PD	<i>p</i> -value ^a
Gain, horizontal <i>VG</i> ^b	0.95 ± 0.04	0.95 ± 0.1	0.86 ± 0.1	<0.0001
Gain, vertical <i>VG</i> ^b	0.98 ± 0.1	0.99 ± 0.1	0.86 ± 0.1	0.002
Gain, <i>MG1</i> ^b	0.91 ± 0.1	0.86 ± 0.1	0.73 ± 0.1	0.0004
Gain, <i>MG2</i> ^b	0.91 ± 0.2	0.82 ± 0.1	0.62 ± 0.2	<0.0001
% MSP, <i>MG2</i> ^b	10 ± 13	23 ± 26	50 ± 19	<0.0001
% errors, <i>AS</i> ^b	28 ± 21	41 ± 28	49 ± 18	0.001
% errors, <i>MG1</i> ^b	16 ± 11	20 ± 12	32 ± 20	0.002
% errors <i>MG2</i> ^b	37 ± 32	35 ± 31	52 ± 30	0.01

^a *p*-Value corresponds to the analysis of covariance (ANCOVA) with age and gender as covariates for the PD, sibling and control groups. Gender was a significant covariate for %error in the *AS* task only (*p* = 0.04). Age was not significant.

^b Mean ± SD.

Table 3

LRRK2 G2019S mutation positive families.

Family	Status of the family members	LRRK2 mutation	MSP > 35%	Summed UPDRS motor score	UPDRS confidence rating
I	PD	+	+	25	1
	Sibling1	-	-	0	4
	Sibling2	-	-	1.5	3
II	PD	+	+	49	1
	Sibling	+	+	0.5	4
III	PD	+	+	31.5	1
	Sibling	+	-	3	3