Differential progression of proprioceptive and visual information processing deficits in Parkinson's disease.

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Running title: **Pointing in Parkinson's disease**

Number of References: **41**, Figures: **5**, Tables: **1**

Word count for Title: **12**, Abstract: **199** and Text: **4800**

Key words: **Parkinson's disease, Sensorimotor processing, Pointing movements, Visual feedback, Disease severity.**

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Abstract

Indirect evidence suggests that patients with Parkinson's disease (PD) have deficits not only in motor performance, but also in the processing of sensory information. We investigated the role of sensory information processing in PD patients with a broad range of disease severities and in a group of age-matched controls. Subjects were tested in two conditions: pointing to a remembered visual target in complete darkness (DARK) and in the presence of an illuminated frame with a light attached to the index finger (FRAME). Differences in pointing errors in these two conditions reflect the effect of visual feedback on pointing.

PD patients showed significantly larger constant and variable errors than controls in the DARK and FRAME condition. The difference of the variable error in the FRAME and DARK condition decreased as a function of the severity of PD. This indicates that any deficits in the processing of proprioceptive information occur already at very mild symptoms of PD, and that deficits in the use of visual feedback develop progressively in later stages of the disease. These results provide a tool for early diagnosis of PD and shed new light on the functional role of the brain structures that are affected in PD.

Introduction

The accuracy of pointing movements depends to a large extent on the availability of visual and proprioceptive information. When pointing to remembered visual targets in complete darkness, proprioceptive information provides the most reliable source of information about finger position[1,2]. With visual feedback of finger position, the accuracy of pointing increases, especially in the direction of azimuth and elevation and to a lesser extent also in depth (depth refers to radial direction relative to the observer) [2]. These properties of proprioceptive and visual information processing in man explain why errors for pointing to remembered visual targets have 3-D ellipsoidal distributions[3-6] with the long axis directed towards the subject and why pointing becomes more accurate with the availability of visual feedback[7].

Pointing to remembered visual targets has previously been used to investigate deficits in sensory information processing in patients with Parkinson's Disease (PD). PD patients have well known movement abnormalities including bradykinesia (slowness of movement), hypokinesia (lack of movement), akinesia (inability to initiate a movement), tremor and rigidity. In addition to these well-known movement abnormalities, recent studies suggest that PD patients also have deficits in the processing of sensory inputs, particularly in the processing of proprioceptive inputs[8-15]. For example, PD patients were less sensitive in identifying the occurrence and direction of externally imposed movements[8]. Furthermore, PD patients produce larger errors than controls in static joint position sense of the elbow[12] and PD patients are less accurate in detecting limb displacements[15]. PD patients make also larger errors than normal subjects in reproducing a passive finger movement[12] and make larger errors in matching the position of a passively moved finger to the position of a visual target[9]. Because muscle spindle sensitivity is normal in PD[16], the impaired joint

position sense in PD seems primarily of central neural origin. This hypothesis is supported by the finding of reduced sensory-evoked brain activations in cortical (parietal and frontal) and subcortical (basal ganglia) areas in PD patients using positron emission tomography[17]. Furthermore, a reduced level of intracortical inhibition was found in PD patients, which also suggested an abnormal influence of afferent input on corticomotor excitability[14]. In addition to these findings in PD patients, Filion et al.[18] reported an increase in the number, magnitude, and loss of specificity of responses in the basal ganglia of MPTP-treated monkeys to passive limb movement. The latter study suggests, that deficits in motor performance in PD are, at least partly, due to deficits in the processing of sensory (mainly proprioceptive) information in the basal ganglia.

Animal studies have shown that the ability to use sensory information depends on the degree of striatal dopamine loss[19-21]. A minor dopamine deficit in the caudate nucleus only affects its first output station, the substantia nigra pars reticulata. Animals with such a minor dopamine deficit showed a reduction of the ability to use static proprioceptive stimuli in motor control[22-24]. Such animals could only switch between motor programs when external visual cues were available to direct their movement. Therefore, proprioceptive information processing was affected following minor dopamine deficits, but this could be overcome with the use of visual information. More severe dopamine deficits in the Substantia Nigra produce a GABA hyperactivity in the deeper layers of the Colliculus Superior[25]. Animals with a mild GABA hyperactivity in the Colliculus Superior showed a reduced ability to use visual information in switching between motor patterns[26-29]. Extrapolating these results to humans suggests that in an early stage of PD (a mild dopamine deficit), patients will produce larger errors in pointing than age-matched controls in a condition without

visual information, but may perform equally well with the availability of visual feedback. However, with ongoing progression of PD, we hypothesize that patients will produce increasingly larger errors, even in conditions with visual information.

Previous studies on pointing to remembered visual targets in PD have reported that PD patients point less accurately than normal subjects in complete darkness while they are almost as accurate with visual guidance[30-33]. The pointing movements in these studies were only studied in two dimensions[31-33] or in 3D, but then with a limited number of movements to a single target[30]. Due to the limited number of movements, an accurate determination of the constant and variable error in depth, azimuth and elevation could not be done. Moreover, these studies did not test the effect of severity of the disease on the accuracy of pointing.

In this study we have investigated the constant and variable errors of pointing movements to remembered visual targets in PD patients with various degrees of severity of the disease and in a group of age-matched controls. All subjects were tested in two conditions: pointing to a remembered visual target in complete darkness (DARK) and in the presence of an illuminated cubic frame with a light attached to the tip of the index finger (FRAME). The idea behind these experiments was 1) that any differences in pointing errors in the two conditions reflect the effect of visual feedback in pointing by the subject and 2) that any differences in accuracy of pointing in the two conditions in patients with various degrees of PD may reveal insight into the progressive effect of the disease on proprioceptive and visual information processing.

Methods

Patients

This study included 12 patients (10 male, 2 female, age 60 ± 11 years) who fulfilled the UK Brain Bank criteria for idiopathic PD[34]. All patients sustained a clear beneficial response to treatment with levodopa or a dopamine agonist. Controls included 10 healthy elderly subjects that were matched for age and sex (8 male, two female, age 61 ± 10). Five patients had no anti-parkinsonian medication, whereas seven patients had anti-parkinsonian medication in various combinations. The clinical details of the PD patients are given in Table 1. All subjects in this study (both normal subjects and PD patients) had normal vision (or corrected to normal) and did not have oculomotor problems (except for minimal saccadic intrusions during smooth pursuit) or neurological disorders other than PD. We also excluded patients with dementia, a postural tremor of the arms within the first few seconds of assuming a sustained posture (score ≥1 on item 21 of the Unified Parkinson's Disease Rating Scale (UPDRS) [35]) or significant dyskinesias (score >2 on the Modified Dyskinesia Rating Scale) [36]. We did not exclude patients with a "resetting" rest tremor of the arms that became apparent only after several seconds of assuming a sustained posture, *i.e.* well after completion of each individual pointing movement. Patients were examined in a defined "off state" after overnight withdrawal of all antiparkinson medication[38]. All patients had predictable end-of-dose wearing off effects and the interval between start of the experiments and intake of the last medication was at least 12 hrs. Although it may be necessary to withdraw antiparkinson medication for several days to entirely eliminate treatment effects, this approach allows for assessment of parkinsonian manifestations in a fairly stable "off" state[37].

Immediately before the experiments, the patients were clinically examined by an experienced movement disorders specialist (BRB) using the modified Hoehn and Yahr stages and the Unified Parkinson's Disease Rating Scale (UPDRS) [35] (Table 1). The experiments were approved by the Medical Ethical Committee of the University Medical Center of Nijmegen. All subjects gave witnessed and signed informed consent according to the Declaration of Helsinki, but the participants were not informed about the specific purposes of the study.

Experimental setup

Figure 1 shows a schematic overview of the experimental setup. Subjects were seated upright in a chair with their hands on their knees facing a flat backboard (100cm wide x 80cm high) placed at a distance of about 85cm in front of the subjects shoulder. Subjects had to point to the position of one out of five targets, which were presented as illuminated light-emitting-diodes (LEDs) on a metal cross. The cross with targets was positioned reproducibly at a position between the subject and the board with a moveable stick. For each trial one of the LEDs was switched on for one second. After offset of the target LED, the cross was removed by the experimenter such, that the subject could point to the remembered target without touching the metal cross or stick. During target presentation, the center of the cross was at a distance of about 40cm in front of the subject's shoulder (45 cm in front of the backboard) and at a position halfway between the line between the subject's shoulder and the eyes. Four LEDs were positioned on the vertices of the cross, at a distance of 25cm from the center of the cross. A fifth LED was placed on the stick, 25cm behind the center of the cross and 20cm in front of the backboard. All subjects could easily reach all targets without full extension of their arm.

Each target presentation consisted of illumination of one of the five red LED's for a period of 1 second. Onset of the LED-target marked the start of a trial. When the target LED was switched off, the target was quickly removed. Two seconds after target offset, an auditory signal (a tone of 1000 Hz) instructed the subject to start the pointing movement to the remembered target position. Subjects were explicitly instructed to wait for the auditory signal before starting the pointing movement, and to keep the index finger at the position of the remembered target for about half a second before they returned to the initial position.

All subjects made pointing movements to remembered visual targets with their right hand except for two PD patients who pointed with their left hand. These two patients showed almost no signs of PD on their right side but had clear signs on their left side. For these two patients, targets were presented at mirror-symmetric locations relative to the position between the left shoulder and the eyes instead of the regular position between the right shoulder and the eyes.

Subjects were tested in two conditions: pointing to the remembered target in complete darkness (DARK) and pointing in the presence of an illuminated cubic frame with a continuously lit red LED attached to the tip of the index finger (FRAME). In this FRAME condition, a well-defined visual environment was shown to the subject by means of illuminated optic fibers (diameter 2mm) along the edges of the blackboard (100cm wide x 80cm high), with an illuminated cross centered in the middle (100cm wide x 80cm high) and with four 60 cm long illuminated optic fibers orthogonal to the backboard (see figure 1). The frame was visible at all times in the FRAME-condition and the targets were presented within the illuminated cubic frame.

The targets were presented in randomized order in blocks of twenty trials. Subjects started with a block of 20 test trials in the DARK condition and a block of 20

test trials in the FRAME condition in order to become familiar with the experiment. Data of these test trials were not included in further data analyses. Thereafter, subjects were tested in 10 blocks of 20 trials, each randomized over the two conditions. This means that each target was presented 20 times to the subject in both the FRAME and DARK condition. A block of 20 trials lasted about 4 minutes, and after each block, the room lights were switched on for at least 30 seconds to avoid dark adaptation during the test.

Position of the Subject's head, shoulder, arm, and index finger as well as the target position were measured with an OPOTRAK 3020 system (Northern Digital). This system measures the three-dimensional position of infrared-light-emitting-diodes (ireds) with a resolution better than 0.2 mm within a range of about 1.5 m^3. Ireds were placed on the subject's shoulder (acromion), elbow (epicondylus lateralis), and on the tip of the index finger. The position of the LED targets was measured by ireds directly placed on each of the LED's. Subjects were free to rotate their head and were wearing a helmet with six ireds, so that the 3D head orientation could be calculated. Before each experiment, subjects had to look at the OPTOTRAK system with 2 ireds on each of the two eyes. In this way, the position of the eyes relative to the ireds on the head was known. This information was used to calculate the positions of the eyes and the cyclopean eye relative to the orientation of the head in 3D. The position of the tip of the index finger was measured by means of an ired attached to a thimble on the index finger. This thimble also contained a visible red LED that provided the subject with feedback on finger position in the FRAME condition.

Data analysis

Pointing position was defined as the position of the ired on the tip of the index finger at the end of the pointing movement towards the target. Both the constant errors and the variable errors were computed. The constant error is defined as the difference between the target position and the average of all pointing positions to that target. It reflects the general error in planning and execution of the pointing movement. The variable error reflects the distribution of the pointing positions towards a target relative to the average pointing position to that target and reflects the noise in planning and execution. The distribution of the pointing positions for each target is described by the 3-D covariance matrix S_i:

$$S_i = \frac{\sum_{j=1}^{n} \delta_j^i \left(\delta_j^i\right)^T}{n-1}$$

where n is the number of trials to target i and $\delta_j^i = p_j^i - \bar{p}^i$ is the deviation of the finger position p_j^i for trial j to target i relative to the mean pointing position $\bar{p}^i$ to target i. The three orthogonal eigenvectors of the covariance matrix S_i describe the orientations of the variable errors. The corresponding eigenvalues of the matrix give the size of the variable error along the eigenvectors. The total variable error for pointing to a target was computed as the volume of the ellipsoid with the eigenvectors as the three orthogonal axes, each with the length of the corresponding eigenvalue of the covariance matrix for that target. The eigenvalues of the covariance matrix S_i can be scaled to compute the limits that contain 95% of the data (For details, see McIntyre et al.[5]).

Spatial components of the constant errors were computed in a viewer-centered coordinate system with distance (overshoot/undershoot), azimuth (left/right) and elevation (upward/downward), relative to the cyclopean eye. Spatial components of

the variable error were evaluated using the eigenvectors of the covariance matrix. The eigenvector mostly directed towards the eyes will be referred to as the direction of variable error in radial distance. For most targets, this eigenvector was the eigenvector with the largest eigenvalue in both the DARK and FRAME condition (see Fig. 1). The eigenvector that was most dominant in the horizontal (vertical) plane will be referred to as the direction of the variable error in azimuth (elevation).

One control subject showed a constant error in the DARK condition that exceeded the average constant error of control subjects by 2.6 standard deviations. For this reason, this outlier was left out of the statistical analysis, resulting in a total of 9 control subjects and 12 PD patients. Differences in constant errors and variable errors between controls and PD patients were tested using *three way* ANOVA with one *between groups* factor (controls versus PD patients) and two *within* factors (condition: DARK and FRAME, and target location (five targets)). *Two way* ANOVA with one *between groups* factor (controls versus PD patients) and one *within* factor (target location) was used to test for differences between controls and PD patients in the DARK and in the FRAME condition. A Tukey test was used for post hoc analyses. Correlation analyses were conducted to assess the relations between disease severity (UPDRS score) and error size.

Results

Group analysis

Figure 2 illustrates the main findings for pointing to remembered targets in the FRAME condition for control subjects and for PD patients. It shows the pointing positions to remembered targets, the constant error (average pointing position relative to target position) and the variable error (distribution of the pointing positions relative to the average pointing position) for a control subject (left panels) and for a severe PD patient (UPDRS score of 68). The distribution of the pointing positions of the control subjects are characterized by an ellipsoid with the long axis of the distribution oriented toward the subject. This finding was particularly obvious for the FRAME condition. The variable and constant errors are considerably smaller in the FRAME condition than in the DARK condition for control subjects. These results are very similar to data reported before for young normal subjects (range between 20 and 40 years of age; see e.g.[3-7]). For the PD patient both the constant error and the variable error are considerably larger than for the control subject. The data for the PD patient, shown in Figure 2, reveal a clear overshoot of target position. The variable error for the PD patient was particularly enlarged in azimuth and elevation direction.

Figure 3 illustrates the constant and variable errors for the groups of controls and patients in the DARK and FRAME conditions. Pointing errors were consistently smaller for control subjects than for PD patients. This was apparent for both the constant errors (ANOVA, main effect of Group, $F_{1,19}=6.6$, $p<0.05$) and the variable errors (ANOVA, main effect of Group, $F_{1,19}= 5.9$, $p<0.05$). Not surprisingly, the constant and variable errors were smaller in the FRAME condition than in the DARK condition (ANOVA, main effect of Condition, constant error: $F_{1,19} = 79.3$, $p<0.001$;

variable error: $F_{1,19} = 64.0$, $p<0.001$). This effect was found both for the controls and the patients. Although the reduction of the errors in the FRAME condition relative to that in the DARK condition was somewhat larger for controls than for patients, the difference between controls and patients did not reach statistical significance, neither for the constant error (ANOVA, interaction effect of Group by Condition, $F_{1,19} = 0.98$, $p>0.3$) nor for the variable error (ANOVA, interaction effect of Group by Condition, $F_{1,19} = 2.5$, $p>0.1$). Because errors were somewhat larger for patients than for controls, we also calculated the relative decrease of the errors in the FRAME condition, relative to that in the DARK condition. This analysis showed that the relative reduction of the constant error was significantly smaller for patients (29.3 ± 13.1%) than for controls (45.0 ± 17.7%) (unpaired t-test, $p<0.05$). For the variable errors, the relative reduction did not differ significantly between patients (71.4 ± 21.7%) and controls (71.3 ± 30.5%) (unpaired t-test, $p>0.95$).

Analysis of the spatial components of the constant error did not reveal a significant difference between the group of controls and the group of PD patients. However, the scatter of the constant errors was larger for the group of PD patients than for the group of controls in the FRAME condition in radial distance ($p<0.01$), azimuth ($p<0.05$), and elevation ($p<0.05$). The scatter was not significantly different for PD patients and controls in the DARK condition ($p>0.1$; $p>0.5$; $p>0.35$ for radial distance, azimuth and elevation, respectively). Both controls and PD patients showed the largest scatter in radial distance both in the DARK condition (approximately 1.8 times larger than for azimuth and elevation) and for the FRAME condition (approximately 2.8 times larger than azimuth and elevation).

Correlation analysis

The upper panels of Figure 4 show the constant error and the variable error (averaged over all targets) as a function of the severity of PD (UPDRS-score). The constant error (upper left panel in Fig. 3) did not show a significant effect of the severity of PD in the DARK or in the FRAME condition. The average constant error is significantly smaller in the FRAME condition than in the DARK condition ($p<0.001$, paired t-test), but the slope as a function of the UPDRS-score was not significantly different ($p=0.96$) in the two conditions. Therefore, the difference of the constant error in the DARK and FRAME condition, which reflects the effect of visual information on the constant error, did not change with the UPDRS-score ($\rho=-0.06$; lower left panel in Fig. 4).

For the variable error, there is a clear effect of the severity of PD. The variable error increases significantly with the UPDRS-score in the FRAME condition ($\rho=0.49$, $p<0.05$; upper right panel in Fig. 4). The decrease of the variable error with the UPDRS-score in the DARK condition was not significant. The benefit of visual information for pointing to the remembered visual target becomes evident after subtraction of the error in the FRAME condition from that in the DARK condition. A large difference between the variable pointing errors in the DARK and FRAME condition points to a large benefit of visual information about finger position and the reference frame. The reduction of the variable error in the FRAME condition relative to that in the DARK condition showed a large and highly significant negative correlation ($\rho=-0.72$, $p<0.005$) with the severity of PD (lower right panel in Fig. 3).

To obtain more insight in the orientation of the pointing errors relative to the subject, we calculated the spatial components of the variable error in spherical coordinates relative to the subject. The upper panels in figure 5 show the components

of the variable error in radial distance, azimuth and elevation as a function of the severity of PD. The variable error in radial distance, azimuth, and elevation did not show a significant correlation with the severity of PD in the DARK condition (see Fig. 4). In the FRAME condition, the variable error did not show a significant correlation with the severity of PD for radial distance and azimuth direction. However, the variable error did show a significant positive correlation with the severity of PD for elevation ($\rho=0.52$, $p<0.05$).

The lower panels of figure 5 show the difference between the variable errors in the DARK and FRAME condition for each of the spatial components. The differences for azimuth and elevation showed a significant negative correlation with the severity of PD ($\rho=-0.69$, $p<0.01$ and $\rho=-0.76$, $p<0.005$ for azimuth and elevation, respectively). The difference of the variable error in the FRAME and DARK condition showed no relation with the severity of PD for the radial direction.

Discussion

In this study we investigated the effect of the severity of PD on the accuracy of pointing movements to remembered visual targets. On average, PD patients pointed less accurately than controls in the DARK and FRAME condition, which was evident from the larger constant errors in both conditions and from the larger variable error in the DARK condition compared to controls. The severity of PD hardly affected the constant error, but appeared to have a large effect on the variable error: the beneficial effect of visual feedback decreased markedly with increasing severity of PD.

Adamovich et al.[30] studied pointing to remembered targets in PD patients in a similar DARK condition and in a condition with a continuously lit LED on the finger

but without visual information about the visual environment (so called “FINGER condition”). In agreement with our results, they reported that PD patients had larger variable and constant errors than controls in pointing to remembered targets in the DARK condition. In their FINGER condition they found larger variable errors for PD patients than for controls, but no significant difference between controls and patients was found for the constant error. In our FRAME condition, PD patients showed a significantly larger constant error than controls, but the variable errors were not significantly different. Therefore, we conclude that PD patients point less accurately than controls, especially in the absence of visual information, which is in agreement with results of previous studies on pointing movements in PD patients[30-33].

Subtracting the error in the FRAME condition from the error in the DARK condition reveals the effect of visual information in pointing movements. Control subjects showed a decrease in both the constant error and variable error in the FRAME condition, which was in agreement with previous observations on pointing to remembered visual targets[3-7]. PD patients showed a similar reduction in variable error and constant error between the FRAME and DARK condition. The main new finding of this study is a significant decrease of the *difference* of the variable error in the DARK and FRAME conditions as a function of the severity of PD (see lower right panel of Fig. 4). This means that with increasing severity of PD, patients are less able to use visual information to reduce the variability in their movements. This conclusion is supported by the specific effect of visual information on the spatial components of the variable error. The decrease of the variable error between the DARK and FRAME conditions was significantly correlated to the severity of PD for azimuth and elevation, but not for radial direction. This is exactly what one would expect if an effect of vision was involved since Van Beers et al. [2] showed that vision mainly

contributes to the accuracy in azimuth and elevation direction and less so in radial direction.

In principle, errors in pointing movements to remembered visual targets can be attributed to various factors, such as the misperception of the target position, errors in spatial memory, errors in the transformation from visual information to an appropriate motor command, or to a deficit in proprioceptive information processing of the arm. The obvious question then is: what is the underlying mechanism that is responsible for the larger error in PD patients? It has been hypothesized that spatial memory might be affected in PD patients. This hypothesis is not compatible with the notion that mild to moderately affected PD patients make the same errors as controls when pointing to a remembered visual target with a Light-Emitting-Diode (LED) on their pointing fingertip in complete darkness[30] or when pointing to a remembered visual target with the eyes closed[34]. This is compatible with our finding that PD patients did not show significantly different variable errors in the FRAME condition relative to control subjects (see right panel of Fig. 3). Moreover, analysis of the spatial components of the constant error did not reveal differences between controls and PD patients in DARK and FRAME condition. These results argue against the hypothesis that misperception of target position or spatial memory might be responsible for the larger errors in PD patients. In addition, Ketcham et al. [33] found an increase in the variability of end-point errors to remembered target locations in early PD patients. Since neither the delay, nor the number of items nor the sequence familiarity of the targets affected the end-point errors, this observation suggested that PD patients have an impairment in memory-motor transformation rather than an impairment in spatial memory. Other evidence against a possible role of spatial memory on pointing errors comes from Hodgson et al.[39] who reported that PD patients and control subjects did not differ in

the accuracy of eye movements to a single target (see also[40,41]). Therefore, we conclude that there is no evidence for misperception of target location or for an impairment in spatial memory to explain the larger pointing errors to remembered visual targets found in PD patients.

During the execution of a pointing movement, sensorimotor information can be used to correct for errors in end-point positions. In the absence of visual cues, subjects have to rely mainly on proprioceptive information to guide their index finger to the remembered visual target position[2-4]. Therefore, the observation of larger variable errors in the DARK condition for PD patients than for controls suggests that patients are less able to use proprioceptive information, in agreement with previous studies[9-15,42]. Neither the variable error nor the constant error showed a significant relation with the severity of PD in the DARK condition. Maschke et al.[15] reported that the percentage of errors in detecting passive displacement of the arm increases with the severity of the disease. Since this study dealt with passive arm displacements, whereas our study dealt with errors in active arm positioning, these results are not in conflict. These observations suggest that the deficit in the use of proprioceptive information occurs at an early stage of PD, and is hardly affected by further disease progression. In early stages of the disease, the deficit in proprioceptive information processing is compensated by using visual feedback, because the variable error in the FRAME condition was the same for mildly affected PD patients and controls. However, with progression of the disease, the availability of visual information no longer helps to improve the variable error, indicating a deficit in visual information processing to guide pointing movements.

Taken together, our main conclusion is that pointing movements in PD are impaired due to a deficit in processing of proprioceptive information, which appears

early in the course of the disease, and by a visual feedback problem, which emerges in later stages of the disease.

Acknowledgments

We wish to thank the patients and volunteers who participated in this study. We thank T. van Dreumel and H. Kleijnen for assistance in building the experimental setup, and we are grateful to G. van Lingen for designing the software to drive the experiment. N.L.W. Keijsers and B.R. Bloem were supported by a research grant of the Prinses Beatrix fonds.

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Table 1. Characteristics of PD patients

No.	Sex	Age	Disease Duration	H & Y stage	UPDRS score	Medication (per 24 hours)
1	M	71	1	2	18	-
2	M	74	5	2	47	-
3	M	54	4.5	3	38	LC(3x125), DRA (4x0.25)
4	M	67	2	2.5	54	-
5	M	52	4	2	35	-
6	M	56	12	2	33	DRA(3x1), S(2x5)
7	F	72	1.5	2	30	LC(3x62.5)
8	M	37	1.5	2	37	DRA(3x2)
9	M	58	4	2.5	32	-
10	M	72	7	2.5	43	LC(5x 137.5), DRA(3x5), Am (2x100)
11	F	63	1.5	2	26	An (7x2)
12	M	52	16	3	68	LC (9x125), DRA (4x4), Am (2x100), C (4x200), S(2x5)
Mean		60	5.0	2.3	38	
SD		11	4.7	0.5	13	

H & Y = Hoehn and Yahr, medication: LC – levodopa / carbidopa ; DRA – dopamine receptor agonist; Am - Amantadine; C - anticholinergic; S - Selegeline

Legends of Figures

Figure 1.

Schematic overview of the experimental setup. Subjects were seated upright facing a flat backboard. During target presentation, the center of the cross was at a distance of about 40cm in front of the subject (45cm in front of the backboard) and at a position halfway between the line between the subject's shoulder and the eyes. Four targets were on the vertices of the cross, which were 25cm from the center of the cross. A fifth target was placed on a stick, 25cm from the center of the cross. The illuminated optic fibers in the FRAME condition are presented as bold lines.

Figure 2.

Top (upper panels) and side (lower panels) view of pointing positions (dots) to the 5 targets for a control subject (left panels) and a severe PD patient (right panels) in the FRAME condition. Stars indicate the actual position of the target, squares indicate the average pointing position, and ellipses indicate the 95% confidence intervals. All targets and pointing positions are presented in an orthogonal coordinate system with the origin at the right shoulder of the subject.

Figure 3.

Mean constant error (left panel) and variable error (right panel) for controls and PD patients. The variable error for pointing to a target was computed as the volume of the ellipsoid with the eigenvectors as the three orthogonal axes, each with the length of the corresponding eigenvalue of the covariance matrix for that target (see methods). *=significant difference ($P<0.05$). Error bars represent the standard deviation.

Figure 4.

Relation between the constant error (left upper panel) and variable error (right upper panel) as a function of the UPDRS score (severity of the disease). Errors are shown for the FRAME condition (asterisks, dashed line) and the DARK condition (circles, solid line). Lower panels show the difference of constant error (lower left panel) and variable error (lower right panel) in the DARK and FRAME condition for each patient as a function of the UPDRS score of that patient. Vertical bars on the left hand side of the upper panels represent the range of errors (mean error plus or minus the standard deviation) for control subjects in the DARK condition (black bars) and in the FRAME condition (gray bars). Vertical bars in the lower panels indicate the range of the mean plus or minus the standard deviation of the difference of errors in the DARK and FRAME condition for the control subjects.

Figure 5.

Upper panels show the spatial components of the variable error in radial distance (upper left panel), azimuth (upper middle panel) and elevation (upper right panel) as a function of the UPDRS score (severity of the disease). Errors are shown for the FRAME condition (asterisks, dashed line) and the DARK condition (circles, solid line). Lower panels show the difference between the spatial components of the variable error in the DARK and FRAME condition. Vertical bars on the left hand side of the panels in the upper row represent the range of the mean error plus or minus the standard deviation for age-matched control subjects in the DARK condition (black bars) and in the FRAME condition (gray bars). Vertical bars in the lower panels represent the range of the mean plus or minus the standard deviation of the difference

of the spatial components of the variable error in the DARK and FRAME condition for the control subjects.

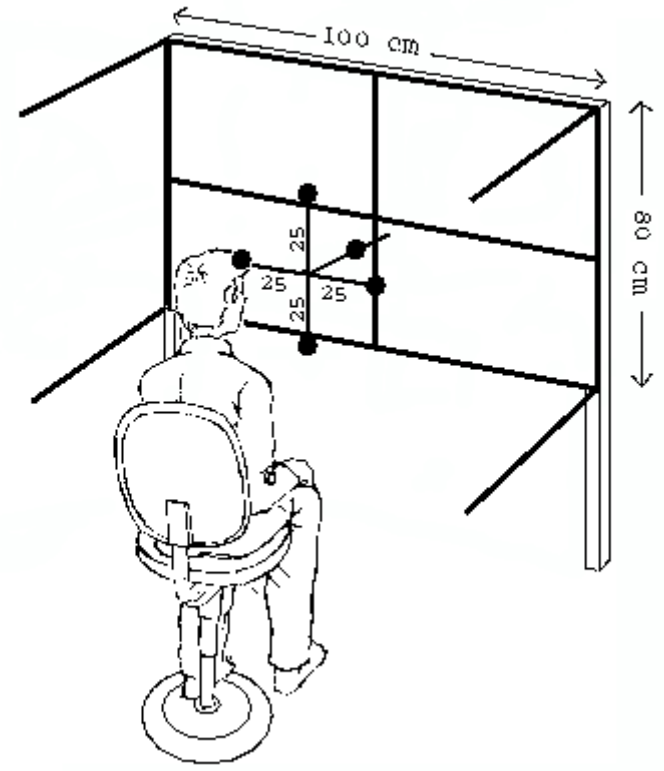

Figure 1.

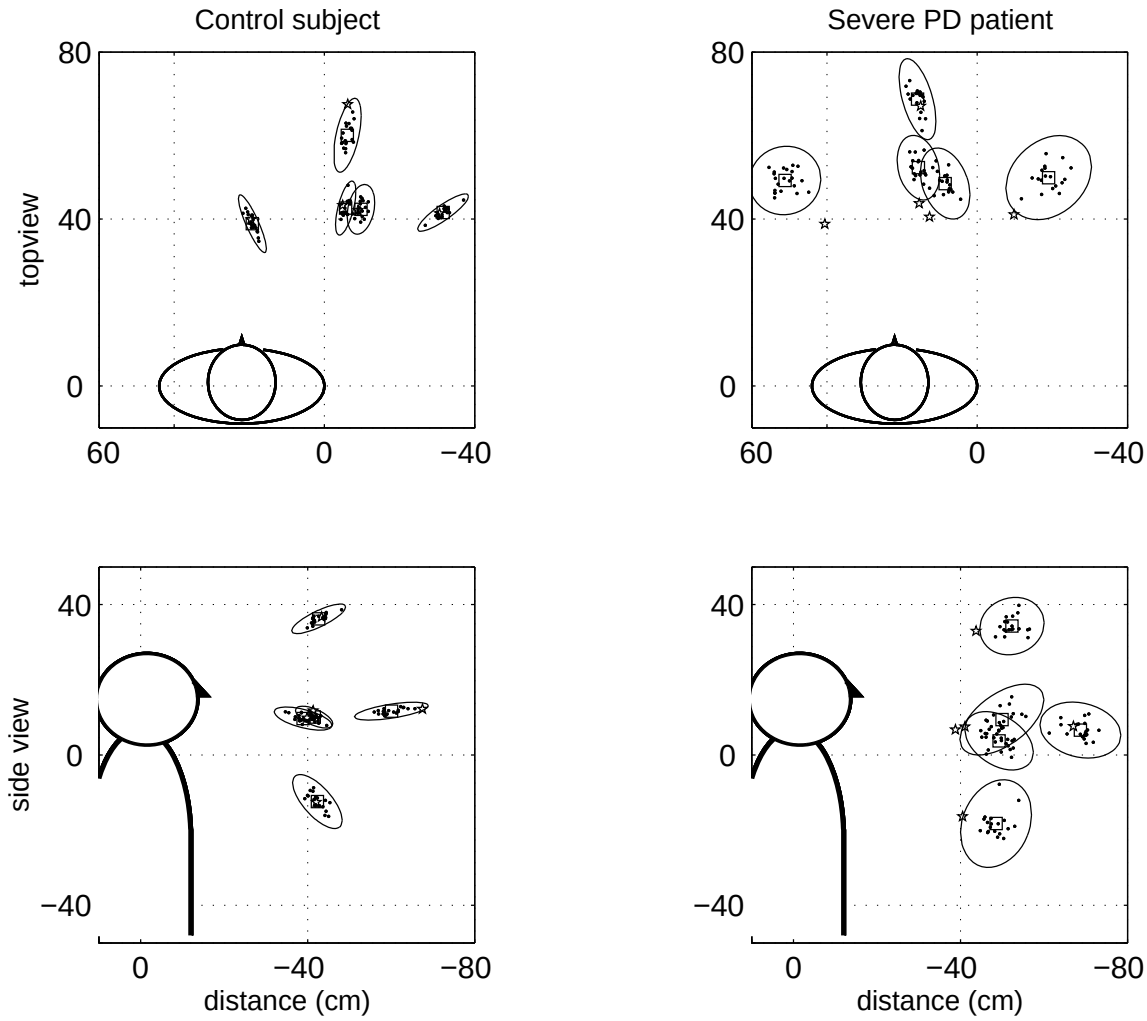
Control subject
Severe PD patient
topview
side view
distance (cm)
distance (cm)
80
40
0
60
0
−40
−80

Figure 2.

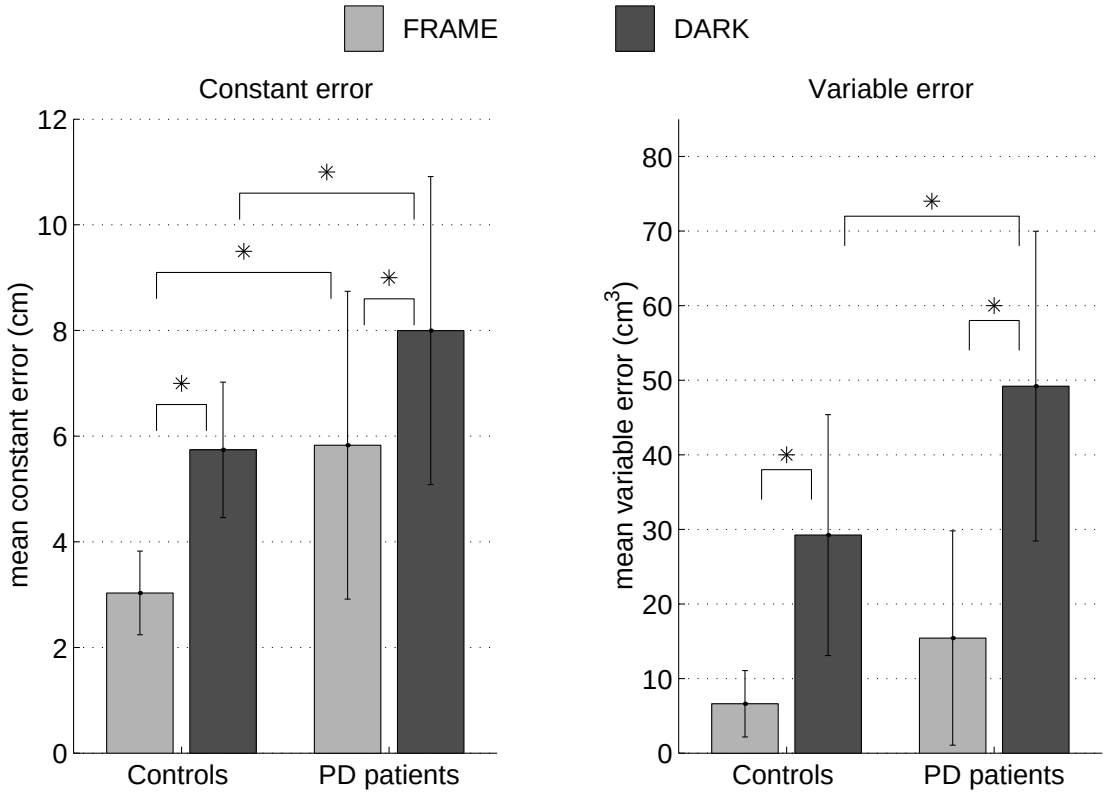
FRAME
DARK
Constant error
mean constant error (cm)
0
2
4
6
8
10
12
Controls
PD patients
Variable error
mean variable error (cm3)
0
10
20
30
40
50
60
70
80
Controls
PD patients

Figure 3.

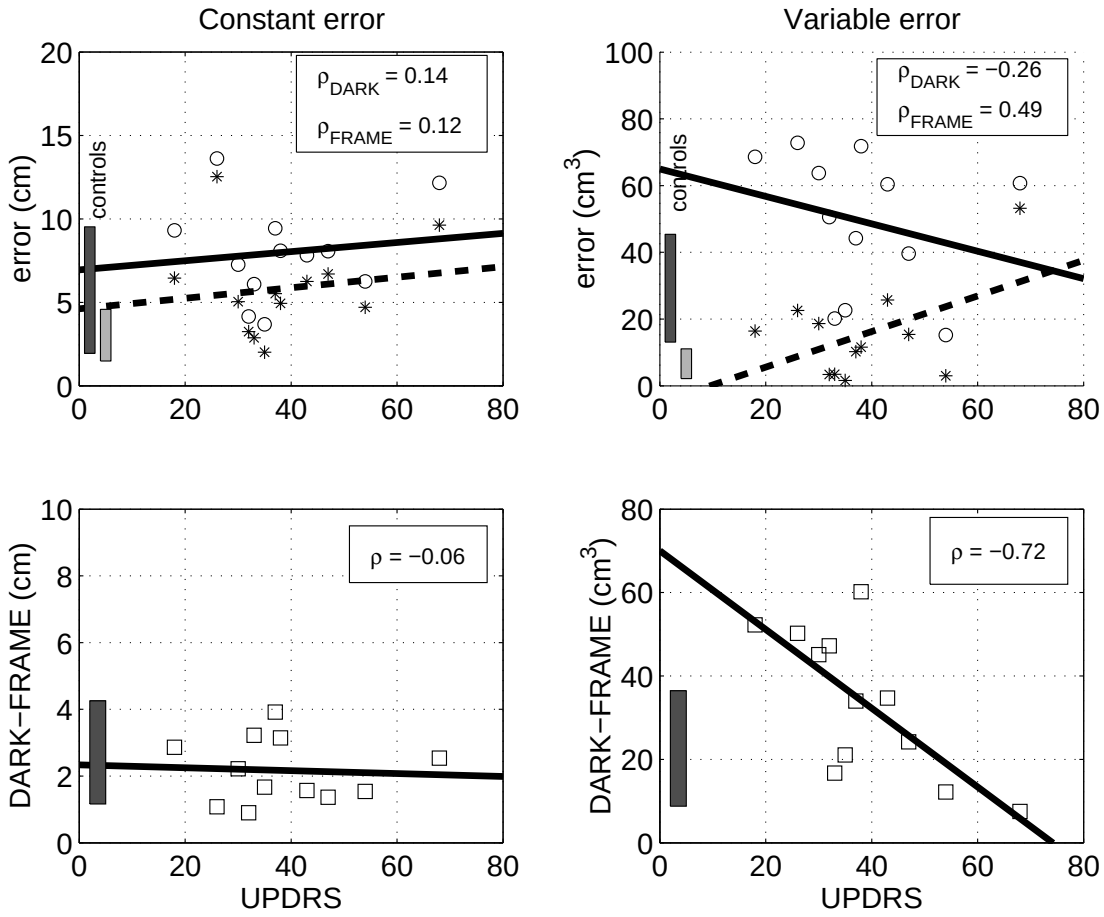
Constant error
Variable error
error (cm)
error (cm^3)
controls
ρ_{DARK} = 0.14
ρ_{FRAME} = 0.12
ρ_{DARK} = −0.26
ρ_{FRAME} = 0.49
DARK−FRAME (cm)
DARK−FRAME (cm^3)
ρ = −0.06
ρ = −0.72
UPDRS
UPDRS

Figure 4.

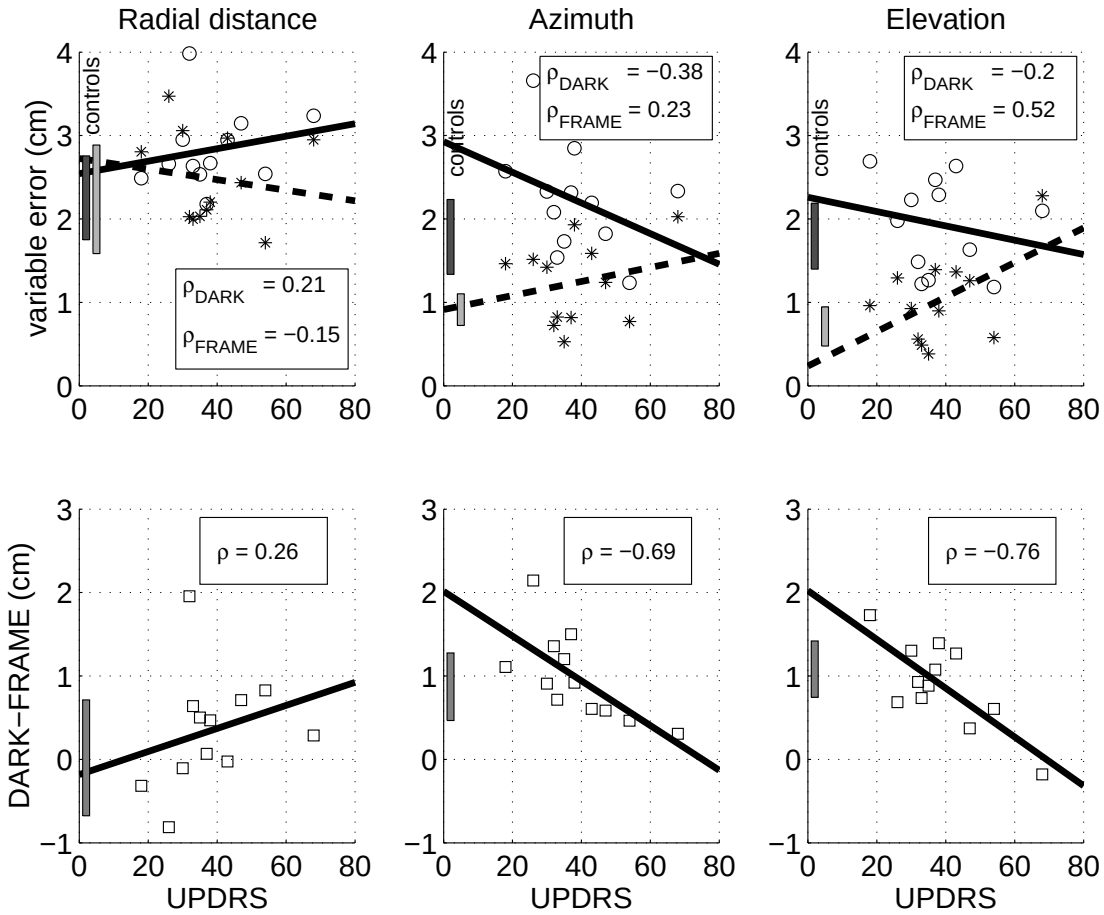
Radial distance
Azimuth
Elevation
variable error (cm)
controls
ρDARK = 0.21
ρFRAME = −0.15
ρDARK = −0.38
ρFRAME = 0.23
ρDARK = −0.2
ρFRAME = 0.52
DARK−FRAME (cm)
ρ = 0.26
ρ = −0.69
ρ = −0.76
UPDRS

Figure 5.