

Axial kinesthesia is impaired in Parkinson's disease: Effects of levodopa

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ABSTRACT

Integration of sensory and motor inputs has been shown to be impaired in appendicular muscles and joints of Parkinson's disease (PD) patients. As PD advances, axial symptoms such as gait and balance impairments appear, which often progresses to complete inability stand or walk unaided. The current study evaluates kinesthesia in the axial musculature of PD patients during active postural control to determine whether impairments similar to those found in the appendages are also present in the hip and trunk. Using axial twisting, we quantified the detection threshold and directional accuracy of the hip relative to the feet (i.e. Hip Kinesthesia) and the hip relative to the shoulders (i.e. Trunk Kinesthesia). The relation of kinesthetic threshold to disease progression as measured by UPDRS and the effect of levodopa treatment on kinesthesia were assessed in 12 PD compared to age-matched controls. Subjects stood unaided while passively twisted at a very low constant rotational velocity ($1^\circ/s$). The results showed that accuracy in determining the direction of axial twisting was reduced in PD relative to healthy control subjects in the hip (PD-ON: 81%; PD-OFF: 91%; CTL = 96%) and trunk (PD-ON: 81%; PD-OFF: 88%; CTL = 95%). Thresholds for perception of axial twisting were increased when PD subjects were ON levodopa versus OFF in both the hip ($p < 0.01$) and the trunk ($p < 0.05$). The magnitude of decrease in sensitivity due to being ON levodopa was significantly correlated with the increase in UPDRS motor scores (Hip: $r = 0.90$, $p < 0.01$ and Trunk: $r = 0.60$, $p < 0.05$). This effect was not significantly correlated with equivalent levodopa dosage. PD subjects with disease onset on the left side of their body showed significantly higher axial thresholds than subjects with right PD onset ($p < 0.05$). In conclusion, deficits in axial kinesthesia seem to contribute to the functional impairments of posture and locomotion in PD. Although levodopa has been shown to improve appendicular kinesthesia, we observed the opposite in the body axis. These findings underscore the dissociable neurophysiological circuits and dopaminergic pathways that are known to innervate these functionally distinct muscle groups.

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Introduction

Motor symptoms in Parkinson's disease (PD) have been found to be associated with impairment in the integration of somatosensory inputs (Konczak et al., 2009). Much of this evidence has focused on the kinesthetic impairments of appendicular muscles and joints (Klockgether et al., 1995; Konczak et al., 2007; Maschke et al., 2003; Schneider et al., 1987; Zia et al., 2000). As PD progresses symptoms in gait and posture become more and more apparent (Hoehn and Yahr, 1967), which may be due to progressive impairment of proximal and axial musculature. Axial muscles also play an important role in anticipatory postural adjustments to stabilize posture during limb movements (Hesse, 1943; Massion, 1994). A recent cross-sectional study identified axial impairment as the strongest covariate of disability and reduced quality of life (Muslimovic et al., 2008), thus,

the consequences of impaired axial musculature to posture, gait, and motor control appear to be far reaching.

Measuring kinesthesia along the body axis presents a number of complications. One is that measurement techniques that are easily applied to limbs and digits because they are easy to manipulate independently and bilaterally are not always applicable to the trunk and hip. Few studies of axial kinesthesia can be found in the literature and none specifically addressing PD, while numerous assessments of the appendicular kinesthesia can be found (Klockgether et al., 1995; Konczak et al., 2007; Maschke et al., 2003, 2006; Schneider, et al., 1987; Zia et al., 2000, 2002). Among them active and passive slow arm movements without visual feedback (Klockgether et al., 1995) and elbow joint position sense during bilateral passive arm movements (Zia et al., 2000) have shown impairments in PD limb kinesthesia. Other tests on distal muscles and joints have shown that detection thresholds to skin pressure (Schneider et al., 1987) and weight perception on the fingers are impaired even in early stages of PD (Maschke et al., 2006). Evidence of limb and distal muscle kinesthetic deficits in PD also comes from studies which examined vibration-induced errors during active movement of the wrist (Rickards and

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Cody, 1997) and ankle (Khudados, et al., 1999). However, due to the en bloc nature of the body axis many of these above techniques for limb assessment would be difficult to apply to the trunk or hips.

A second complication faced when measuring axial kinesthesia is that the threshold for detecting trunk position is known to decrease when a subject is supine compared to when standing in an active postural state (Jakobs et al., 1985). This suggests that in order to determine what effect axial kinesthesia has on PD functional impairment, measurements should be taken while the subject is standing unsupported. To accomplish this, a unique device that we have employed in a number of postural and motor tasks recently (Franzen et al., 2009; Gurfinkel et al., 2006; Wright et al., 2007a,b) was used in this study. This device allows axial segments to be rotated about the horizontal plane while the subject actively balances unsupported. This type of rotation involves no imposed shifts in body mass or changes in orientation of the body relative to gravity. There are a couple of advantages to these design characteristics. First, axial bending may confound threshold measures of axial musculature when reorientation of the head or a shift in center of mass occurs, since vestibular or foot proprioceptive thresholds may be reached before axial muscle and vertebral somatosensory thresholds. Second, many of the trunk's anterior (e.g. abdominal external and internal obliques and abdominal transverses) and posterior muscles (e.g. erector spinae and multifidus) have a pinnate orientation. Therefore, these muscles will be changed in length more effectively by rotation than by hip and trunk flexion/extension. The functional importance of axial rotation and segmental coordination about the horizontal plane is evident during locomotion, and perhaps more importantly, changes in the coordination between thoracic and pelvic segments can be seen even in the earliest stages of PD gait impairment (Huxham et al., 2008; Murray et al., 1978; Vaugoyeau et al., 2003, 2006). Thus, keeping the axial muscles active during measurement of kinesthesia and assessing them during functionally relevant actions is important to our understanding of the role of axial kinesthesia in postural control.

An additional consideration for assessing axial rigidity is that the pathways and neurotransmitter activity connected with proximal versus axial musculature are dissociable. This was highlighted in our recent study on axial rigidity in PD, which provided evidence that, unlike appendicular rigidity, axial muscle tone is not reduced by levodopa (Wright et al., 2007b). Therefore, it is difficult to know whether the effects of levodopa and dopamine agonist drug therapy on kinesthesia involving distal muscles can be assumed to apply to axial kinesthetic thresholds either. This is further complicated by the

fact that drug effects on distal muscles are still poorly understood. At least one study has shown levodopa worsens elbow joint proprioception (O'Suilleabhain et al., 2001) while another study suggests improvement (Klockgether et al., 1995). Therefore, to understand the effects of drug therapy on axial kinesthesia, it should be evaluated independent of distal musculature.

A final consideration was undertaken in this study due to the well-known asymmetry of motor symptoms at PD onset, as well as a growing body of research that suggests a perceptual asymmetry exists (Ebersbach et al., 1996; Harris et al., 2003; Hovestadt et al., 1987; Starkstein et al., 1987; Wright et al., 2007a). We recently found a leftward perceptuomotor asymmetry in PD during reaching tasks, which occurred independent of the side of disease onset (Wright et al., 2007a), however, many others have found evidence for perceptual left-neglect that occurs predominantly in patients with left-sided PD onset (LPD) (Davidson et al., 2005; Ebersbach et al., 1996; Harris et al., 2003; Lee et al., 2001). Though these perceptual asymmetries have been established in visuospatial and perceptuomotor tasks, whether they extend to body-centered kinesthetic asymmetries in axial musculature has not yet been investigated.

To summarize the primary goals of this study which are aimed at furthering our understanding of kinesthetic deficits in PD: 1) we evaluated axial kinesthesia and determined if it is correlated with disease progression and functional impairments, 2) we evaluated what effect levodopa drug therapy has on axial kinesthetic thresholds, and 3) we determined if there is a lateral asymmetry in axial kinesthesia that correlates with the PD affected side. As in all studies of kinesthesia, changes in sensitivity are used as a marker for how well the calibration between ascending sensory input and conscious processing is tuned and if a threshold change subsequently translates to real functional impairment.

Methods

Subjects

A total of 26 subjects participated in this study. Twelve subjects (66 ± 11 years old) had Parkinson's disease (PD) and were undergoing levodopa treatment. Fourteen subjects were healthy age-matched controls (65 ± 10 years old). The patients were selected based on being $H\&Y \geq 1.5$, which is characterized as PD with axial involvement (Table 1). All subjects provided informed consent in accordance with

Table 1
PD subject information.

PD Sub	Side	Duration of PD	Age	Ht	Wt	Sex	UPDRS Motor Part III					H&Y	Medication	
							Total		Rigid	Axis	PIGD		L-dopa	Other
							ON	OFF	OFF	OFF	OFF			
1	L	14	64	160	59	F	13	22	3	13	6	2.5	300	Am, DA
2	L	10	81	157	52.2	F	5	24	1	11	5	2	500	DA, Sel
3	L	7	69	178	104.3	M	20	35	9	12	4	3	1000	
4	L	10	71	178	77.1	M	39	55	12	21	5	3.5	1050	
5	L	4	53	165	70.3	F	17	37	5	9	3	3	300	DA
6	L	8	79	178	77.1	M	29	33	8	18	9	3	600	DA
7	R	18	59	173	74.8	M	36	50	8	20	12	3	500	Am, DA
8	R	17	74	175	66.7	M	33	54	16	30	8	3	1200	Am, DA, Sel
9	R	7	51	178	68	M	5	21	4	8	2	2	500	DA
10	R	7	50	170	70.3	M	19	20	3	6	5	1.5	1250	Am, DA
11	R	7	64	180	90.7	M	9	18	2	3	0	2	300	DA, AntiCh
12	R	9	73	173	77.1	M	23	32	5	12	3	2	300	DA
Avg	—	9.8	65.7	172	74.0	—	20.7	33.4	6.3	13.6	5.1	2.5	—	—
Avg	Controls (n = 14)		64.5	170	71.0	—	—	—	—	—	—	—	—	—

Duration of PD in years. Ht, height in cm; Wt, weight in kg; Side, side of disease onset; Rigid, Rigidity (UPDRS Item 22); Axis, Axial Symptoms in UPDRS (Items 20, 22, 26–30); PIGD, Postural Instability and Gait Difficulty (UPDRS Items 27–30); L-dopa, daily dose in mg/day; AntiCh, anti-cholinergic; Am, amantadine; DA, dopamine agonist; Sel, Selegiline.

local ethics committee regulations for human subjects' studies and the Helsinki Declaration.

PD subjects were tested in the morning after abstaining from anti-Parkinsonian medication overnight; the wash-out period was at least 12 h in the OFF medication state. Subjects OFF medication were assessed with the motor part of the United Parkinson's Disease Rating Scale (UPDRS) prior to participating in the experimental protocol. All subjects were able to stand for periods of greater than 15 min without rest. After the subjects completed the OFF medication portion of the protocol, they took their normal morning dosage of medications. Once PD subjects reported that they felt "ON", at least 45 min after taking their medication, the UPDRS motor score was obtained. The UPDRS scores in the ON (20.7 ± 11.6 SD) versus OFF antiparkinson medication (33.4 ± 13.4 SD) showed a highly significant decrease ($p < 0.0001$). The protocol was then repeated in the ON state.

Protocol

A torsional rotation device, which consists of a steel frame surrounding a rotating platform was used to twist axial segments of the body about the horizontal plane of a freely standing subject (Gurfinkel et al., 2006; Wright et al., 2007b). A unique feature of the torsional rotation device is that the platform rotates the lower body relative to a fixed upper body. The frame and the rotating platform each have a fixation point for a rigid aluminum rod that attaches to the subject with a harness at the opposite end. This attachment ensures that the lower part of the body axis remains fixed relative to earth, while the upper part is rotated about a vertical axis passing through the trunk roughly collinear with the spine (Fig. 1). The platform rotated $\pm 10^\circ$ clockwise (CW = Right) and counterclockwise (CC = Left) in a trapezoidal pattern at a very slow velocity ($1^\circ/\text{s}$) with reversals in rotational direction not exceeding $12^\circ/\text{s}^2$ angular acceleration (Fig. 2). Four directions of platform rotation were used in each condition: CW from 10° left to 0° (CW10-0), CW from 0° to 10° right (CW0-10), CC from 0° to 10° left (CC0-10), CC from 10° right to 0° (CC10-0), with variable length pauses between each, as well as occasional sham trials in which no

rotation occurred. The subject was asked to hold a bi-directional manual switch in their hands at approximately waist-height, which they were instructed to press as soon as rotation was perceived and the direction of rotation could be identified. Because the lower body is rotated relative to the upper body, axial rotation is not veridically perceived as platform rotation. Instead, the platform is perceived as stationary and the upper body is perceived as rotating in the direction opposite of platform rotation (Wright et al., 2007a). Therefore, a "correct" response (i.e. a HIT) is CW indication of upper body rotation, when the platform is actually rotating the lower body CC. Each direction was tested at least 3 times per subject per condition and the order of rotations was counterbalanced. The button-push induced a ± 5 V change, which was recorded in synchrony with the platform position at 50 samples/s using Spike2 software (Cambridge Electronic Devices, Cambridge, UK) and analyzed offline using Matlab software (Mathworks, Natick, MA).

In both experimental conditions, Trunk and Hip Kinesthesia, we collected two dependent measures: threshold of detection of axial rotation and direction of perceived axial rotation. In one condition (PD: $n = 12$; CTL: $n = 14$), we quantified the thresholds to axial rotation of the trunk relative to the fixed hips (Trunk Kinesthesia). A harness, snugly attached to the subject's shoulders on one end was attached on the other end to the steel frame by a double-hinge that allowed the subject to sway in the horizontal plane, but not rotate in yaw. In other words, the shoulders were rigidly fixed to the external rigid frame to prevent torsional rotation while the platform under the subject rotated the feet and pelvis. The feet and pelvis were rotated together by the platform, thus isolating twisting to the thoracolumbar region (Fig. 1, left). To rotate the hips with the feet, a rod connected to the platform was fixated to the hips. The subject wore a padded, rigid-framed, butterfly-shaped pelvic band taken from a thoracolumbar orthoses. The pelvic band was modified with an attachment for linking to the platform rod. The link between the pelvic band and the platform was single-hinged to allow free anterior-posterior translation, while allowing no rotation of the hips relative to the feet.

In the other condition (PD: $n = 9$; CTL: $n = 12$), the kinesthetic threshold of hips relative to lower body axial rotation (Hip

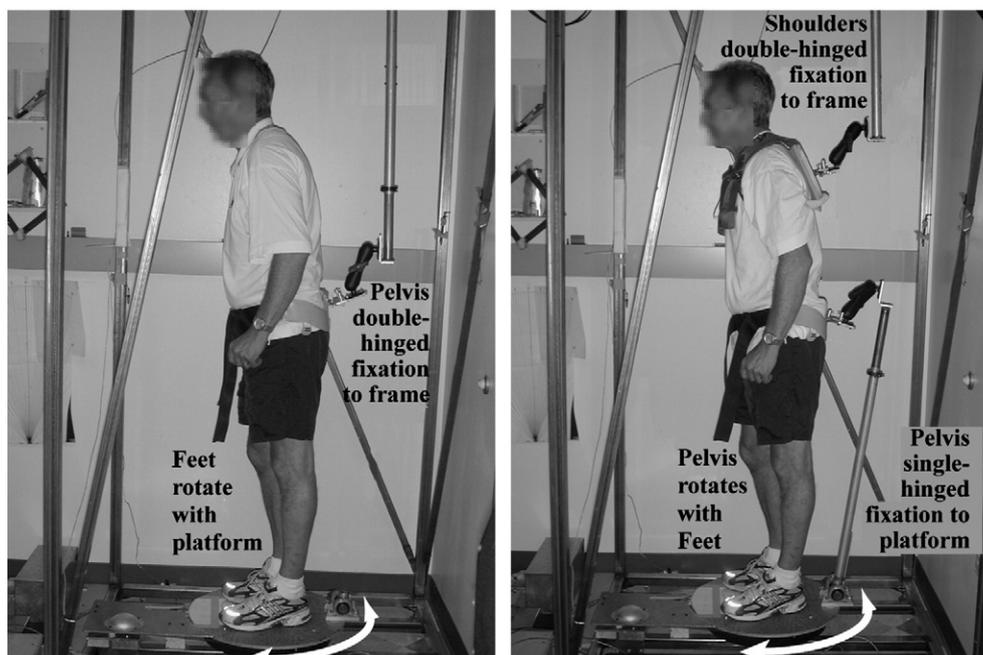


Fig. 1. Left: In the Hip Kinesthesia condition, the torsional platform rotates (white arrow arc) the feet relative to the pelvis that is fixed against rotation by a double-hinge to allow for normal sway excursions and provide no postural support. Right: In the Trunk Kinesthesia condition, the platform rotates (white arrow arc) the feet and pelvis together relative to the upper trunk. The pelvis is fixed to the rotating support surface by a single-hinge allowing anterior-posterior sway, while the shoulder girdle is fixed against rotation by a double-hinge to a fixation frame. Both the Trunk and Hip configurations require active postural control and provide no support. The subject held a bi-directional button with both hands at waist-height (not pictured).

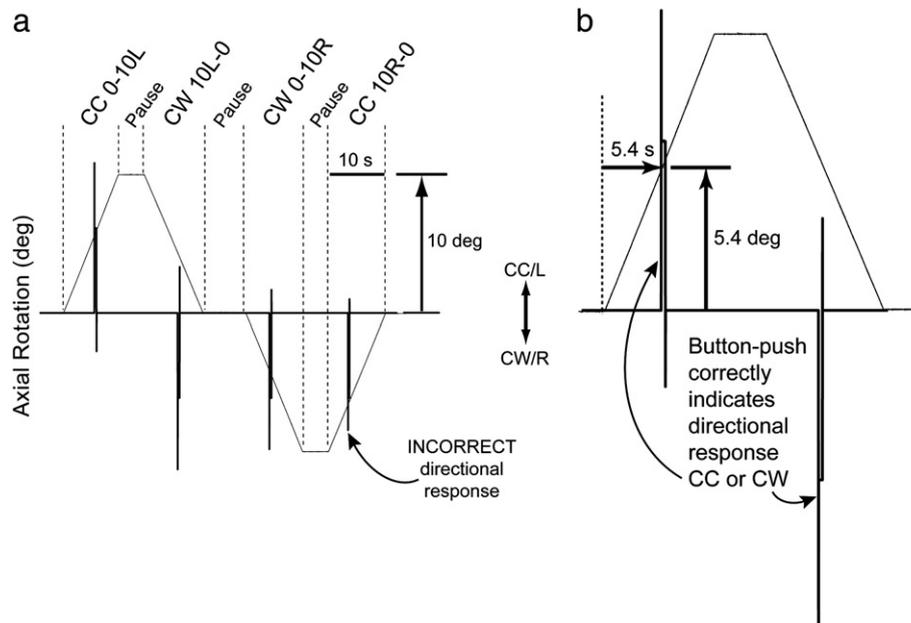


Fig. 2. The proprioceptive stimulus and directional button-push response show how threshold and direction are measured. Axial rotation (thin line) is 10° CC/Left (up) or CW/Right (down) at $1^\circ/\text{s}$. a) The four directions with pauses in between (separated by vertical dotted lines) are CC from 0° to 10°L , CW from 10°L to 0° , CW from 0° to 10°R , or CC from 10°R to 0° , where 0° is considered a neutral, untwisted bodily configuration. Voltage signals (thick vertical spikes) show directional button-push response (CC = up, CW = down). The CW directional spike in the bottom left corner depicts a MISS, whereas all other spikes depict HITS. b) An expanded view of CC 0-10L, pause, CW 10L-0 test phases. If the response (thick line) occurs 5.4 s after platform rotation onset (dotted line), then the amount of axial rotation equals 5.4° , which is the kinesthetic threshold for that trial. An upward voltage spike indicates the subject perceived CC axial rotation and a downward voltage spike indicates the perception of CW axial rotation. To avoid more than 10° of axial abduction, CW 0-10L was always followed by CC 10L-0 and CC 0-10R was followed by CW 10R-0, however adduction from 10° to 0° could be followed by either CW 0-10R or CC 0-10L.

Kinesthesia) was tested using the same rotation parameters as during the Trunk condition. The fixations of the hip allowed the legs to be passively rotated relative to a fixed pelvis. The pelvic band was attached via a double-hinged bar to the rigid frame, while the feet were rotated by the support platform. The shoulders were completely free in this condition. As the platform rotated the feet, the pelvis remained fixed relative to earth, thus isolating the hip and lower extremities (Fig. 1, right). Again, subjects held a bi-directional button in both hands at waist-height to indicate the onset and direction of perceived direction.

In both conditions, the double-hinged connections to the platform and frame allowed for unrestrained postural sway translations in the horizontal plane without rotation, which created a relatively natural mechanical environment for quiet stance. Subjects were required to maintain standing equilibrium, but the unconstrained motions in the horizontal plane precluded using the fixations as a spatial reference. The fixation linkages provided the degrees of freedom necessary to spontaneously sway within the normal base-of-support, therefore kinesthetic thresholds were measured with the subject in an active postural state engaged in maintaining upright posture, rather than in an less active state such as during supported stance or while lying supine. The attachments to the body and fixation linkages were counterweighted with springs so no unnatural loading could affect postural behavior. Because the Hip and Trunk attachments took time to remove and reattach, the trials were grouped such that all Hip condition trials were run together and all Trunk condition trials together. Also, the attachments for the Hip condition were not built until a few subjects had already been tested in the Trunk condition, however, all subsequent subjects were run in counterbalanced order. This order was also counterbalanced in ON and OFF conditions for PD subjects.

Data analysis

For both Hip and Trunk conditions, the threshold for detecting axial rotation was determined for each subject in each direction. At least three

trials per direction were collected for each subject and a mean was calculated for the thresholds. Either repeated-measures ANOVA (PD-ON versus PD-OFF medication) or one-way ANOVA (PD versus controls) were used to compare threshold values. Subjects' button-push response also indicated direction of rotation, so the accuracy of each response was tabulated and an overall percent "HIT" rate was assessed for each subject in each condition. If a subject indicated the wrong direction or failed to respond before the 10° limit of rotation was reached, it was counted as a "MISS". Non-parametric Fischer Exact tests for small samples were used to assess any differences in HIT/MISS rates between PD-ON, PD-OFF, and controls. The Pearson's product moment correlation was used to quantify the interrelation of variables in all regressions. Paired t-tests were used to compare PD subjects ON versus OFF medication. Unpaired t-tests were used to compare PD subjects to controls. Significance was set at $\alpha \leq 0.05$.

The UPDRS Part III was used to measure disease progression and severity in the PD subjects. The UPDRS Part III includes items to clinically quantify the level of various motor abilities in PD subjects. These items are grouped according to their body location and their functional relevance. Our study analyzed the functional measure "postural instability and gait difficulty" (PIGD), which includes UPDRS items 27–30. Also, a measure of axial symptoms included UPDRS item 20 resting tremor of legs, item 22 (neck and leg rigidity), item 26 (leg agility), and items 27–30 (PIGD). We used the variable of kinesthetic thresholds when ON-OFF medication to examine the change in kinesthetic threshold across these states. Correlating this variable with overall clinical measures such as disease severity, PIGD, and axial symptoms informs us of any relation between the patient's functional state and improvement or decline in the experimental dependent measure.

Results

The accuracy in determining the direction of axial rotation was impaired in PD subjects relative to healthy age-matched controls. Kinesthetic deficits were also evident by the higher thresholds for detecting the onset of axial rotation. Sensitivity to axial rotation was lower when ON levodopa medication versus OFF. The change in

threshold when ON versus OFF medication was also significantly correlated with disease severity. Side of disease onset also affected PD sensitivity.

Directional sensitivity

Although all groups performed above 50% chance in both Hip and Trunk Kinesthesia conditions, significant differences in accuracy of directional indication were observed between subject groups (Fig. 3a). In the Hip condition, PD-ON performed at 81%, PD-OFF at 91% and controls at 96% HIT-rates. The difference between PD-ON versus OFF was significant ($p < 0.03$), and PD-ON versus controls ($p < 0.001$). In the Trunk condition, PD-ON accuracy was 81%, PD-OFF was 88%, and controls were 95%. PD subjects ON medication performed significantly worse than controls ($p < 0.002$), and had a tendency to perform worse than controls when OFF medication ($p = 0.06$, n.s.) (Fig. 3b).

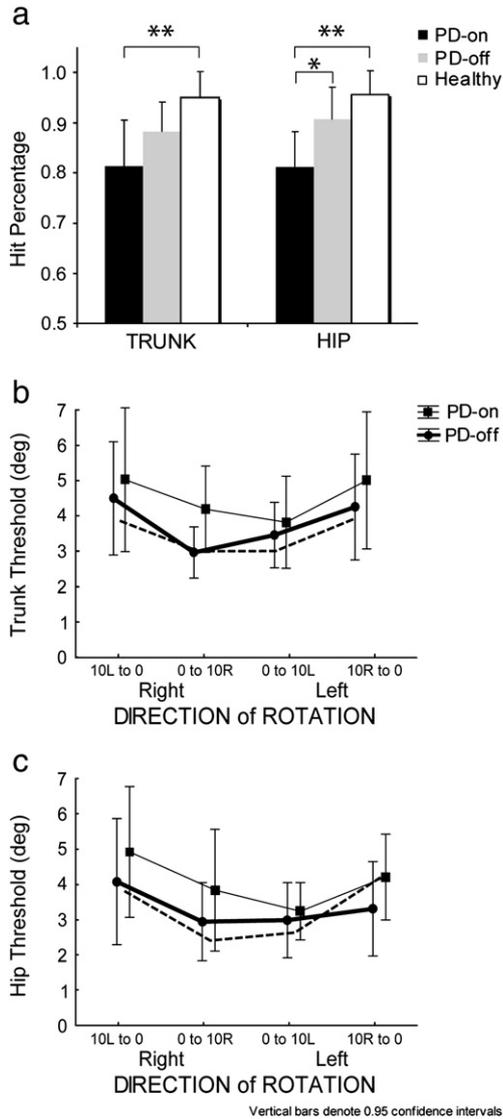


Fig. 3. Accuracy of perceiving the direction of axial rotation and threshold of detecting the onset of axial rotation. a) The average percentage of accurate responses for PD subjects ON (black bar) or OFF (gray bar) medication, and age-matched control (white bar) show a significant difference (*, $p < 0.05$; **, $p < 0.01$) between groups during TRUNK (left) and HIP (right) rotation. (bars indicate standard error), b) thresholds for detection of TRUNK rotation in PD subjects is greater when ON (thin line, squares) versus OFF (circles) medication ($p < 0.05$), c) thresholds for detection of HIP rotation in PD subjects is greater when ON versus OFF medication ($p < 0.01$). In b. and c., control subjects are indicated by dotted line and error bars indicate 95% confidence intervals.

Threshold of sensitivity

The sensitivity threshold to rotation of the hip was significantly higher in PD subjects ($F_{1,8} = 11.7$, $p = 0.009$) when ON medication compared to when OFF (Fig. 3c). The trunk kinesthetic threshold was less affected when ON versus OFF, showing only a non-significant trend ($F_{1,10} = 4.60$, $p = 0.058$, n.s.) that was dependent on whether rotating from a symmetrical or asymmetrical axial state (Fig. 3b). The effect of starting rotation from an asymmetrical state (“10 L to 0” and “10 R to 0”, in Fig. 3) compared to starting rotation from a symmetrical straight-ahead facing state (“0 to 10L” and “0 to 10R”) showed a higher threshold in all subjects, controls and PD alike. Moreover, in PD subjects this directional effect was significant both when ON ($p < 0.05$) and OFF ($p < 0.05$) medication.

Both hip and trunk kinesthetic sensitivity in PD subjects whose disease onset was on the left (LPD) was significantly higher than for those whose disease onset was on the right side (RPD) ($F_{1,7} = 6.78$, $p < 0.05$) (Fig. 4a). A number of significant statistical interactions were also found when we analyzed the effects of rotation direction and medication. We found a significant statistical interaction when rotating the trunk toward the affected side due to medication ($F_{1,9} = 5.15$, $p < 0.05$). RPD subjects had higher axial sensitivity than LPD subjects and only showed a reduction in sensitivity when rotated towards their affected side. Whereas LPD, in addition to having lower sensitivity, their sensitivity decreased even more when ON-meds, regardless of whether they were rotated to the affected or unaffected side (Fig. 4b).

Correlations in kinesthetic sensitivity relative to dopamine effects

The relationship between clinical UPDRS measures and the change in kinesthetic sensitivity due to levodopa usage revealed that the

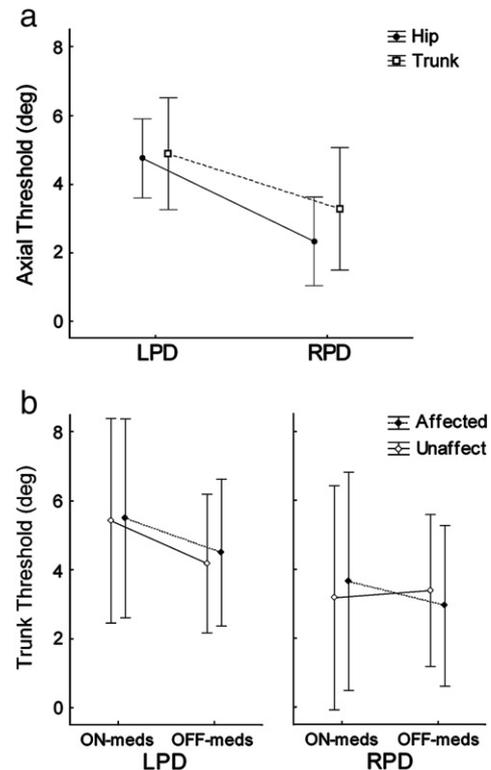


Fig. 4. Asymmetries in PD with left (LPD) versus right (RPD) disease onset. a) LPD have higher axial kinesthetic thresholds than RPD in both the trunk and hip ($p < 0.05$), b) trunk kinesthetic threshold shows an interaction between LPD and RPD when ON versus OFF medication, depending on whether rotating the affected or unaffected side. The sensitivity of the unaffected side of RPD did not decrease when ON medication ($p < 0.05$). Error bars indicate 95% confidence intervals.

differences in threshold when ON and OFF medication (i.e. “ON–OFF”) were positively correlated with clinical measures (Fig. 5). This correlation was most robust for the hip thresholds ($r = 0.90$, $p < 0.01$, Fig. 5a). When only considering the axial symptoms as measured by the axial part of the UPDRS, a significant positive correlation with the levodopa-induced change in hip threshold was also found ($r = 0.86$, $p < 0.01$, Fig. 5b). The change in trunk kinesthetic threshold “ON–OFF” had slightly weaker correlations with the full UPDRS scale ($r = 0.55$, $p = 0.08$, Fig. 5d) and axial symptoms ($r = 0.60$, $p < 0.05$, Fig. 5e). The “ON–OFF” effect of levodopa on axial kinesthetic thresholds also showed significant positive correlations with postural instability and gait difficulties (PIGD) in the hip ($r = 0.72$, $p < 0.05$, Fig. 5c) and trunk ($r = 0.74$, $p < 0.01$, Fig. 5f).

Discussion

Our study showed that PD subjects were significantly less accurate in determining the direction of axial rotation than age-matched healthy control subjects. We found that levodopa drug therapy had an unexpected negative effect on axial kinesthesia by increasing the thresholds in both the hip and trunk. Clinical measures of disease progression and functional impairment were significantly correlated with the change in axial kinesthetic thresholds when going ON and OFF their antiparkinson medication. Finally, the side of PD onset affected the axial kinesthetic thresholds, with LPD showing greater symptoms.

Effects of levodopa on axial kinesthesia

A very clear relation between axial kinesthetic sensitivity and levodopa usage in PD was found in this study. However, levodopa has a negative impact on axial kinesthesia. Although we also saw increases in threshold and worse accuracy when OFF medication relative to healthy controls, the differences were significantly larger when ON. The size of the kinesthetic deficit was not correlated with levodopa dosage amount, however, it was related to overall disease

severity. This relationship was not a direct correlation with UPDRS scores though. That is, UPDRS scores increased neither with the kinesthetic thresholds when OFF medication nor with the kinesthetic thresholds when ON medication. Rather, PD subjects whose disease symptoms were rated worst showed the greatest difference in their axial kinesthetic threshold when ON compared to OFF medication (“ON–OFF”). In other words, increases in disease severity correlated with the greatest increase in kinesthesia due to medication (see Fig. 5a and d). By looking at the change when ON versus OFF medication, we found that the most severe PD subjects may not necessarily have the lowest axial sensitivity, but rather it was those PD subjects with the largest “ON–OFF” threshold difference. That no correlation with levodopa dosage size was found may be explained by the fact that individuals with the most advanced disease symptoms do not necessarily take the most medication. To summarize the antiparkinson drug effects, the fluctuation from ON to OFF appears to have a more debilitating effect on axial kinesthetic sensitivity than dosage size, but being ON medication does result in a significant decrease in sensitivity.

Hypertonicity and kinesthesia

In a previous study with many of the same PD patients used in this study, we measured axial rigidity (i.e. the resistance to axial rotation) (Wright et al., 2007b). Despite finding a relation between disease severity and kinesthetic thresholds (Fig. 5), no significant correlation was found between the level of hypertonicity and kinesthetic thresholds. This finding seems to run counter to the hypothesis that increasing rigidity underlies increasing kinesthetic axial thresholds (Klockgether et al., 1995). However, we cannot discount the fact that there may not be a one-to-one relation between the two variables, but instead an all-or-none relationship. In other words, an upper limit for tonic level of muscle activity may exist. Above this limit improper integration of sensory information can alter the kinesthetic threshold, but by how much it alters the threshold depends on other factors not identified by our current methods.

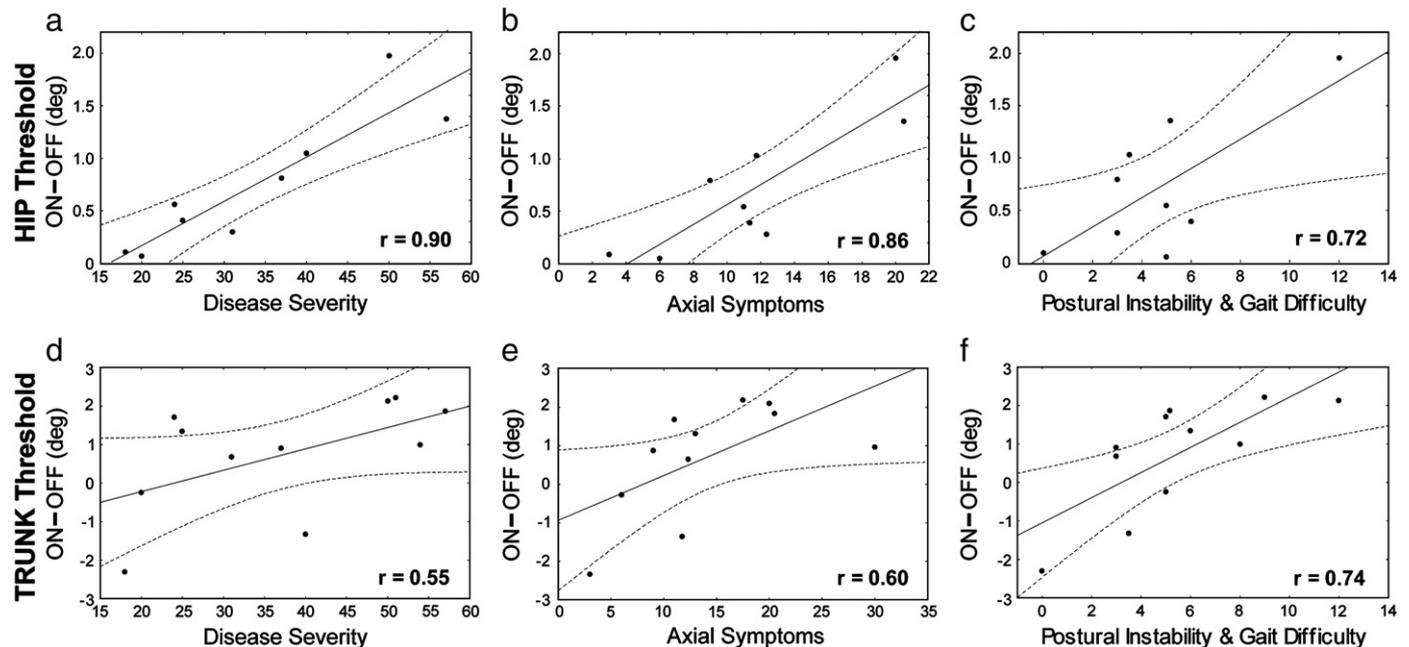


Fig. 5. Levodopa-induced changes in threshold when ON versus OFF are positively correlated with disease severity (UPDRS scores when OFF meds), axial symptoms (Axial-UPDRS scores OFF meds), and postural instability and gait disturbance (PIGD-UPDRS scores OFF meds). A positive value for “ON minus OFF” (y axis) indicates that the threshold increased when ON-meds, i.e. sensitivity decreased when ON-meds. (Top row) a) Disease severity ($r = 0.90$, $p < 0.01$), b) axial symptoms ($r = 0.86$, $p < 0.01$), and c) PIGD ($r = 0.72$, $p < 0.05$) positively correlated with levodopa-induced change in HIP threshold. (Bottom row) d) Disease severity ($r = 0.55$, $p = 0.08$, n.s.), and e) axial symptoms ($r = 0.60$, $p < 0.05$) showed weaker correlations with the levodopa-induced change in TRUNK threshold than in the hip, but f) PIGD had a similar correlation in the trunk ($r = 0.74$, $p < 0.01$) as in the hip. Dotted lines indicate 95% CI.

Altered axial kinesthesia affects functional measures

Individual parkinsonian symptoms have been shown to have dissociable effects on behavioral outcomes (Zetusky et al., 1985). For example, PD “fallers” tend to have postural instability, hypertonicity, and bradykinesia, but not tremor, and falling is not found to be reversible by dopamine therapy (Koller et al., 1989). A look at axial symptoms in PD reveals that these directly impact posture and gait (Franzen et al., 2009; Van Emmerik et al., 1999; Wright et al., 2007b). Although some studies have suggested that PD patients can be classified within subgroups, such as those with tremor-dominance and those with dominant symptoms of postural instability and gait difficulty (Jankovic et al., 1990; Zetusky et al., 1985), we did not set our inclusion/exclusion criteria based on these classifications. However, regression analysis using subsets of the UPDRS scores were used to determine how specific sets of related symptoms may correlate with kinesthetic deficits. Two of these subsets included axial symptoms and a more specific subset for postural impairment and gait difficulties. The “ON–OFF” threshold difference was strongly correlated with axial symptoms (Fig. 5b and e), while even stronger correlations were found with PIGD (Fig. 5c and f). Since there was no correlation between kinesthetic threshold when ON relative to PIGD, we can surmise that increasing kinesthetic thresholds do not directly correlate with worsening PIGD. So by itself, being ON levodopa does not predict a worsening in PIGD or axial symptoms in our sample, rather the negative impact seems to derive from the size of the difference in sensitivity when ON versus OFF medication.

It has been proposed before that a primary disturbance to PD function may lie in the changes in the gating and integration of sensory inputs which then affect motor outputs (Abbruzzese and Berardelli, 2003; Konczak et al., 2009). Because the mapping between sensory inputs and motor outputs is adaptable and in need of up-to-date precise calibration, motor behavior may be very susceptible to the fluctuations in kinesthetic sensitivity that occur when going back and forth between ON and OFF. Furthermore, even if the PD patient is very consistent and compliant in adhering to his dosage routine, spontaneous fluctuation between subjectively feeling “ON” and “OFF” their medication still can occur and is a well-known phenomenon in PD (see UPDRS Part IV, Complications in Therapy, Items 36–39). It has been reported that levodopa medication may have no effect or even negative effect on postural stability and gait problems (Horak et al., 1996; Koller et al., 1989). This negative effect on postural and motor impairments may be due to the frequent and unpredictable ON/OFF fluctuations, insofar as the fluctuations affect the fine tuning of sensorimotor control necessary for these tasks.

Asymmetry in kinesthesia depends on disease onset side

The current findings revealed an asymmetry in axial sensitivity, which depends on the side affected at Parkinson's disease onset. Subjects with left disease onset (LPD) showed significantly higher kinesthetic thresholds in both the hip and trunk. Functional asymmetries in PD have been linked to the side of nigrostriatal neuron loss in humans (Kempster et al., 1989; Kumar et al., 2003) and a similar explanation may underlie these axial asymmetries. Bilateral basal ganglia pathways project to areas in the brainstem involved in locomotor and postural control, such as the midbrain locomotor region and pedunculopontine tegmental nucleus (Takakusaki et al., 2004, 2008). Lateral axial asymmetries in PD may be directly caused by contralateral basal ganglia–cortical–spinal loops. Conversely, as the Hoehn and Yahr scale indicates, unilateral symptoms start distally with axial symptoms only beginning to appear at level 2 and above. Therefore, axial deficits may be compensations for early appendicular deficits (Wright et al., 2007a,b). Postural stability and controlled mobility require constant activity of axial muscles and any change to the center of mass via movement of the distal parts of the body must

be compensated by proximal segmental stabilization. Thus, a chronic lateralized change starting with the appendages may induce a chronic axial compensation.

Our findings that LPD have greater kinesthetic deficits than RPD, suggest a causal link with the perceptual deficits that many others have described in LPD. However, most of the prior evidence comes from visual and visuospatial tasks (Davidsdottir et al., 2005; Ebersbach et al., 1996; Harris et al., 2003; Lee et al., 2001; Starkstein et al., 1987). In our study, we are focused on a purely proprioceptive input that does not need to be mapped to exocentric coordinates, i.e. deciding between clockwise or counterclockwise rotation could be made entirely within an egocentric mapping. Using such body-centered coordinates, we surmise that this process does not overlap with that driving visual spatial motor imagery (Amick et al., 2006). Furthermore, our kinesthetic measure excluded visual feedback, which ensures us that the dopamine-affected receptors in the retina which may underlie visual bias in PD (Bodis-Wollner, 2003; Harris et al., 2003) is not the same mechanism underlying this axial kinesthetic asymmetry. Although our current findings do not determine if kinesthetic asymmetry precedes the motor asymmetry and visual biases or vice versa, the fact that both visual and kinesthetic asymmetries seem to predominantly affect LPD may mean that both originate from early asymmetrical nigrostriatal neuron loss.

Conclusions

The kinesthetic sensitivity of axial musculature is impaired in PD, especially when using levodopa medication. The kinesthetic deficit may be specific to a patient's subjective state of feeling ON or OFF caused by their medication. As the disease progresses, medication tends to become less efficacious resulting in ON/OFF fluctuations. Increasing the dosage does not usually help. The current evidence suggests that it is not simply a matter of PD axial thresholds being outside the population norms, rather it is the size of within-patient threshold change that occurs when going back and forth between ON and OFF. It would be interesting to investigate whether the calibration of other sensorimotor, perceptual, or cognitive processes is also sensitive to the size of the threshold changes in PD. Notwithstanding side-effects like subjective ON/OFF fluctuations, increased axial rigidity, decreased kinesthetic sensitivity, and secondary symptoms like dyskinesia, PD patients still highly prefer to take their medication. However, a growing body of evidence appears to show that despite the “freeing” effects of levodopa therapy, there are downsides of which both patients and clinicians should be aware.

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