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MULTISENSORY DETERMINANTS OF ORIENTATION PERCEPTION IN PARKINSON'S DISEASE

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Abstract—Perception of the relative orientation of the self and objects in the environment requires integration of visual and vestibular sensory information, and an internal representation of the body's orientation. Parkinson's disease (PD) patients are more visually dependent than controls, implicating the basal ganglia in using visual orientation cues. We examined the relative roles of visual and non-visual cues to orientation in PD using two different measures: the subjective visual vertical (SVV) and the perceptual upright (PU). We tested twelve PD patients (nine both on- and off-medication), and thirteen age-matched controls. Visual, vestibular and body cues were manipulated using a polarized visual room presented in various orientations while observers were upright or lying right-side-down. Relative to age-matched controls, patients with PD showed more influence of visual cues for the SVV but were more influenced by the direction of gravity for the PU. Increased SVV visual dependence corresponded with equal decreases of the contributions of body sense and gravity. Increased PU gravitational dependence corresponded mainly with a decreased contribution of body sense. Curiously however, both of these effects were significant only when patients were medicated. Increased SVV visual dependence was highest for PD patients with left-side initial motor symptoms. PD patients when on and off medication were more variable than controls when making judgments. Our results suggest that (i) PD patients are not more visually dependent in general, rather increased visual dependence is task specific and varies with initial onset side, (ii) PD patients may rely more on vestibular information for some perceptual tasks which is reflected in relying less on the internal representation of the body, and (iii) these effects are only present when PD patients are taking dopaminergic medication.

Key words: gravity perception, Parkinson's disease, perceptual upright, subjective visual vertical, visual dependence.

Patients with Parkinson's disease (PD) have been shown to rely more on visual information than age-matched controls in a number of spatial tasks related to perceived orientation (Proctor et al., 1964; Danta and Hilton, 1975; Bronstein et al., 1990, 1996; Azulay et al., 2002; Davidsdottir et al., 2008). Greater reliance on visual information in patients with PD has been particularly apparent when setting a line to vertical (Proctor et al., 1964; Danta and Hilton, 1975; Azulay et al., 2002) or when executing visually guided movements (Cooke et al., 1978; Messier et al., 2007). Given the long-established history of reports of increased visual dependence in patients with PD in perceptual orientation tasks, here we address the extent to which visual dependence is a general trait of the Parkinsonian brain and whether it arises from how patients with Parkinson's disease integrate multisensory information.

Although PD was originally characterized by Hoehn and Yahr (1967) as a motor system disorder, PD is now regarded as a disease affecting sleep (Garcia-Borreguero et al., 2003), emotional well being (Oertel et al., 2001), cognition (see Cronin-Golomb and Amick, 2001 for a review), visuo-spatial deficits (Stern et al., 1983; Boller et al., 1984; Hovestadt, 1987; Ransmayr et al., 1987; Richards et al., 1993; Cronin-Golomb and Braun, 1997; Hocherman, 1998; Lee et al., 2001a,b; Davidsdottir et al., 2005; Kemps et al., 2005), as well as sensation and perception. Sensory deficits include visual (Bodis-Wollner et al., 1987; Davidsdottir et al., 2005; see Archibald et al., 2009 for a recent review), vestibular (Reichert, 1982), and proprioceptive (Klockgether et al., 1995; Jobst et al., 1997; Adamovich et al., 2001; Contreras-Vidal and Gold, 2004; Maschke et al., 2003; Vaugoyeau et al., 2007) information processing all of which are critical in the perception of orientation (see Howard, 1982 for a review).

Setting a line or rod to the visually perceived gravitational vertical indicates what is known as the subjective visual vertical (SVV; see Howard, 1982 for a review). When a rod is surrounded by a tilted square frame, the extent to which an observer's judgment of the SVV is influenced by visual information can be assessed (the rod-and-frame test; Witkin and Asch, 1948b). Observers who set the rod closer to the orientation of the frame are said to be more "field [visually] dependent" than those who set the rod closer to the true gravitational vertical (Witkin et

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Abbreviations: BPD, Parkinson's disease patients with bilateral initial motor signs; FE, frame effect; LPD, Parkinson's disease patients with left initial motor signs; PD, Parkinson's disease; PD_{off}, Parkinson's disease patients off medication; PD_{on}, Parkinson's disease patients on medication; PU, perceptual upright; RE, room effect; RPD, Parkinson's disease patients with right initial motor signs; RSD, right side down; SVV, subjective visual vertical; UPDRS, Unified Parkinson Disease Rating Scale.

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al., 1954). Patients with PD exhibit an increased dependency on vision when judging the SVV (Azulay et al., 2002) or the horizontal equivalent (Davidsdottir et al., 2008).

The SVV is affected not only by the orientation of the visual environment but also by the body's orientation relative to gravity (Aubert, 1861; Müller, 1916; Witkin and Asch, 1948a; Dyde et al., 2006, see Howard, 1982; Mittelstaedt, 1983 for reviews). Recently, Dyde et al. (2006) developed the Oriented CHAracter Recognition Test to measure the contributions of visual and non-visual cues on the perceptual upright (PU): a measure of "which way is up" or, more specifically, the orientation at which objects appear most upright relative to the observer (Rock and Heimer, 1957; Rock, 1973; Corballis et al., 1978; Jolicoeur, 1985; Dyde et al., 2006). Like the SVV, the PU is influenced by orientation information from vision, an internal representation of the body and the vestibular system (Mittelstaedt, 1983, 1988; Oman, 2003; Dyde et al., 2006).

Whether non-visual cues are more or less relied upon by patients with PD is unknown. Given that PD patients have deficits in their posture and gait, including rigidity, akinesia and, in particular, tremor, and that they show deficits in processing proprioceptive information (Klockgether et al., 1995; Jobst et al., 1997; Adamovich et al., 2001; Maschke et al., 2003; Contreras-Vidal and Gold, 2004; Vaugoyeau et al., 2007), we suspected that these deficits might impair the sense of the body, which may in turn reduce the reliability of the representation of the body's orientation the extent with which such cues are relied upon in determining the SVV and PU. Further, given that dopamine replacement therapy has been shown to induce deficits in the processing of proprioceptive information (O'Suilleabhain et al., 2001; Maschke et al., 2005; Schettino et al., 2006; Jacobs and Horak, 2006; Tunik et al., 2007; Mongeon et al., 2009) we further suspected that particular reliance on one sensory cue (e.g. vision) over others (e.g. vestibular and body sense) may be different when PD patients are medicated using dopaminergic medication.

The present study was designed to evaluate orientation perception in PD patients using both the SVV and PU. We assessed the contribution of vision by testing the SVV and PU against visual backgrounds of various orientations. The relative contributions of the non-visual cues of body orientation and gravity were assessed by measuring the SVV and PU while lying on one side under which conditions the orientation of gravity and the body are orthogonal. If observers rely more on their representation of the body then the SVV and the PU will be closer to the body's orientation, if they rely more on gravity, the settings will be closer to the orientation of gravity. Comparison of the SVV and PU in PD patients lying on their side with those of controls allows us to look for changes in the relative weighting of these non-visual cues. To discern which neural processes are involved in any changes to the SVV and PU, patients with PD were tested while both on and off dopaminergic medication.

EXPERIMENTAL PROCEDURES

Participants

Twelve participants diagnosed with idiopathic PD according to the UK Brain Bank Criteria (Gibb and Lees, 1988) were recruited from the Movement Disorders Clinic of the Toronto Western Hospital (mean age=65.8, s.d.=11; eight males; Table 1). Parkinsonian disability was assessed using the Unified Parkinson Disease Rating Scale (UPDRS; Table 1). PD patients had mild-moderate disease severity with a mean disease duration of 4.6 years (s.d.=3.3), median Hoehn and Yahr stage 2.5 (range: 1–2.5). Four PD patients had initial motor signs of the disease occurring on the left side of the body (LPD), five on the right side of the body (RPD) and three bilaterally (BPD). PD patients were all on stable anti-Parkinsonian medication: levodopa and/or dopamine agonist, pramipexole or ropinirole; five patients were on pramipexole. Two patients were taking trihexyphenydyl for tremor. Note that due to the heterogeneity of medications taken we acknowledge that the

Table 1. Patient demographics

Age	Sex	PD dur. (y)	Init. side	UPDRS I	UPDRS III	UPDRS III #29	UPDRS III #30	L-dopa (mg/d)	L-dopa Eq. (mg/d)	Other PD drugs (mg/d)
80	**M**	**2**	**BPD**	**1**	**16 (31)**	**0 (1)**	**0 (1)**	**300**	**300**	
70	**M**	**3**	**BPD**	**2**	**16 (27)**	**1 (1)**	**1 (1)**	**600**	**600**	
63	**M**	**3**	**RPD**	**0**	**8 (17)**	**1 (1)**	**1 (1)**	**0**	**300**	
47	**F**	**3**	**LPD**	**0**	**11 (16)**	**0 (0)**	**0 (0)**	**0**	**400**	
47	**F**	**3**	**LPD**	**2**	**12 (23)**	**0 (0)**	**0 (0)**	**0**	**300**	
74	**M**	**4**	**LPD**	**1**	**20 (28)**	**0 (1)**	**1 (1)**	**300**	**450**	**Trihexyphenydyl (6)**
55	**M**	**4**	**RPD**	**0**	**18 (29)**	**0 (0)**	**0 (0)**	**150**	**450**	
67	**M**	**5**	**RPD**	**3**	**9 (20)**	**0 (1)**	**0 (1)**	**0**	**250**	
77	**F**	**6**	**RPD**	**0**	**12 (15)**	**0 (0)**	**0 (0)**	**0**	**300**	**Entacapone (800)**
75	F	3	BPD	1	14	1	1	500	500	
68	M	11	RPD	0	23	0	1	500	950	Trihexyphenydyl (2)
67	M	12	LPD	1	10	1	1	1000	1075	Entacapone (800)

Duration since PD diagnosed (PD Dur.) is given in years. Initial side of PD motor symptoms (Init. Side) is given as right (RPD), left (LPD) and bilateral (BPD). UPDRS I assesses mentation, behaviour and mood across four subscales each with a 4-point scale for a possible total score of 16 points. UPDRS III PD_{on} medication, and (PD_{off}), as rated in the clinic (maximum score total score of 108). UPDRS subscales for gait (item 29) and postural stability (item 30) are also given. Symptom severity increases with higher scores on all UPDRS scales. Total daily dose of levodopa (L-dopa) and levodopa-equivalent (L-dopa Eq.; calculated using standard methods: Krack et al., 1998) are shown in mg/day. Other PD medications are also listed for each patient. Patients who elected to withdraw from medication are highlighted in bold.

conclusions drawn concerning the effects of medication in this study can only be tentative. The mean motor UPDRS part III medication score was 15.7 (s.d.=7.2) for medicated PD patients. Nine participants agreed to be tested with an overnight withdrawal of PD drugs. The mean PD_{off} motor UPDRS score was 15.7 (s.d.=7.8). No patient had significant gait or balance issues: thus the maximum UPDRS gait or balance sub-score was 1. No patient exhibited or reported freezing or falling behaviour when either on or off medication. Exclusion criteria included: cognitive impairment (Mini Mental State Examination; <26), vestibular or visual deficits, poorly corrected visual acuity, disabling tremor or dyskinesia that would preclude lying still, and use of benzodiazepines. These criteria were confirmed by each patient's physician.

The patient's spouses or friends acted as the control group (mean age=61.9, s.d.=10.3, five males). They had no neurological, visual or vestibular problems and there was no difference in age compared to the patient group ($t_{(1,23)}$=0.92, P=0.37). PD patients and controls were capable of understanding the response criteria, were able to press buttons on a gamepad and received no feedback regarding their performance in the experiment. All patients with PD were tested while taking their regularly prescribed dopaminergic medication (PD_{on}). Nine patients with PD were also tested while off their medication (PD_{off}; after a 12-h washout). For those patients tested while both on and off medication, testing occurred over the course of two successive days where the order of being medicated or not for the first testing day was randomized across patients. Institutional ethical approval was obtained and all participants gave informed written consent according to the guidelines of the University Health Network and the York University Research Ethics Boards in compliance with the 1964 Declaration of Helsinki.

Convention

The orientation of all stimuli (including the direction of gravity) was defined with respect to the body mid-line of the participant. 0° refers to the orientation of the longitudinal body axis. Positive tilt is clockwise. The orientation of the screen was constant relative to the observer for all conditions.

Apparatus

Participants either sat on a padded chair (Fig. 1a) or lay on a padded hospital gurney (Fig. 1b) on their right side with their head supported by foam blocks to ensure that their head was at 90° relative to gravity. Participants viewed stimuli presented in the fronto-parallel plane on an Apple iBook laptop computer with a resolution of 48 pixels/cm (21 pixels/°). Peripheral vision was masked to a circular screen of diameter 35° by viewing through a circular tunnel that also maintained the viewing distance at 25 cm. Participants responded by pressing either a left or right button on a gamepad using their left and right thumbs respectively.

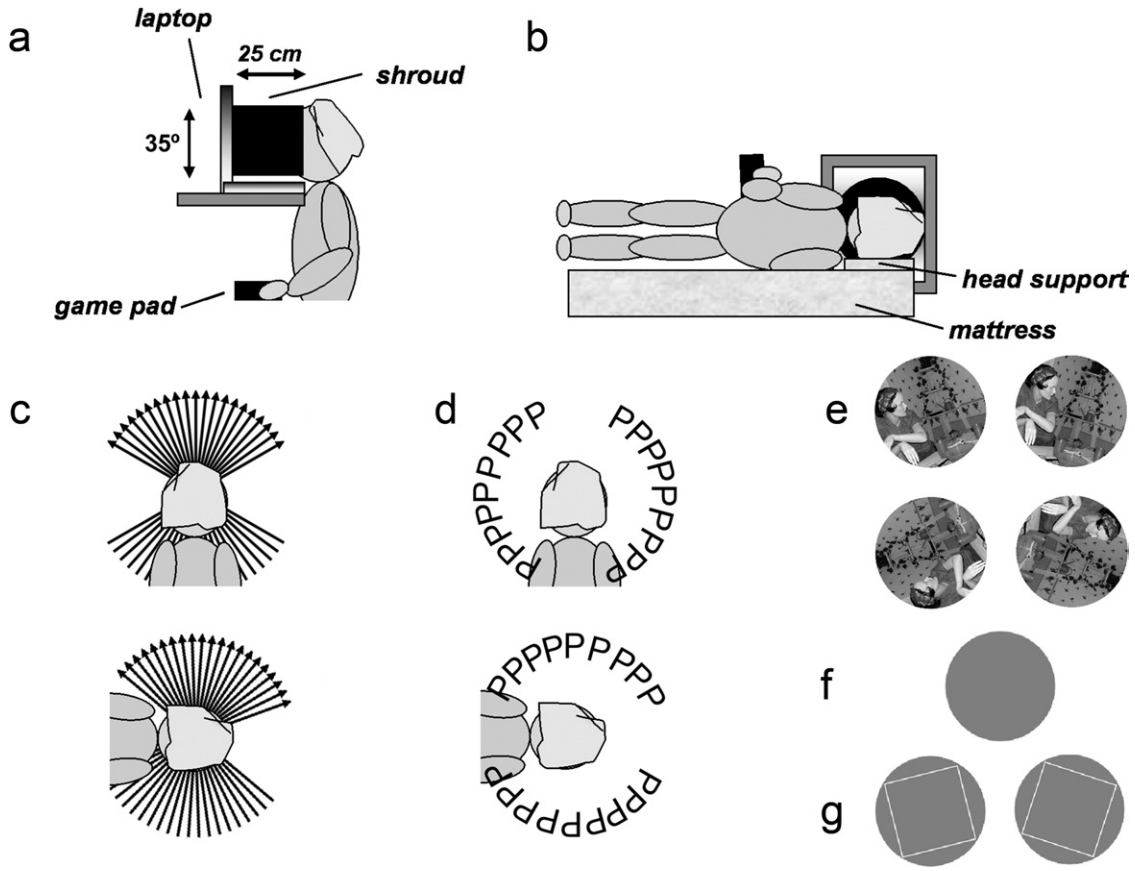

Fig. 1. Apparatus. The two body postures used in these experiments: upright (a) and right-side-down (RSD; b). Participants viewed the display through a shroud to obscure all peripheral vision. Viewed through the shroud, the screen subtended a 35° diameter circle at a distance of 25 cm. Schematic depiction of arrow line orientations used for the SVV task shown relative to the head when upright and RSD (c). Note the range for RSD is shifted clockwise by 10° relative to gravity. Schematic depiction of letter character orientations used for the PU task when upright and RSD (d). Note that these are not shown to scale relative to the head and that all arrow lines and characters were actually presented centrally relative to the observer. The highly polarized visual backgrounds (e), grey background (f) and frame backgrounds (g) used in the experiment.

Stimuli for determining the subjective visual vertical

We determined the SVV using a variant of the "luminous line" technique. A simple arrow line probe (18°×0.5° of visual arc, see Fig. 1c) was presented for 500 ms and oriented about a central fixation point (formed by a white dot projecting 0.45° of visual arc). For testing the SVV when upright, the probe line was presented in 21 orientations (from −60° to +60° in 6° increments; Fig. 1c). For testing the SVV when right-side-down (RSD) the range of line orientations was shifted by 10° clockwise relative to gravity (i.e., from −140° to −20° in 6° increments; Fig. 1c) to account for the fact that the perception of gravity for most participants is biased between gravity and body orientation for tilts greater than 60° in the absence of visual cues in this direction (Van Beuzekom and Van Gisbergen, 2000; Dyde et al., 2006). Pilot studies on normal populations suggested this did not induce significant range effects. Comparisons were always made between data collected using the same range of probe orientations. The arrow line probe was superimposed on a 35° diameter circular background picture which was either rich in visual cues for up (Fig. 1e), a neutral grey background of the same mean luminance as the polarized display (Fig. 1f), or a square white frame (29.7°×29.7° of visual arc) against the same neutral grey background (Fig. 1g). The visual frame was presented when upright only and was oriented ±18° relative to the head. These orientations were selected to match stimuli used by Azulay and colleagues (2002) in assessing visual dependence in PD. The polarized visual scene was also displayed at ±18° and at ±112.5° as these orientations yield peak effects in biasing the PU in normal participants (Dyde et al., 2006). Note that this sample of background orientations is known to have large effects (see Dyde et al., 2006). Stimuli were displayed for 500 ms and then replaced with a screen of the same mean luminance containing the fixation dot. Participants reported whether the line appeared tilted to the left or right of gravitational vertical by pressing either the left or right buttons on the gamepad respectively.

Stimuli for determining the perceptual upright

To monitor the PU, we used the Oriented CHAracter Recognition Test (Dyde et al., 2006). A 'p' symbol (3.1°×1.9° of visual arc) was presented for 500 ms at the fixation point. For both upright and RSD body postures the letter probe was presented in 18 orientations from 30° to 150° and 210° to 345° relative to the head in increments of 15° (Fig. 1d). These orientations were selected to capture the transition points of where a "p" is equally likely to be perceived as a "d" (see Dyde et al., 2006). The character probe was superimposed on one of the 35° diameter circular background pictures (Fig. 1e–g). Stimuli were displayed for 500 ms and then replaced with a screen of the same mean luminance. Participants reported whether the character appeared as the letter "p" or "d."

For each participant, data collection occurred over two consecutive days. Where applicable, patients were tested after having withdrawn from their medication for at least 12 hours on either the first or second day of testing. Controls and patients with PD who elected not to withdraw from medication were also tested on both days (i.e., they repeated all the conditions twice). Each day of testing consisted of four blocks of trials: SVV upright, SVV RSD, PU upright, PU RSD. All trials using one task (e.g., the SVV) were completed before running all the trials using the other task (e.g., PU). The order of testing with and without medication was balanced. Within a block, trials were randomized.

Each block of trials started with a set of practice trials against the grey background. For the SVV the 21 oriented lines were repeated seven times in random order for a total of 147 practice trials. Participants reported whether the line probe was oriented counter clockwise or clockwise (i.e., left or to the right) relative to the direction of gravity. The direction of gravity was defined as the "direction in which a ball would fall if dropped." For the PU practice trials the letter "p" was presented in 18 orientations repeated seven times in random order for a total of 126 practice trials. Participants reported whether the presented character looked more like the letter "p" or the letter "d." Practice trials took no more than 5 min to collect. To pass criterion each set of trials had to show a clear transition from left to right for the SVV, from "p" to "d" and "d" to "p" for the PU. All participants were found capable of performing both tasks.

In the SVV upright condition there were thus 21 (line)×7 (background: grey, frame ±18°; room ±18° and ±112.5°)=147 combinations. In the SVV RSD task there were 105 combinations (i.e., grey and the four room backgrounds only). Each combination was presented seven times for a total of 1029 and 735 presentations respectively. In the PU upright task there were 18 (letter)×7 (background: grey, frame ±18°; room ±18°; ±112.5°)=126 combinations. In the PU RSD task there were 90 combinations (i.e., grey and the four room backgrounds only). Each combination was presented seven times for a total of 882 and 630 presentations respectively.

Analysis

For the SVV, a sigmoid (Eq. 1) was fitted to the percentage of times the line was judged clockwise relative to gravity as a function of line orientation. The orientation of the line probe at which it was equally likely to be judged tilted clockwise or counter-clockwise from gravitational vertical was taken as the SVV. For the PU, two sigmoids were fitted to the percentage of times the observers identified the character as a "p" as a function of character orientation to determine each of the p-to-d and d-to-p transitions—when participants were equally likely to respond "p" or "d"—for each visual background in each body orientation. The average of the two angles at which these transitions occurred was taken as the PU.

$$y=\frac{100}{1+e^{-\left(\frac{x-x_0}{b}\right)}}\% \quad (1)$$

Where x_0 corresponds to the 50% point and b is the standard deviation (so that b^2 is the variance).

RESULTS

SVV and PU measured against a grey background

By measuring the SVV and PU against a grey background we were able to assess the effect of non-visual cues and also assess whether there were any consistent biases. When upright all participant group estimates of the SVV and PU were aligned with gravity (0°, for the exact values see Tables 2 and 3). The SVV and PU measured against a grey background with the body oriented RSD reflect the extent to which gravity and body orientation contribute to perceptions of up in the absence of visual information. When RSD, SVV judgments were significantly shifted away from the actual direction of gravity (−90°) towards the body (0°) by about 17° (i.e., at −73°; see Table 2) there were no significant differences between groups. For the PU when RSD, judgments were significantly shifted away from gravity by about 49° (i.e., to −41°; see Table 3) there were no significant differences between groups.

Rod-and-frame test (SVV)

The rod-and-frame test measures the effect of visual frame orientation on estimates of the SVV. In order to check for

Table 2. Average subjective visual vertical (SVV)

Visual	Body	Group	SVV	s.e.	One-sample *t*-tests			One-way ANOVA		
					df	*t*	*P*	*F*	*P*	Bonferroni *P*
Grey	Up	PD_{off}	0.9°	1.4	8	0.69	0.510	0.31	0.738	>0.05 PD_{off}–PD_{on}
		PD_{on}	0.3°	1.3	11	0.19	0.850			>0.05 PD_{off}–control
		Control	−0.5°	1.1	12	0.45	0.661			>0.05 PD_{on}–control
	RSD	**PD_{off}**	**−68.1°**	**8.8**	**8**	**2.50**	**0.037**	0.43	0.653	>0.05 PD_{off}–PD_{on}
		PD_{on}	**−73.0°**	**5.3**	**11**	**3.21**	**0.008**			>0.05 PD_{off}–control
		Control	**−76.8°**	**5.8**	**12**	**2.27**	**0.042**			>0.05 PD_{on}–control
Frame	Up	PD_{off}	1.1°	2.6	17	0.42	0.683	0.09	0.917	>0.05 PD_{off}–PD_{on}
		PD_{on}	−0.1°	2.6	23	0.27	0.979			>0.05 PD_{off}–control
		Control	−0.2°	1.6	25	0.13	0.897			>0.05 PD_{on}–control
Room	Up	PD_{off}	0.2°	2.0	35	0.12	0.909	0.97	0.382	>0.05 PD_{off}–PD_{on}
		PD_{on}	−3.2°	1.9	47	1.55	0.129			>0.05 PD_{off}–control
		Control	−0.5°	1.3	51	0.41	0.686			>0.05 PD_{on}–control
	RSD	**PD_{off}**	**−65.3°**	**4.4**	**35**	**5.59**	**<0.001**	0.33	0.718	>0.05 PD_{off}–PD_{on}
		PD_{on}	**−66.6°**	**3.7**	**47**	**6.38**	**<0.001**			>0.05 PD_{off}–control
		Control	**−69.6°**	**3.5**	**51**	**5.77**	**<0.001**			>0.05 PD_{on}–control

Average SVV values for the PD_{off}, PD_{on}, and control groups obtained from each combination of visual background (grey, frame background, room background) and body orientation (Up, right-side-down; RSD). For the frame and room backgrounds, SVV values have been collapsed across all background orientations to look for biases or asymmetries. Positive values are clockwise relative to the observer. Standard errors represent the inter-subject variance of these values. One sample *t*-tests indicate whether the average SVV was significantly different from the orientation of gravity when upright (0°) and when RSD (−90°). One-way ANOVA and Bonferroni pair-wise comparison tests indicate whether the average SVV was significantly different across the participant groups. Significance ($P<0.05$) is highlighted in bold text.

biases or asymmetries between when the frame was tilted clockwise or counter clockwise, we collapsed the conditions with the frame tilted left and right relative to the participant. The results are shown in Table 2. To assess the effect of the rod-and-frame test we took the difference between the SVV with the +18° frame and the SVV with the −18° frame. We call this difference the frame effect (FE) where positive FE values indicate bias in the direction of the frame's tilt. The SVV of all groups was significantly influenced by the frame when oriented upright, with the PD_{on} group (22.9°±2.1°) significantly more influenced than controls (11.4°±1.9°; $P=0.02$). The PD_{off} (13.6°±5.1°) group had less of a FE than the PD_{on} group, but this difference did not reach significance ($P=0.12$; Table 4). The PD_{off} group was also not significantly different from the control group ($P>0.05$; Table 4).

PU-frame test

The PU-frame test measures the effect of visual frame orientation on estimates of the PU. The effect of the frame is calculated using the FE in the same way as for the rod-and-frame test (see above). The PU was not significantly influenced by the tilted frame background for any of the groups (Table 4).

Table 3. Average perceptual upright (PU)

Visual	Body	Group	PU	s.e.	One-sample *t*-tests			One-way ANOVA		
					df	*t*	*P*	*F*	*P*	Bonferroni *P*
Grey	Up	PD_{off}	−1.3°	2.6	8	0.51	0.627	0.49	0.606	>0.05 PD_{off}–PD_{on}
		PD_{on}	2.4°	2.1	11	1.16	0.270			>0.05 PD_{off}–control
		Control	−0.1°	3.0	12	0.04	0.971			>0.05 PD_{on}–control
	RSD	**PD_{off}**	**−44.6°**	**9.4**	**8**	**4.82**	**0.001**	0.35	0.744	>0.05 PD_{off}–PD_{on}
		PD_{on}	**−43.3°**	**10.0**	**11**	**5.19**	**<0.001**			>0.05 PD_{off}–control
		Control	**−35.3°**	**6.5**	**12**	**8.40**	**<0.001**			>0.05 PD_{on}–control
Frame	Up	PD_{off}	0.7°	2.2	17	0.29	0.774	0.48	0.584	>0.05 PD_{off}–PD_{on}
		PD_{on}	−0.5°	2.3	23	0.22	0.983			>0.05 PD_{off}–control
		Control	−2.2°	2.1	25	1.07	0.294			>0.05 PD_{on}–control
Room	Up	PD_{off}	0.8°	3.5	35	0.23	0.820	0.15	0.956	>0.05 PD_{off}–PD_{on}
		PD_{on}	−0.5°	2.9	47	0.16	0.870			>0.05 PD_{off}–control
		Control	−1.5°	2.5	51	0.61	0.544			>0.05 PD_{on}–control
	RSD	**PD_{off}**	**−38.2°**	**5.7**	**35**	**9.97**	**<0.001**	**8.02**	**0.002**	>0.05 PD_{off}–PD_{on}
		PD_{on}	**−50.5°**	**4.8**	**47**	**8.18**	**<0.001**			>0.05 PD_{off}–control
		Control	**−25.4°**	**3.8**	**51**	**17.01**	**<0.001**			**0.001 PD_{on}–control**

Average PU values for the PD_{off}, PD_{on}, and control groups obtained from each combination of visual background (grey, frame background, room background) and body orientation (Up, RSD). See table 2 for statistics conventions.

Table 4. Average frame effect (FE)

Task	Group	FE	s.e.	One-sample *t*-tests			One-way ANOVA		
				df	*t*	*P*	*F*	*P*	Bonferroni *P*
SVV	PD_{off}	13.6°	5.1	8	**2.47**	**0.039**	**4.67**	**0.017**	>0.05 PD_{off}–PD_{on}
	PD_{on}	22.9°	2.1	11	**10.44**	**<0.001**			>0.05 PD_{off}–control
	Control	11.4°	1.9	12	**5.44**	**<0.001**			**0.02 PD_{on}–control**
PU	PD_{off}	2.5°	4.0	8	0.39	0.709	0.38	0.689	>0.05 PD_{off}–PD_{on}
	PD_{on}	6.8°	3.8	11	1.51	0.157			>0.05 PD_{off}–control
	Control	3.0	2.4	12	0.86	0.410			>0.05 PD_{on}–control

Average FE values for the PD_{off}, PD_{on}, and control groups obtained with the frame background with the body upright for the SVV and PU tasks. Positive values indicate a bias in the direction of the frame's orientation. See table 2 for statistics conventions.

The effect of a polarized room on the SVV

When upright all SVV estimates against a room background were centered about gravity, and were shifted away from gravity towards the body when RSD (Table 2).

To assess the effect of room orientation on SVV we took the maximum shift in the positive direction minus the maximum shift in the negative direction. We call this the room effect (RE). The RE is an indication of the extent to which visually derived orientation cues influence the SVV. In the upright posture an effect of group was found where the PD_{on} group was more influenced by room orientation than controls (Table 5).

A significant main effect of initial side of motor symptom onset was found for the PD_{on} SVV upright RE using a one-way ANOVA with Bonferroni corrections ($F_{(2,11)}$= 10.9, P=0.004; see Fig. 2). Here LPD patients (n=4, mean=39.4°±3.2°) were significantly more effected by the room background than RPD patients (n=5, mean=18.9°± 2.2°; P=0.004), but were no different than patients with bilateral initial motor symptoms (BPD; n=3, mean=27.5°± 4.0°; P=0.124). Note that this effect was not significant for the PD_{off} group (see Fig. 2), suggesting that this effect may be attributable to medication. No significant relationships were found between patient motor symptoms and perceptual measures. When RSD, all groups were significantly influenced by the room background (Table 5) with no significant differences between groups.

The effect of a polarized room on the PU

When upright all PU estimates were centered about gravity, and were shifted away from the body and towards gravity when RSD (Table 3). The PD_{on} group (−50.5°±4.8°) was more influenced by the direction of gravity than controls (−25.4°±3.8°) who were more influenced by body orientation (P=0.001). Note that this is comparable to a similar trend found against the grey background where the PD_{on} PU was closer to gravity than controls (see Table 3). Although the PD_{off} group (−38.2°±5.7°) was also more influenced by gravity than controls, and less influenced by gravity than the PD_{on} group, these differences did not reach significance (P>0.05). No significant effect of initial side of motor symptom onset was found for the PU RE (see Fig. 2). No differences were found for the PU RE when comparing upright and RSD (Table 5). No significant relationships were found between patient motor symptoms and perceptual measures.

Variability in estimating the SVV and PU

To assess the precision with which PD patients performed these perceptual tasks compared to controls we looked at

Table 5. Average room effect (RE)

Task	Body	Group	RE	s.e.	One-sample *t*-tests			One-way ANOVA		
					df	*t*	*P*	*F*	*P*	Bonferroni *P*
SVV	Up	PD_{off}	19.2°	3.0	8	**6.38**	**<0.001**	**4.45**	**0.020**	>0.05 PD_{off}–PD_{on}
		PD_{on}	27.9°	3.2	11	**8.83**	**<0.001**			>0.05 PD_{off}–control
		Control	16.9°	2.3	12	**7.20**	**<0.001**			**0.01 PD_{on}–control**
	RSD	PD_{off}	23.0°	2.5	8	**9.16**	**0.012**	0.39	0.680	>0.05 PD_{off}–PD_{on}
		PD_{on}	30.1°	5.0	11	**6.07**	**<0.001**			>0.05 PD_{off}–control
		Control	25.6°	6.8	12	**3.76**	**0.003**			>0.05 PD_{on}–control
PU	Up	PD_{off}	40.5°	5.3	8	**7.62**	**<0.001**	1.30	0.288	>0.05 PD_{off}–PD_{on}
		PD_{on}	42.8°	6.4	11	**6.66**	**<0.001**			>0.05 PD_{off}–control
		Control	31.2°	4.8	12	**6.45**	**<0.001**			>0.05 PD_{on}–control
	RSD	PD_{off}	45.8°	14.1	8	**3.24**	**<0.001**	0.11	0.897	>0.05 PD_{off}–PD_{on}
		PD_{on}	41.2°	6.5	11	**6.36**	**<0.001**			>0.05 PD_{off}–control
		Control	38.7°	10.8	12	**3.60**	**0.003**			>0.05 PD_{on}–control

Average RE values for the PD_{off}, PD_{on}, and control groups obtained with the room background paired with each body orientation (up, RSD) for the SVV and PU tasks. Positive values indicate a bias in the direction of the room's orientation. See table 2 for statistics conventions.

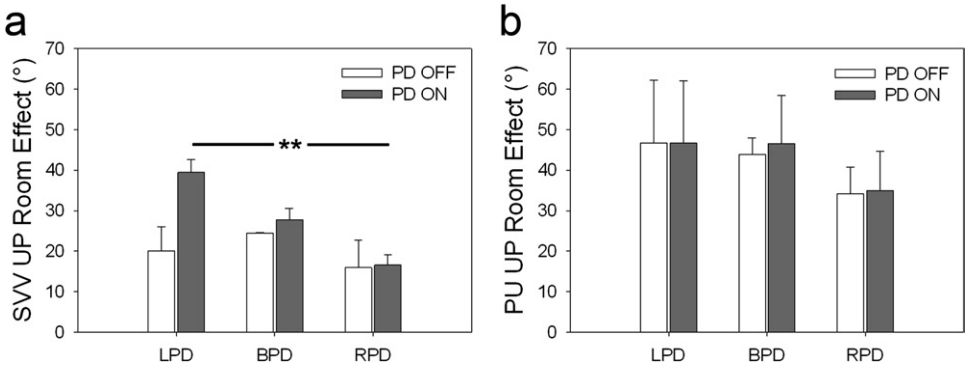

Fig. 2. Initial onset side of PD motor symptoms. Average SVV (a) and PU (b) room effects when oriented upright for the PD_{off} (white) and PD_{on} (grey) groups split according to the initial side of motor symptoms (left-side initial onset: LPD; bilateral initial onset: BPD; right-side initial onset: RPD). Standard error values are also given which represent the inter-subject variance of these values. ** $P<0.01$.

the standard deviations of the sigmoidal functions (for the PU task we took the mean standard deviation from the two functions). A mixed-design repeated measures ANOVA of the upright data (Background×Group×Task: Fig. 3a, Table 6a) was performed using Greenhouse–Geisser corrections for multiple comparisons and violations of sphericity. The results showed that the PD_{on} group was significantly more variable than controls ($P=0.02$). There was also a significant effect of the type of background ($P=0.02$) with the grey background producing the least variance and the room producing the most, however there were no significant differences in variances among the backgrounds. Finally, PU judgments were more variable than SVV judgments ($P=0.001$). Another mixed-design repeated measures ANOVA which included RSD data and excluded the frame background (Body×Background×Group×Task: Fig. 3b, Table 6b) found that the PD_{off} and PD_{on} groups were significantly more variable than controls ($P=0.03$; $P=0.01$ respectively). The room background contributed to higher variability than the grey background ($P=0.001$). Variability also increased when RSD ($P=0.003$). Finally, PU judgments were more variable than SVV judgments ($P=0.002$). No differences were found between the PD_{on} and PD_{off} groups ($P>0.05$).

DISCUSSION

Patients with mild to moderate PD when both on and off medication were much more variable when estimating the orientation of the SVV or the PU compared to age-matched controls.

Patients with PD were more influenced by the orientation of a visual scene than age-matched controls when judging the orientation of a line relative to gravity. This effect was only evident when patients were taking dopaminergic medication. This increased visual dependence was not universal, however: despite the increased visual dependency of the SVV in PD, the PU of PD patients was not more influenced by the orientation of the visual background compared to normal age-matched controls. Thus,

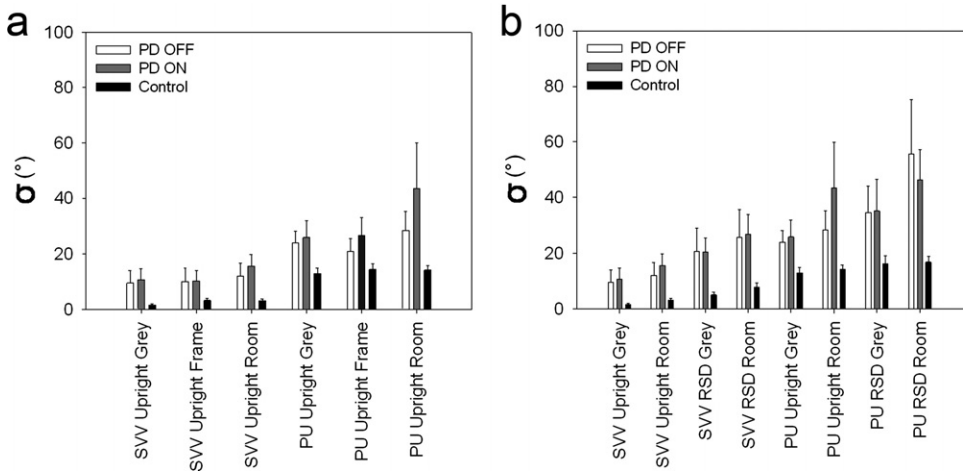

Fig. 3. SVV and PU variability. Average standard deviations (σ) derived from the cumulative sigmoidal function for the SVV task (Eq. 1) and the average mean standard deviations from the two sigmoidal functions for the PU task from the grey, average frame, and average room backgrounds while oriented upright for the SVV and the PU (a). Average mean standard deviations for the grey and average room backgrounds while oriented upright and RSD for the SVV and the PU (b). These values represent the square root of the intra-subject variance for each task. Standard error values are also given which represent the inter-subject variance of these values. Values are given for the PD_{off} (white), PD_{on} (grey) and control (black) groups.

Table 6. Variability statistics

	F	*P*	Bonferroni *P*
A			
Background	**5.41**	**0.019**	>0.05 $PD_{off}-PD_{on}$
Background×group	2.17	0.115	>0.05 PD_{off}−control
Background×task	1.34	0.255	**0.02 PD_{on}−control**
Background×group×task	0.78	0.478	>0.05 Grey−frame
Group	**4.05**	**0.022**	>0.05 Grey−room
Task	**12.05**	**0.001**	>0.05 Frame−room
Group×task	0.38	0.683	
B			
Body	**9.80**	**0.003**	>0.05 $PD_{off}-PD_{on}$
Body×group	1.36	0.264	**0.03 PD_{off}−control**
Body×task	0.01	0.944	**0.01 PD_{on}−control**
Body×group×task	0.28	0.759	
Background	**12.13**	**0.001**	
Background×group	2.11	0.130	
Background×task	2.20	0.143	
Background×group×task	0.87	0.417	
Body×background	0.81	0.372	
Body×background×group	1.78	0.178	
Body×background×task	0.08	0.773	
Body×background×group ×task	1.42	0.249	
Group	**6.27**	**0.003**	
Task	**11.01**	**0.002**	
Group×task	0.35	0.707	

A mixed-design repeated measures ANOVA and Bonferroni pair-wise comparison tests of Background (grey, average frame, average room)×Group (PD_{off}, PD_{on}, Control)×Task (SVV, PU) (a). A mixed-design repeated measures ANOVA and Bonferroni pair-wise comparison tests of Body (Upright, RSD)×Background (grey, average frame, average room)×Group (PD_{off}, PD_{on}, Control)×Task (SVV, PU) (b). Significance ($P<0.05$) is highlighted in bold text.

visual dependence in Parkinson's disease depends on the measure used to assess the perceived direction of "up."

Our results further suggest that patients with PD relied less on the internal representation of their bodies and more on gravitational information to determine their PU. The PU of normal controls was shifted about 25° towards gravity from their body centre line, indicating a greater reliance on their body orientation than on gravity. In PD patients the PU was displaced by 38° and 51° for the PDoff and PDon groups respectively, indicating an increased reliance on gravity compared to controls, which may be exacerbated by medication as this displacement relative to controls was only evident when patients were taking dopaminergic medication. These results are summarized in Fig. 4 in which the width of the shaded segments indicates the effect of vision on the orientation of the SVV and PU for the two body orientations.

What can account for these changes in relying more or less on sensory cues for orientation perception in PD? Direct sensory changes are reported mainly in more severe cases of PD (Flowers and Robertson, 1995) and there have been recent reports of visual changes reported in less severe cases of PD (Davidsdottir et al., 2005; see Archibald et al., 2009 for a review) and thus the changes in visuo–spatial behaviour observable here in less severe cases could be the result of visual problems in PD. However, as the patients in the present study were assessed for visual and vestibular function and showed no obvious defects an alternative explanation is required. We speculate that our results reflect problems associated with sensorimotor integration (see also Gotham et al., 1988; Richards et al., 1993). The integration of multisensory information may underlie the disturbances we found in the perception of the apparent vertical (see also Azulay et al., 2002) and the perceptual upright, as well as other tasks requiring multisensory integration (Adamovich et al., 2001; Brown et al., 2006; Messier et al., 2007). We further discuss this possibility below.

The possible influence of dopamine replacement therapy on perceptual measures

We found that patients with PD when both on and off medication were much more variable when estimating the orientation of the SVV or the PU compared to age-matched controls. This suggests that the lack of precision with which PD patients made their estimates was unaffected by dopaminergic medication. Whether PD patients were on or off their medication did, however, affect where their SVV and PU estimates were compared to controls. Since we were unable to find any differences in the sensory contributions to the SVV and PU in PD patients who were off their medication compared to non-PD controls, this raises the intriguing possibility that the effects we observed for medicated PD patients were not due to Parkinsonism but rather were an effect of medication. This is consistent with the sensorimotor literature where dopamine replacement therapy fails to resolve, or even worsens the processing of proprioceptive information (O'Suilleabhain et al., 2001; Maschke et al., 2005; Schettino et al., 2006; Jacobs and Horak, 2006; Tunik et al., 2007; Mongeon et al., 2009; but see Almeida et al., 2005). This would explain why patients with PD when medicated are more influenced by one cue (vision or gravity) than controls, as a decrease in depending on the body, presumably related to impaired proprioceptive processing, would likely lead to an increase in depending on visual and/or gravitational cues.

The possible influence of dopamine replacement therapy on perceptual measures such as the SVV has perhaps been ignored because differences between on and off medication states previously did not reach significance (Azulay et al., 2002). We suggest that because dopaminergic medication can have either a negligible or worsening effect on processing proprioceptive information that variation within the PD population may account for this lack of within-subjects medication effect. This suggests that future studies need to use large numbers of PD patients while on and off medication in order to characterize the effect of medication while accounting for individual differences. While the lack of a significant difference between PD patients while off and while on medication could be attributable to the small number of patients in our sample ($n=9$) who elected to go off their medication for the duration of our tests, Azulay et al. (2002) using the same rod-and-frame test did not find an effect of medication in a

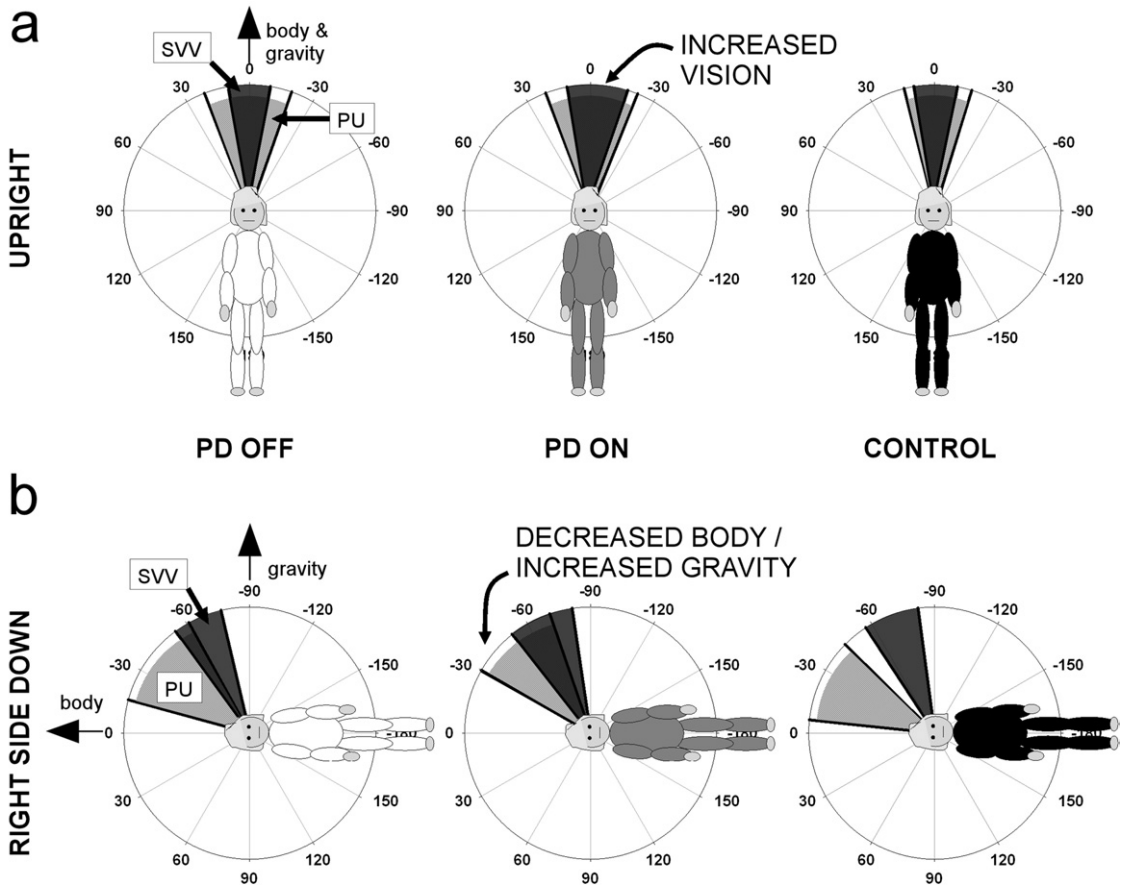

Fig. 4. A polar summary in head coordinates of the effect of the visual background for the SVV (light grey shaded area) and PU (dark grey shaded area) for the PD_{off} (white figure), PD_{on} (grey figure) and control (black figure) groups while oriented upright (a) and RSD (b). The shaded segments indicate the full extent of effect that the orientation of the visual background had on the respective measures.

larger PD population sample of 21 participants while also carefully monitoring medication dosage.

"Visual dependence" in PD

The effects of a tilted visual scene on perceived orientation as measured using the SVV have long been investigated in the non-PD population where it has been found that estimates of the SVV are biased in the same direction as visual orientation cues (Asch and Witkin, 1948; Witkin and Asch, 1948b; Mittelstaedt, 1988; Howard and Childerson, 1994; Guerraz et al., 1998; Dyde et al., 2006) and similar effects have been established using the PU (Dyde et al., 2006; Barnett-Cowan et al., in press). The increased effect of frame orientation on judgments of the SVV in patients with PD observed in this study is in agreement with previous reports suggesting that patients with PD are more influenced by the rod-and-frame illusion than age-matched controls (Proctor et al., 1964; Danta and Hilton, 1975; Azulay et al., 2002). Further, we have also shown that patients with PD are more influenced by the orientation of a visual scene rich in polarized cues than age-matched controls.

An increased dependency on vision in patients with PD has also been suggested based on an increased sensitivity to full-field motion causing patients to sway more in response to visual motion (Bronstein et al., 1990). Bronstein et al. (1996) however later found that patients with PD showed no significant difference from age-matched controls when asked to set a rod to vertical in the presence of a rotating visual field. They interpreted this as contradicting the suggestion of an increased visual dependency in PD patients. The mean visually induced effects that Bronstein et al. (1996) observed, however, did show a trend towards being larger than controls which is consistent with the present and other psychophysical studies that have reported significant increases in the effect of vision in PD patients (Proctor et al., 1964; Danta and Hilton, 1975; Azulay et al., 2002; Davidsdottir et al., 2008).

It would appear from our results, and those of others (Bronstein et al., 1990; Azulay et al., 1999, 2002; Davidsdottir et al., 2008), that when medicated PD patients are more visually dependent than age-matched controls. However, we caution against applying such a broad description to characterize orientation perception in this clinical group: we did not find an increased effect of vision on the perceptual upright among patients with PD. Instead we suggest that patients with PD may rely more on vision for orientation perception tasks associated with self orientation and

navigation (Proctor et al., 1964; Danta and Hilton, 1975; Bronstein et al., 1990; Azulay et al., 1999, 2002; Brown et al., 2006; Davidsdottir et al., 2008) but their reliance on vision orientation information when recognizing objects in the environment is indistinguishable from a normal population.

The internal representation of the body in PD

What do our results reveal about the Parkinsonian brain? We showed that when medicated, patients with PD were less reliant on their sense of body orientation and more reliant on gravitational information when judging the perceptual upright compared to age-matched controls. Why might this be the case?

Although the perceived direction of gravity and the visual surround are derived from sensory information, the contribution of the body is derived from an internal representation of a person's long body axis (or idiotropic vector; see Mittelstaedt, 1983, 1988). This body representation can be considered as a personal reference independent from external references, which is influentual when performing perceptual orientation tasks (Mittelstaedt, 1983, 1988; Oman, 2003; Dyde et al., 2006). Internal model theory proposes that a representation of the body is generated using copies of motor signals, sensory information, knowledge of physical laws, and expectations based on recent history which update the memory of the body (von Holst and Mittelstaedt, 1950; Mayne, 1974; Wolpert et al., 1995; Merfeld et al., 1999; McIntyre et al., 2001; Barnett-Cowan et al., 2005; see Knoblich et al., 2006 for a recent review).

Patients with PD often have deficits in processing proprioceptive information (Klockgether et al., 1995; Jobst et al., 1997; Adamovich et al., 2001; Contreras-Vidal and Gold, 2004; Maschke et al., 2003) which might contribute to known problems in the PD population concerning gait (Ivanenko et al., 2000a,b; Bove et al., 2001, 2002; Courtine et al., 2001; Verschueren et al., 2002, 2003), posture imbalance (Eklund, 1969; Kavounoudias et al., 1999; Roll et al., 1989), and sensorimotor control (Klockgether et al., 1995; Jobst et al., 1997; Adamovich et al., 2001; Maschke et al., 2003; Almeida et al., 2005; Jacobs and Horak, 2006; Mongeon et al., 2009). These deficits in processing proprioceptive information and our results which show that PD patients rely less on the internal representation of the body's orientation suggest that the internal representation of the body may be "impaired" in PD. This is at least the case in its use in influencing the perceptual upright—certainly in the light and potentially in the dark—but not in a general sense since there was no change in its influence in assessing the SVV. This then may lead to a lesser reliance on a PD patient's internal sense of body orientation in some conditions in favour of relying on vestibular information in determining the PU.

The increased variance noted in PD patients' PU and SVV judgments may arise from relying less on the sense of body orientation: it seems unlikely to arise from vision on which equal or more emphasis is placed. Why though might the increased reliance on body be most evident when patients are medicated—when their tremor and gait symptoms are minimized? Earlier work from Horak and colleagues (1992) and more recently by Wright and colleagues (2007) indicate that patients with PD have poorer kinesthetic abilities after levodopa medication compared to when they were unmedicated. Mongeon and colleagues (2009) also found that PD patients perform poorly in pointing tasks when only proprioceptive information is available, but that this effect only became significantly different from a normal control group when the PD patients were taking dopaminergic medication. These and our findings are in line with other studies which indicate that dopamine replacement therapy does not restore, or can even worsen, the processing of proprioceptive information (O'Suilleabhain et al., 2001; Maschke et al., 2005; Schettino et al., 2006; Jacobs and Horak, 2006; Tunik et al., 2007; but see Almeida et al., 2005). Thus we hypothesize that the internal representation of the body schema may be less reliable in PD particularly during dopamine replacement therapy. While we did not find any significant relationships between the severity of patients' motor symptoms and performance on the PU task, our PD population sample may not have been extensive enough to effectively test this claim as none of our patients had significant gait or balance issues. A larger sample size would also allow for assessing the role of sex differences and visual dependence in PD which from our previous work would suggest that female patients with PD would be more influenced by visual information in the SVV task than males, while no differences between the sexes are predicted for the PU (see Barnett-Cowan et al., in press).

Neural correlates of "which way is up"

The influence of visual information on the SVV plays more of a role in LPD compared to RPD patients. These results confirm recent findings from Davidsdottir and colleagues (2008) who measured visual dependence in PD by having patients estimate the horizontal position of a line within a tilted frame and also found that LPD patients are more visually dependent than RPD patients. Why the dissociation? Increased dependency on vision in the perception of the SVV has been associated with lesions to right hemisphere parietal areas (De Renzi et al., 1971) and specifically to the parieto-insular vestibular cortex (PIVC; Brandt et al., 1994). Increased dependence on vision for the SVV task could be related to putamen atrophy in PD, which has been linked to the PIVC (Bottini et al., 2001). The putamen receives inputs from somatosensory, visual and vestibular areas (Rolls and Johnstone, 1992; Lobel et al., 1998; Bottini et al., 1994, 2001; Graziano and Gross, 1993; Wenzel et al., 1996). Further, the initial side of motor symptom dysfunction in PD has been associated with parietal lobe dysfunction (Cronin-Golomb and Braun, 1997; Amick et al., 2006; Schendan et al., 2009). Consistent with this, LPD patients present with more pronounced disturbance on orientation perception tests than RPD patients (Blonder et al., 1989; Lee et al., 2001a,b; Harris et al., 2003). Thus one could speculate that the SVV principally relies on right hemisphere parietal areas which have connections to the basal ganglia, which could explain errors in verticality per-

ception in PD. Interestingly, we did not find an effect of initial side of motor symptom onset for the PU, suggesting that the PU is more equally represented across both hemispheres. We suggest that this dissociation in estimating the SVV and PU supports the argument that the SVV and the PU are quite different orientation perception tasks which refer to unique representations in the brain as to "which way is up" (Dyde et al., 2006; Barnett-Cowan et al., in press).

Clinical applications

Is there a relationship between orientation perception and motor symptoms in PD? And might an understanding of such a relationship be of clinical relevance? Unfortunately we were not able us to test the relationship between our perceptual measures and falling behaviour as the PD patient scores for postural stability following a sudden pull of the shoulder (retropulsion test) ranged from 0 (normal maintenance of balance) to 1 (recovers unaided). This relationship should therefore be tested using a PD population sample which includes more severe PD patients who are more susceptible to postural instability and falls. We do however speculate that overreliance on gravitational information in assessing the correct orientation to view objects may be related to PD symptoms which are poorly responsive to medication and which might lead to dangerous falls. The problem with falling does not seem to be directly attributable to patients' motor deficits (Horak et al., 2005; Jacobs et al., 2005) and does not usually arise from failure, for example, to maintain correct balance during walking. An interesting point here is that these symptoms, like our observed changes in the use of vision and body cues, are generally not improved by anti-Parkinsonian medications (Poewe and Granata, 1997; Kompoliti et al., 2000; Sethi, 2008). In addition, balance impairments in patients with PD have been shown to be resistant to dopaminergic treatment (Bohnen and Cham, 2006). We further speculate that some of the instability in patients with PD may be due to them being more variable in estimating the orientation of their bodies relative to their surroundings. This might result in them placing less emphasis on their body's orientation, making them more vulnerable to falling and that this tendency may even be aggravated by dopaminergic medication. Given that sensory issues may not be readily alleviated or are worsened by dopaminergic medication, we propose non-medicine based strategies to re-calibrate the relative weightings of visual, body, and vestibular inputs to the normal range: such strategies might be incorporated into the physical therapies used to assist PD patients with the motor deficits associated with the disease. Future research is required to assess these speculations as well as to establish whether there is a relationship between changes in the SVV and PU with real world function.

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