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RESEARCH ARTICLE

Proprioceptive recalibration following implicit visuomotor adaptation is preserved in Parkinson's disease

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Abstract

Individuals with Parkinson's disease (PD) and healthy adults demonstrate similar levels of visuomotor adaptation provided that the distortion is small or introduced gradually, and hence, implicit processes are engaged. Recently, implicit processes underlying visuomotor adaptation in healthy individuals have been proposed to include proprioceptive recalibration (i.e., shifts in one's proprioceptive sense of felt hand position to match the visual estimate of their hand experienced during reaches with altered visual feedback of the hand). In the current study, we asked if proprioceptive recalibration is preserved in PD patients. PD patients tested during their "off" and "on" medication states and age-matched healthy controls reached to visual targets, while visual feedback of their unseen hand was gradually rotated 30° clockwise or translated 4 cm rightwards of their actual hand trajectory. As expected, PD patients and controls produced significant reach aftereffects, indicating visuomotor adaptation after reaching with the gradually introduced visuomotor distortions. More importantly, following visuomotor adaptation, both patients and controls showed recalibration in hand position estimates, and the magnitude of this recalibration was comparable between PD patients and controls. No differences for any measures assessed were observed across medication status (i.e., PD off vs PD on). Results reveal that patients are able to adjust their sensorimotor mappings and recalibrate proprioception following adaptation to a gradually introduced visuomotor distortion, and that dopaminergic intervention does not affect this proprioceptive recalibration. These results suggest that proprioceptive recalibration does not involve striatal dopaminergic pathways and may contribute to the preserved visuomotor adaptation that arises implicitly in PD patients.

Keywords Visuomotor adaptation · Proprioceptive recalibration · Parkinson's disease · Implicit · Aftereffects · Vision

Introduction

In Parkinson's disease (PD), the basal ganglia–cortical circuitry is compromised due in part to the progressive degeneration of dopaminergic neurons in the substantia nigra. In general, PD is characterized as a motor disorder, associated with postural instability (Duncan and Earhart 2012; Mancini et al. 2008; McNeely et al. 2012), and impairments in motor coordination (Adamovich et al. 2001; Almeida et al. 2002; Poizner et al. 1998). Despite these motor deficits, evidence from visuomotor adaptation studies suggests that PD patients are able to adapt their movements when reaching in a virtual environment with altered visual feedback of their hand. In fact, PD patients have demonstrated comparable visuomotor adaptation to healthy control participants under conditions in which a small (e.g., 30°) visuomotor distortion was introduced (e.g., Isaias et al. 2011; Marinelli et al. 2009; Semrau et al. 2014), or the visuomotor distortion

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was introduced gradually (Takiyama et al. 2020; Venkatakrishnan et al. 2011). For instance, Isaias et al. (2011) found that PD patients showed equivalent visuomotor adaptation to healthy controls when reaching to targets with a cursor that was abruptly rotated 30° relative to the motion of their dominant hand. Using a similar abrupt 30° visuomotor rotation, Marinelli et al. (2009) and Bedard and Sanes (2011) also found that the rate of adaptation was comparable between medicated PD patients and controls. Finally, Semrau et al. (2014) tested both medicated and non-medicated PD patients, and found again comparable adaptation rates between PD patients and controls when having to adapt to a 30° visuomotor rotation that was introduced abruptly. Taken together, these studies suggest that rates of adaptation and overall performance are similar between PD patients and controls when a small 30° visuomotor rotation distortion is introduced. Furthermore, experiments involving healthy control participants have shown that individuals typically remain unaware of these small visuomotor rotations, and hence primarily engage implicit processes when adapting their reaches (Neville and Cressman 2018; Modchalingam et al. 2019; Vachon et al. 2020; Wang et al. 2011; Werner et al. 2015).

In contrast to this preserved visuomotor adaptation, motor learning has been shown to be impaired in PD patients relative to controls when a large visuomotor distortion (e.g., 60°) is introduced abruptly. For example, two studies have reported smaller aftereffects and greater directional errors in patients compared to controls after they were introduced to a 90° visuomotor rotation (Contreras-Vidal and Buch, 2003) or a 60° rotation (Venkatakrishnan et al. 2011). However, Venkatakrishnan et al. (2011) found that when the 60° visuomotor rotation was introduced gradually, patients showed comparable reach aftereffects to those produced by healthy controls. Likewise, Mongeon et al. (2013; see also Messier et al. 2007) found that both medicated and non-medicated patients showed slower and smaller amounts of adaptation compared to controls when exposed to a noticeably large, suddenly introduced three-dimensional visuomotor distortion (displacement of 13.5 cm), but no difference when the displacement was gradually introduced and unnoticeable to the patients. Based on these findings, it has been suggested that PD selectively impairs the ability to learn from large, consciously detected visuospatial errors, when explicit or strategic processes are typically engaged (Mongeon et al. 2013). In contrast, visuomotor adaptation is preserved in PD when a small visuomotor distortion is introduced in the absence of awareness, presumably due to the preservation of implicit processes.

We have previously demonstrated that proprioceptive recalibration is one implicit process that may contribute to visuomotor adaptation (Modchalingam et al. 2019). Specifically, we have shown that reaching with altered visual feedback of the hand in a virtual reality environment leads to changes in movements and sense of felt hand position in healthy control participants (Cressman and Henriques 2009, 2010; Cressman et al. 2010; Salomonczyk et al. 2011, 2012, 2013; Clayton et al. 2014; Zbib et al. 2016; Ruttle et al. 2018), and cerebellar patients when the visuomotor distortion is gradually introduced (Henriques et al. 2014). These sensory changes, which we term proprioceptive recalibration, reflect adjustments in participants' sense of felt hand position arising due to the realignment of proprioception onto the new visuomotor coordinate system to eliminate, or at least reduce, the spatial discrepancy between visual and proprioceptive signals related to hand position (i.e., participants begin to feel their hand is shifted in the direction that they see it).

The first aim of the current study was to determine if proprioceptive recalibration is preserved in PD. We had PD patients adapt to a small, gradually introduced visuomotor distortion. By keeping the distortion small (i.e., 30° or 4 cm) and introducing it gradually, we expected PD patients to adapt their movements implicitly and to a similar extent as control participants. We then looked to determine if PD patients demonstrated proprioceptive recalibration. We hypothesized that proprioceptive recalibration would be present in PD patients. Furthermore, we hypothesized that the observed deficits in proprioceptive processing in PD patients (Zia et al. 2000; Zia, et al. 2002; Konczak et al. 2008, see also Konczak et al. 2009 for a review), and their overreliance on visual information during reaching (Adamovich et al. 2001; Mongeon et al. 2015), would lead to increased proprioceptive recalibration in PD patients compared to healthy controls. Specifically, because proprioception tends to provide less accurate information regarding the hand's position in space in PD patients compared to healthy controls, we expected these proprioceptive signals to be less resistant to change than the more accurate proprioceptive signals experienced by a healthy population. This preserved (and possibly enhanced) proprioceptive recalibration in the PD patients may then be implicated in their continued ability to implicitly adapt to a visuomotor distortion.

The second aim of our study was to determine whether dopaminergic medication affects this proprioceptive recalibration. Many of the studies described above examined sensorimotor processing in medicated patients, yet a few studies have examined the effect of dopaminergic medication on sensorimotor processing in PD. Moreover, the previous studies examining the influence of medication on sensorimotor processing have yielded conflicting results, with some reports suggesting that dopaminergic medication improves sensorimotor performance during locomotion and proprioceptive acuity of the arm and wrist (Almeida et al. 2005; Li et al. 2010; Rickards and Cody 1997), while others indicate that dopaminergic medication does not alleviate

performance and may make sensorimotor deficits worse (Jacobs and Horak 2006; Maschke et al. 2006; Mongeon et al. 2009, 2013). Thus, given the questions surrounding the influence of dopaminergic medication on sensorimotor processing, we tested patients both off (i.e., PD off) and on (i.e., PD on) medication.

Methods

Participants

Seventeen adults diagnosed with Parkinson's disease (mean age = 61.0 years, range = 40–78 years, 5 female; mean disease duration 5.8 years) were recruited from the Toronto Western Hospital Movement Disorders Clinic to participate in both experiments in this study. Thirteen (E1: rotated visual feedback experiment; mean age = 63.4 years, range = 43–80 years, 9 female) and fourteen (E2: translated visual feedback experiment; mean age = 58.1 years, range = 42–71 years, 5 female) age-matched, healthy adults also participated in the study described below. Two sets of healthy age-matched control participants were collected, since those that participated in the rotated visual feedback session were collected much earlier and their data published in a study examining the influence of aging on visuomotor adaptation and proprioceptive recalibration (Cressman et al. 2010). By the time we began this study with PD patients, we were only able to re-recruit three participants from the original control group. All participants provided informed consent in accordance with the institutional ethics review boards. Participants were screened for depression and dementia using the Beck Depression Inventory II (BDI-II) and the Mini-Mental State Examination (MMSE), respectively. All participants were free of other neurological or psychological disorders and had normal or corrected-to-normal vision. All PD patients were treated with dopaminergic medications (Table 1). To assess the impact of dopaminergic medication, each patient was tested during the practically defined "off" state, i.e., at least 12 h following the last intake of antiparkinsonian medication, and in the "on" state, 1–2 h after taking the first dose of antiparkinsonian medication of the day. During each testing session, patients were evaluated using the Unified Parkinson's Disease Rating Scale (UPDRS (Fahn and Elton 1987)) and were found to have mild-to-moderate PD (Stages II–III (Hoehn and Yahr 1967)).

Patient PD9 was excluded from analyses due to changes in their proprioceptive estimates across reach training conditions being greater than mean group changes + 3 standard deviations. Patient PD10 was excluded from analyses due

Table 1 Clinical features of patients with Parkinson's disease

Participant	Sex	Age	Dominant hand	Affected side	UPDRS motor score		H and Y stages	Duration of disease (years)	Medication[a]
					OFF	ON			
PD1	M	57	R	R	39	31	2	4	LC E P
PD2	M	65	R	R	40	26	2	8	LC P S
PD3	F	71	L	L	39	18	2.5	11	LC R
PD4	M	52	R	L	45	23	2.5	7	LC P
PD5	M	52	R	R	38	16	2.5	9	LC
PD6	M	47	L	R	49	22	2.5	10	LC A RO
PD7	F	78	R	R	36	22	2	3	LC
PD8	M	68	R	R	49	36	3	5	LC R RO
PD9[b]	M	73	L	L	49	39	3	6	LC
PD10[b]	F	59	L	L	25	16	2	6	ET P
PD11[b]	F	67	R	R	41	29	3	5	LC
PD12	M	40	R	L	25	18	2	3	LC P
PD13	M	69	R	L	38	30	2	3	LC
PD14	M	65	R	L	23	13	2	1	LC
PD15[b]	F	63	R	R	25	NA	2	4	LC R
PD16	F	60	R	R	16	14	2	6	LC P
PD17	M	64	R	L	31	25	2.5	7	LC LB R RO
Mean		61.7			35.8	23.6	2.3	5.8	

[a]*LC* levodopa + carbidopa, *LB* levodopa + benzerazide, *A* amantadine, *E* entacapone, *ET* ethopropazine, *P* pramipexole, *R* rasagiline, *RO* ropinirole, *S* selegiline

[b]participants were excluded from analyses

to erratic and inconsistent reaches in the absence of cursor feedback. Specifically, errors on their no-cursor reaches described below following training with aligned cursor feedback were as great as 90°, compared to minimal errors when cursor feedback was provided. Finally, patients PD11 and PD15 were also excluded from analyses, as they failed to complete the experiments. Results reported include data from the remaining 13 PD patients, and 13 age-matched participants in E1 and E2, as one control participant from Experiment 2 was excluded due to their inability to reliably indicate the position of their hand in the Proprioceptive Estimate task described below.

General experimental set-up

A side view of the experimental set-up is provided in Fig. 1a. Participants were seated in a height-adjustable chair, so that they could comfortably see and reach to all target and marker locations presented on an opaque, reflective surface. Participants grasped the vertical handle of a two-joint robot manipulandum mounted in the horizontal plane with their right hands (Interactive Motion Technologies). Visual stimuli were projected from a monitor (Samsung 510 N, refresh rate 72 Hz) installed 17 cm above the robot onto a reflective surface positioned between the monitor and the manipulandum, thus appearing to lie in the same horizontal plane as the robot. The position of the robot manipulandum was recorded throughout all reaching trials at a sampling rate of 50 Hz and a spatial accuracy of 0.1 mm. The room lights were dimmed and the participant's view of their hand was blocked by the reflective surface and a black cloth draped between the experimental set-up and the participant's right shoulder.

General procedure

The study consisted of 3 visuomotor reach training conditions: aligned (Experiments 1 and 2), rotated (Experiment 1), and translated (Experiment 2) cursor-hand feedback, introduced in separate testing sessions (see below). The aligned cursor-hand feedback training condition trials were completed to provide an indication of baseline performance. We included the rotation distortion as it is the most common type of visuomotor distortion and has been shown to lead to visuomotor adaptation in PD (Isaias et al. 2011; Marinelli et al. 2009; Semrau et al. 2014). The translation distortion was included as results from our original paper (Cressman and Henriques 2009) suggested that visuomotor adaptation may be slightly larger for adaptation to a translated cursor than a rotated one, and thus, it was used to maximize the potential effect of visuomotor adaptation on proprioceptive estimates.

PD patients completed each of the three reach training conditions twice, once when they were off and on their

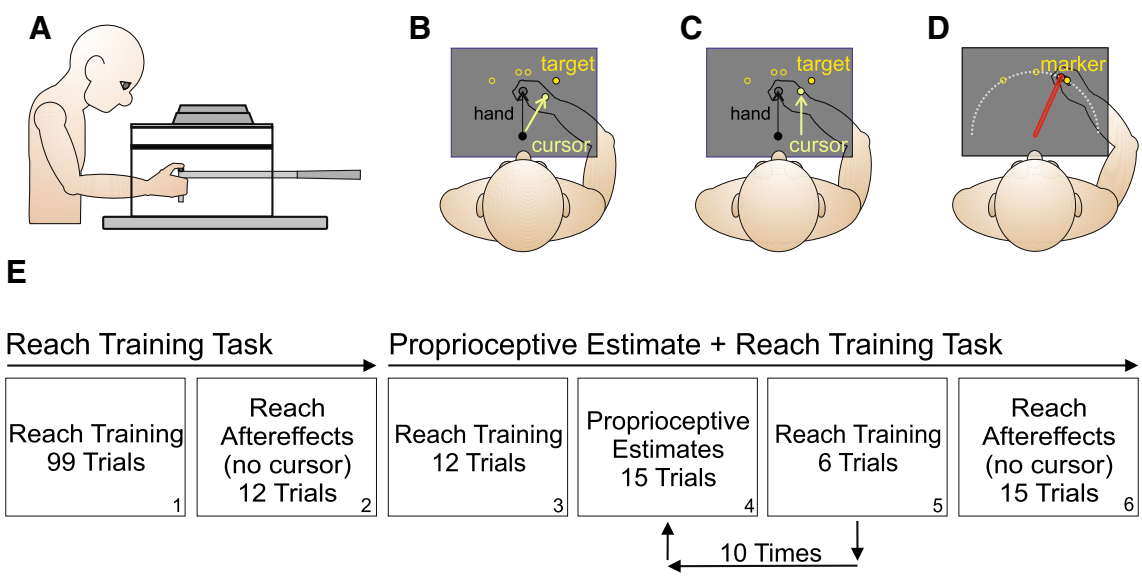

Fig. 1 Experimental set-up and design. **a** Side view of the experimental set-up. **b**–**d** Top view of the experimental surface visible to participants. **b**, **c** Visuomotor distortion introduced in the rotated (Experiment 1) and translated (Experiment 2) reach training trials. The cursor representing the unseen hand was gradually rotated 30° clockwise (Experiment 1, B) or translated 4 cm rightwards (Experiment 2, C) with respect to the actual hand position. Targets (yellow rings) 1 cm in diameter were located 10 cm from the home position (black circle) at 5° and 30° left and right of midline. **d** In the proprioceptive estimate task, participants actively pushed their hand out 10 cm along a constrained linear path (depicted by the red rectangle for the rotated paradigm) from the home position and judged the position of their hand with respect to a reference marker. Reference markers (yellow rings) were located at 0° and 30° left and right of midline. **e** Breakdown of the trials completed within each experimental session (aligned, rotated, and translated cursor-hand feedback conditions)

medication, for a total of six testing sessions. Sessions were completed over 3–6 visits. Each condition involved two tasks (Fig. 2). During the aligned (baseline) condition, participants completed the reach training trials outlined below while seeing a cursor that was veridical, or aligned, with their hand. During the rotated and translated conditions, participants completed the reach training trials while viewing a cursor that was misaligned from the actual location of their unseen hand. During the rotated reaching trials, the cursor was rotated 30° clockwise (CW) relative to the hand position and this distortion was introduced gradually by increments of 0.75° per trial. During the translated reach training trials, the cursor was translated 4 cm rightwards relative to the hand position and this distortion was introduced gradually by 0.1 cm increments per trial. The cursor was represented by a green disc 1 cm in diameter in all conditions. All participants first completed the aligned (baseline) condition, followed later by the rotated or translated conditions; for PD patients, these three conditions were competed twice each: once while off medication and once on medication. The order of the rotated and translated conditions was counterbalanced across PD participants, as was the completion of sessions with respect to medication status. A minimum interval of 2 weeks separated each of the rotated and translated sessions to ensure sufficient wash-out of visuomotor adaptation in patients.

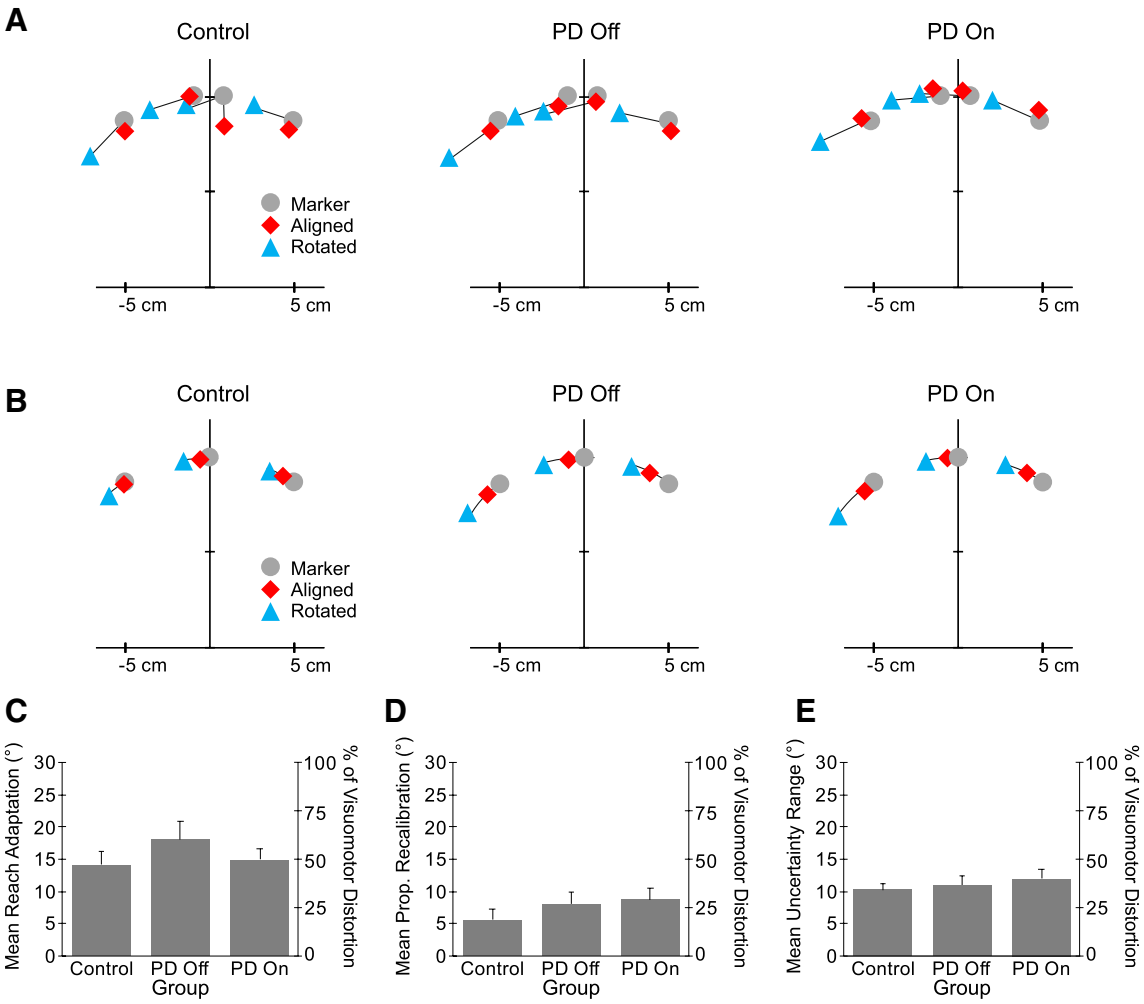

Fig. 2 Experiment 1 (Rotated) Results. **a** Mean 2D hand deviations at reach endpoint for Controls (left), PD off (center), and PD on (right) following reach training with an aligned (diamonds) and rotated (triangles) cursor. **b** Mean 2D proprioceptive biases following training with an aligned (diamonds) and rotated (triangles) cursor are depicted for Controls (left), PD off (center), and PD on (right). In (**a**) and (**b**), the actual target/reference marker positions are represented as grey circles. **c** Mean baseline-subtracted aftereffects at reach endpoint were calculated by subtracting the angular error during no-cursor reach trials following rotated reach training from those following aligned reach training. Results are presented averaged across targets. **d** Mean changes in biases (i.e., proprioceptive recalibration) after training with a rotated cursor compared to an aligned cursor were averaged across reference markers. **e** Mean uncertainty ranges following aligned and rotated reach training. For (**c**), (**d**), and (**e**), error bars reflect the standard error of the mean

Reach training trials and adaptation

While grasping the robot manipulandum with their right hand, participants were instructed to reach to a visual target as quickly and accurately as possible while viewing either an aligned or misaligned cursor (indicated by the filled green circle in Fig. 1b, c) that moved with their hand. The reach targets were located radially 10 cm from the home position at 5° and 30° left (counterclockwise, CCW) and right (CW) of centre (yellow circles in Fig. 1b, c). The home position was located approximately 40 cm in front of the participants along their body midline (indicated by the black filled circle in Fig. 1b, c). This position was not illuminated and visual feedback was provided only when the hand had travelled 4 cm outwards from the home position. The reach was considered complete once the centre of the cursor had moved to within 0.5 cm of the target's centre. At this point, both the cursor and target disc would disappear and participants moved their hands back to the home position in the absence of visual feedback along a linear route. If participants attempted to move outside of the established path, a resistance force [proportional to the depth of penetration with a stiffness of 2 N/mm and a viscous damping of 5 N/(mm/s)] was generated perpendicular to the grooved wall (Cressman & Henriques 2009, 2010; Cressman et al. 2010; Henriques and Soechting 2003; Jones et al. 2010). This grooved wall was provided to facilitate the hand returning to the home position in the absence of vision. The order of the reach training trials was pseudo-randomized, such that participants reached once to 3 of the reach targets, specifically the two peripheral (30°) targets and one of the pair of peri-central (5°) targets before any target was repeated. Participants completed 99 reach training trials (box 1, Fig. 1e).

After completing reach training trials, participants immediately completed 12 no-cursor reaches, 3 reaches to each of the 4 reach targets without visual feedback (box 2, Fig. 1e). These trials were included to determine if participants adapted their reaches in response to the misaligned cursor (i.e., exhibited aftereffects). On these trials, participants were instructed to aim to the target and hold their end position. Once this end position had been maintained for 500 ms, the visual target disappeared and the trial was considered complete. Participants were guided back to the home position by a linear grooved path as described above.

Proprioceptive estimate trials + reach training trials

In this task, proprioceptive estimates and reach training trials (boxes 3–5, Fig. 1e) were systematically interleaved. Participants began by completing an additional 12 reach training trials with a cursor as described above. These reaches were then immediately followed by interleaving sets of 15 proprioceptive estimate trials and 6 reach training trials. The test sequence of 15 proprioceptive estimates followed by 6 reach training trials was completed 10 times, for a total of 222 trials [150 proprioceptive estimate trials (50 at each target) + 72 reach training trials].

A proprioceptive estimate trial began with the participant grasping the robot manipulandum at the illuminated home position, located in the same position, and represented by the same disc as that during reach training trials (though the home position was illuminated in these trials). After 500 ms, this disc disappeared and the participant was instructed to push his or her hand outward along a constrained robot-generated linear path (as described previously and shown by the red rectangle in Fig. 1d). On all trials, once the hand arrived at the end of the path, a reference marker located at 0°, 30° left (CCW), or 30° right (CW) of center and represented by a yellow circle 1 cm in diameter appeared (yellow circles, Fig. 1c). Participants then made a two-alternative forced-choice judgment about the position of their hand (left or right) relative to the reference marker. There was no time constraint for providing a response. After responding, the reference marker disappeared and the participant moved the robot directly back to the home position along a linear route to begin the next trial. The position of the hand with respect to each reference marker was adjusted over trials using an adaptive staircase algorithm (Kesten 1958; Treutwein 1995). For each reference marker, there were 2 staircases, one starting 20° to the left (CCW) of the reference marker and one starting 20° to the right (CW). The 2 staircases were adjusted independently and randomly interleaved as outlined in Cressman and Henriques (2009, 2010).

Participants completed 15 final no-cursor reaches, 3 reaches to each of the 4 previously described reach targets and 3 reaches to a target located at 0° (box 6 in Fig. 1e) immediately after completing the Proprioceptive Estimate + Reach Task to ensure that they were still reaching in a similar manner as before the proprioceptive estimate trials (box 2 in Fig. 2).

Data analysis

The current research looks to establish proprioceptive recalibration in PD patients following visuomotor adaptation. Thus, we first confirmed reach adaptation following reach training trials with a rotated (Experiment 1) and translated (Experiment 2) cursor by examining errors in the no-cursor reach trials. Additional data regarding motor performance during reach training trials are provided in the Supplementary File. Having established reach adaptation, we next looked to compare the effects of visuomotor adaptation on proprioceptive recalibration in Experiments 1 and 2 across groups (between groups: PD off vs control; within groups: PD off vs PD on).

Visuomotor adaptation: aftereffects

To confirm that PD patients were able to successfully adapt their reaches to the gradually introduced visual distortions in this study, we examined reach aftereffects produced in the no-cursor trials. Angular deviations of the hand (Experiment 1) and lateral deviations of the hand (Experiment 2) for all no-cursor reaches were calculated. Angular deviations were defined as the angular difference between a reference vector joining the centre home position and the target and the vector joining the centre home position and position of the reaching hand at reach endpoint. Lateral deviations were defined as the metric difference between a reference vector joining the centre home position and the target and the vector joining the centre home position and position of the reaching hand at reach endpoint. The extent of visuomotor adaptation was examined by looking at the angular deviation of the hand at reach endpoint in the first set of reaches made without a cursor, as no difference in reaches completed before and after the proprioceptive estimate trials was observed during the rotated Experiment 1 for control participants [$t(12) = 1.185$, $p = 0.259$], PD off [$t(12) = 1.16$, $p = 0.286$], or PD on [$t(12) = 1.975$, $p = 0.072$], or during the translated Experiment 2 for control participants [$t(12) < 1$, $p = 0.966$], PD off [$t(12) = -2.030$, $p = 0.065$], or PD on [$t(12) < 1$, $p = 0.786$]. To confirm that participants had indeed adapted their reaches following reach training with a misaligned cursor, we analyzed mean aftereffects using two separate 2 Group (between: control vs PD off; within: PD off vs PD on) × 2 Visual Feedback Condition (within: aligned vs misaligned) × 4 Target (within: 5° CW vs 5° CCW vs 30° CW vs 30° CCW) ANOVAs for both Experiments 1 and 2. Pair-wise comparisons with a Bonferroni correction were administered to determine the locus of significant differences (alpha = 0.05).

Proprioceptive estimates of hand position

To test our main question of whether proprioceptive recalibration arises in PD patients, we first determined the locations at which participants felt their hands were aligned with the reference markers in each testing session. These locations were determined by fitting a logistic function to each participant's responses for each reference marker in each testing session and calculating their bias (the point of 50% probability). In addition to calculating bias, we also determined participants' uncertainty (or precision) by finding the difference between the values at which the response probability was 25% and 75%. Bias and uncertainty related to a particular reference marker were excluded if the associated value was greater than the mean value across all reference markers + 3 standard deviations. Based on this analysis, only 13 (1.3%) of total estimates were excluded. Biases and uncertainty ranges were analyzed using two separate 2 Group (between: control vs PD off; within: PD off vs PD on) × 2 Visual Feedback during reach training (within: aligned vs misaligned) × 3 Marker Location (within: 30° CW vs 30° CCW vs 0°) ANOVA for both Experiment 1 and Experiment 2. Pair-wise comparisons with a Bonferroni correction were administered to determine the locus of significant differences (alpha = 0.05).

Additional analyses

On the chance that the results based on the analyses above did not properly capture potential differences between groups, we further split the PD patients into two groups; one with UPDRS scores higher than the median score and those with scores lower than the median. We then compared whether these two groups differed in terms of aftereffects (i.e., changes in no-cursor reaches following rotated reach training compared to aligned reach training) or proprioceptive recalibration (i.e., changes in proprioceptive biases following rotated reach training compared to aligned reach training). We found that performance for PD who scored higher on the UPDRS did not differ from those who scored lower on UPDRS on either of these two measures, regardless of whether they were off or on medication. Finally, for completeness, we also tested for correlations between UPDRS scores and other demographic metrics (e.g., age, and H and Y stages) with aftereffects and proprioceptive recalibration both for PD off and PD on, and found no significant correlations.

While we had sufficient statistical power to detect significant aftereffects and proprioceptive recalibration in all groups as outlined below, there is the possibility that we had insufficient power to detect what may be small group differences. Thus, we performed (1) comparisons between the three groups (control vs PD off vs PD on medication), rather than the ANOVA with the two between- or two within-subjects categories outlined above (i.e., controls vs PD off and PD off vs PD on medication), and (2) post hoc power analyses to gain insight into what sample size would be necessary to reach statistically significant group differences. ANOVA revealed no significant differences between the three groups with respect to aftereffects or proprioceptive recalibration, and thus, these findings are not reported below. As well, post hoc power analyses revealed that we would need a minimum of 224 participants in Experiment 1 and 2057 participants in Experiment 2 to reach significant group differences with respect to proprioceptive recalibration. These large sample sizes were driven by the small and no effect sizes (defined in accordance with Cohen's d) observed in Experiments 1 and 2, respectively. Together, these findings and the results reported below reveal that performance did not differ between groups.

Results

Visuomotor adaptation: aftereffects

Figure 2a displays mean 2D reach endpoint errors made when participants reached to four different targets (grey circles) without a cursor following aligned (diamonds) and rotated (triangles) feedback training for controls and patients off and on their medication. Figure 3a displays mean 2D reach endpoints made when participants reached to four different targets (grey circles) without a cursor following aligned (diamonds) and translated (triangles) feedback training for controls and patients off and on their medication. Figures 2c and 3c display the mean changes in reach endpoint errors between aligned and distorted cursor conditions (i.e., the aftereffects) for the three groups.

For Experiment 1, we compared control participants with PD off and observed significantly greater leftward reach errors following rotated training compared with aligned training [$F(1, 24) = 71.240$, $p < 0.001$], which did not differ between groups $F(1, 24) = 1.809$, $p = 0.191$). When we compared patients' medication status (i.e., off vs on), we also did not observe any difference in reach aftereffects [$F(1,12) = 1.655$, $p = 0.223$]. Reach aftereffects were consistent across targets (all $p > 0.05$). On average, all participants

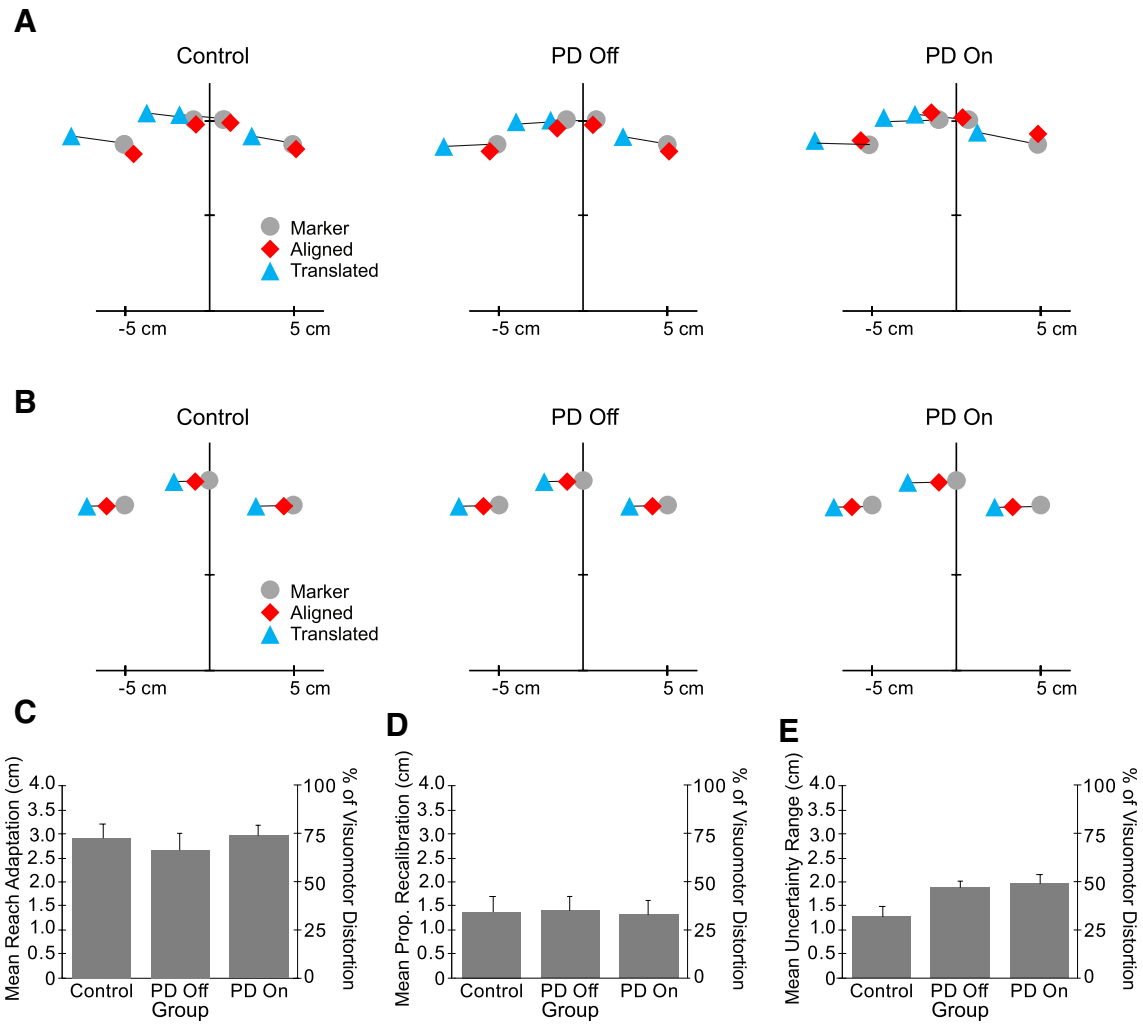

Fig. 3 Experiment 2 (Translated) Results. **a** Mean 2D hand deviations at reach endpoint for Controls (left), PD off (center), and PD on (right) following reach training with an aligned (diamonds) and translated (triangles) cursor. **b** Mean 2D proprioceptive biases following training with an aligned (diamonds) and translated (triangles) cursor are depicted for Controls (left), PD off (center), and PD on (right). In (**a**) and (**b**), the actual target/reference marker positions are represented as grey circles. **c** Mean baseline-subtracted aftereffects at reach endpoint were calculated by subtracting the lateral deviations during no-cursor reach trials following translated reach training from those following aligned reach training. Results are presented averaged across targets. **d** Mean changes in biases (i.e., proprioceptive recalibration) after training with a translated cursor compared to an aligned cursor were averaged across reference markers. **e** Mean uncertainty ranges following aligned and translated reach training. For (**c**), (**d**), and (**e**), error bars reflect the standard error of the mean

reached approximately 16° more leftwards of the target following training with a rotated cursor compared to after training with an aligned cursor; these aftereffects represent just over 50% of the induced visuomotor distortion (Fig. 2c). We also analyzed hand deviations at peak velocity and observed similar results: participants' aftereffects were on average 19° more leftwards following rotated training. A paired *t* test, conducted for each group, revealed that PD off had slightly greater aftereffects at PV compared to reach endpoint [$t(12) = -3.306$, $p = 0.006$]. There were no differences between aftereffects measured at peak velocity and reach endpoint for controls [$t(12) = -2.033$, $p = 0.065$) or PD on [$t(12) = -1.253$, $p = 0.234$]. Together, these results suggest that reaches made without cursor feedback were fairly straight with minimal correction, except for PD off, who attempted to correct their movements slightly (4°) during the open-looped reaches.

For Experiment 2, we also observed significantly leftward reach errors following translated training compared with aligned training [$F(1, 24) = 154.218$, $p < 0.001$], which did not differ between control participants and PD off [$F(1, 24) < 1$, $p = 0.601$]. When we compared patients' medication status (i.e., off vs on), we also did not observe any difference in reach aftereffects [$F(1, 12) < 1$, $p = 0.496$]. On average, all participants reached approximately 2.8 cm more leftwards of the target following training with a translated cursor compared with an aligned cursor. These aftereffects did not differ across targets (all $p > 0.05$), and represent nearly 70% of the induced distortion (Fig. 4c). Similar to Experiment 1, we also analyzed hand deviations at peak velocity and observed similar results: participants' aftereffects were on average 3.47 cm more leftwards following translated training compared to aligned training. For all groups, the errors at PV were significantly larger at PV compared to movement EP; paired t tests revealed differences for controls [$t(12) = -3.628$, $p = 0.003$]; PD off [$t(12) = -3.436$, $p < 0.001$]; and PD on [$t(12) = -3.995$, $p = 0.002$]. These results suggest that all participants made slight (0.6 cm) corrections during open-looped reaches. Importantly, the consistency in the magnitude of aftereffects across groups suggests that patients adapted their movements to a similar extent as controls at movement endpoint, and that medication did not enhance or worsen performance.

Proprioceptive recalibration

Bias

Having confirmed that PD patients were able to adapt to a visuomotor distortion and adapt their reaches to a similar extent as control participants, we then tested our main research questions of whether such visuomotor adaptation also leads to significant recalibration of hand proprioception, and if this proprioceptive recalibration differs depending on medication status.

Figure 2b displays mean 2D proprioceptive biases in Experiment 1 measured after training with an aligned cursor and rotated cursor at each of the three reference marker locations for control participants, PD patients off medication, and PD patients on medication. Grey circles denote marker locations, diamonds denote biases following reach training with an aligned cursor, and triangles denote biases following reach training with a rotated cursor. For all participants, we see that, on average, estimates of hand location were biased slightly to the left after reaching with an aligned cursor. The mean bias following aligned training (averaged across all reference markers) was 3.0°, 6.3°, and 5.3° leftwards of the markers for control participants, PD off, and PD on medication, respectively. Biases for PD off did not significantly differ from that of control participants following either aligned or rotated training [$F(1,24) < 1$, $p = 0.356$]. In addition to finding that patients had similar proprioceptive acuity as control participants, we found that proprioception was recalibrated for both groups (5.5° and 8.0° for controls and PD off, respectively; see Fig. 2d). Specifically, after reaching with a cursor that was rotated with respect to actual hand position, participants perceived their hand to be aligned with the visual reference

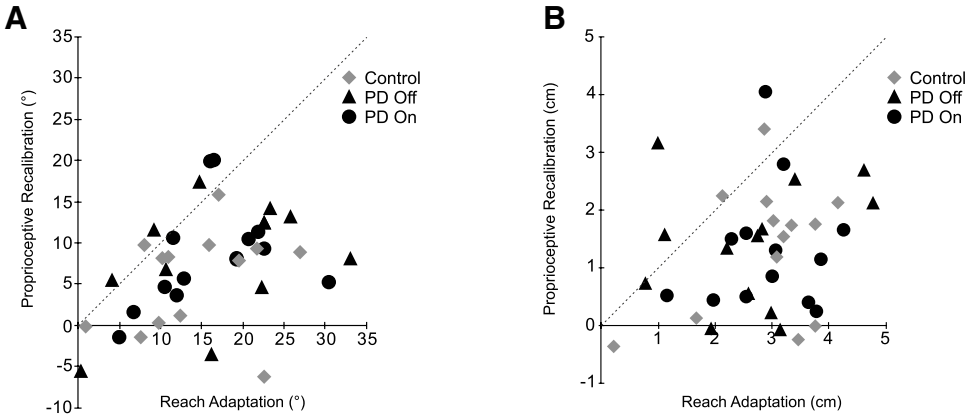

Fig. 4 Proprioceptive recalibration as a function of reach aftereffects for Controls (grey diamonds), PD off (triangles), and PD on (circles) in Experiment 1 (**a**) and Experiment 2 (**b**)

marker when it was shifted significantly to the left of the biases following aligned cursor training by an average of 6.7° [$F(1,24) = 28.180$, $p < 0.001$]. When we compared patients' medication status (i.e., off vs on), we did not observe any difference in the magnitude of recalibration [$F(1,12) < 1$, $p = 0.641$]. This leftward shift in bias was comparable across all marker locations [Control vs PD off: $F(2,48) < 1$, $p = 0.493$; PD off vs PD on: $F(2, 24) = 1.04$, $p = 0.369$].

We see similar results in Experiment 2. Again, after confirming that patients were able to adapt to a lateral shift, we next tested our main questions concerning whether such visuomotor adaptation leads to a recalibration of hand proprioception. Like Fig. 2b, Fig. 3b displays mean 2D biases at each of the three reference marker locations for control participants, PD patients off medication, and patients on medication (symbols the same as those in Fig. 2b). As previously observed, for all participants, we see that average estimates of hand location were slightly biased to the left after reaching with an aligned cursor. The mean bias was 0.9 cm, 1.0 cm, and 1.4 cm leftwards of the marker for control participants, PD off, and PD on, respectively. As with Experiment 1, we found that following reach training with a translated cursor, estimates of hand position were significantly shifted by an average of 1.3 cm more leftwards of the aligned estimates [Control vs PD off: $F(1,24) = 40.181$, $p < 0.001$; PD off vs PD on: $F(1,12) = 12.487$, $p = 0.004$; Fig. 3d). We compared this shift in bias between controls and PD off medication, and observed no difference between groups [$F(1,24) < 1$, $p = 0.919$], or between patients' medication status [$F(1,12) = 1.026$, $p = 0.331$]. Recalibration was comparable across all marker locations [Control vs PD off: $F(2,48) < 1$, $p = 0.755$; PD off vs PD on: $F(2, 24) = 1.519$, $p = 0.239$].

Overall, proprioceptive recalibration was approximately 25% and 34% of the induced visuomotor distortions in Experiments 1 and 2, respectively. With respect to reach aftereffects observed, proprioceptive recalibration was approximately 47% of the reach adaptation observed in both Experiments. In Fig. 4, we plot changes in participants' proprioceptive estimates as a function of their reach aftereffects. From Figs. 4a and b, we see that (1) the majority of participants recalibrated proprioception to some extent; (2) in most instances, proprioceptive recalibration was less than visuomotor adaptation; and (3) the magnitude of proprioceptive recalibration was similar regardless of the level of visuomotor adaptation obtained. In accordance with this last observation, analysis did not reveal a significant correlation between the magnitude of proprioceptive recalibration and the level of visuomotor adaptation achieved across all participants (i.e., control, PD off, and PD on) in either Experiment 1 or 2 (both $p > 0.05$).

Uncertainty

Figures 2e and 3e display uncertainty ranges. With respect to Experiment 1, uncertainty was on average 10.2°, 12.1°, and 13.0° for control participants, PD off, and PD on, respectively, following reach training with an aligned cursor. When we compared patients off medication with control participants, we did not observe any difference in the magnitude of uncertainty [$F(1, 24) < 1$, $p = 0.643$]. As well, no differences were observed between aligned and rotated conditions [$F(1, 24) = < 1$, $p = 0.371$] or across marker locations [$F(2, 48) = 2.722$, $p = 0.076$]. Finally, we found no difference in uncertainty between PD patients off and on medication [$F(1,12) < 1$, $p = 0.592$]. In Experiment 2, we observed a significant difference in uncertainty between PD off and control participants [$F(1,24) = 4.662$, $p = 0.041$], such that PD off were 26% more uncertain in their responses (1.84 cm), compared to control participants (1.46 cm). Uncertainty was comparable across visual feedback conditions [$F(1,24) = 2.494$, $p = 0.127$], and reference marker locations [$F(2, 48) = 1.030$, $p = 0.365$]. As well, uncertainty was comparable between PD off and PD on [$F(1,12) < 1$, $p = 0.721$]. In general, these results suggest that precision of estimates of hand position was not influenced by visual feedback during reach training trials. However, PD patients, both off and on medication, were slightly less consistent in their proprioceptive estimates compared to controls when making estimates in the horizontal direction.

Discussion

The goal of the present study was to investigate the possible role of the basal ganglia and dopaminergic input to this structure, in proprioceptive recalibration. We did this by testing whether implicit reach adaptation to a visuomotor distortion leads to changes in hand proprioception in PD patients both off and on medication, as shown in healthy controls. Before assessing proprioceptive recalibration, we first confirmed the previous findings that PD patients were able to adapt to small, gradually introduced visuomotor distortions when off and on medication (Semrau et al. 2014). As expected, we found that all participants were unaware of the visuomotor distortion, as revealed by post-experiment verbal reports. Furthermore, all participants adapted their reaches to the visuomotor distortions in Experiments 1 (rotated) and 2 (translated), and the magnitude of aftereffects was the same between PD off and age-matched control participants and between PD off and PD on medication in both experiments as shown previously (e.g., Isaias et al. 2011; Marinelli et al. 2009; Semrau et al. 2014). After establishing visuomotor adaptation, we next looked to determine if participants recalibrated their sense of felt hand position.

We found that after adapting to the visuomotor distortions, estimates of unseen hand position shifted leftwards for PD off compared to their estimates following training with an aligned cursor. Moreover, this shift occurred in the direction consistent with reach adaptation and was comparable in magnitude to the shift observed in control participants, suggesting that processes underlying proprioceptive recalibration are retained in PD patients. Likewise, we found similar amounts of proprioceptive recalibration in PD during clinically defined "off" and "on" medicated states, suggesting that dopaminergic medication neither improves nor worsens proprioceptive and sensorimotor processing in mildly-to-moderately affected PD patients. Altogether, these results suggest that for smaller distortions that are introduced gradually (i.e., up to 30° or 4 cm), PD patients are able to adapt their reaches and recalibrate proprioception at levels comparable to healthy adults.

Finally, our paradigm also enabled us to rigorously measure patients' proprioceptive acuity at the effector endpoint (i.e., the hand). On average, patients were fairly accurate in estimating the position of their hand, such that they aligned their hand with the reference markers comparably to control participants following both aligned and rotated reach training. PD did lead to a slight increase regarding the uncertainty of their hand position estimates compared to controls, but this was only found in Experiment 2 when horizontal position from the target was assessed. Previous work by van Beers and colleagues (1998) has consistently shown that one's sense of proprioception is less precise in the horizontal compared to vertical direction. Thus, it is not surprising that group differences arose with respect to uncertainty in this direction. Together, our results indicate that while PD patients may be slightly poorer at joint estimates and even spatially recalling proprioceptive hand position, perceptual estimates of current end-effector positions are not noticeably impaired overall.

Visuomotor adaptation in PD

Previously, reach adaptation to misaligned visual hand feedback in PD patients has been shown to depend on the magnitude of the initial error; that is, patients produced similar learning curves and reach aftereffects compared to healthy controls when the distortion was relatively small in size (e.g., 30° rotation: Semrau et al. 2014; Isaias et al. 2011; Marinelli et al. 2009; Bedard and Sanes 2011), or larger in size but introduced gradually compared to abruptly (Mongeon et al.2013; Venkatakrishnan et al. 2011). While poorer adaptation to abruptly introduced large distortions could be due to movement impairments typical of PD (i.e., bradykinesia, rigidity, reduced movement amplitudes), previous results (e.g., Contreras-Vidal and Buch 2003; Venkatakrishnan et al. 2011) also suggest the role of different brain regions in adaptation under different contexts. For instance, together, the results suggest that learning a gradually introduced distortion recruits cerebellar-dependent mechanisms typical of implicit, error-based learning (i.e., updating an internal model), while learning a large, abruptly introduced distortion that leads to participant awareness and engagement of explicit cognitive strategies recruits basal ganglia-related circuitry.

Previous studies exploring implicit adaptation in PD have reported impaired retention and recall of these newly learned sensorimotor mappings. For example, after a wash-out period, patients showed no savings (faster re-adaptation) in subsequent learning trials, even as little as 24 h after the initial training (Bedard & Sanes, 2011; Marinelli et al. 2009). Recent work suggests that short-term retention may be driven by the recall of explicit aiming strategies (Morehead et al. 2015), leading to the deficits observed in PD. Thus, at this time, we suggest that while dopaminergic transmission has shown to be necessary for facilitating motor learning (McEntee et al. 1987; Seidler et al. 2010) and coding prediction errors involved in learning (Galea et al. 2012), dopaminergic pathways are not responsible for the formation of updated sensorimotor mappings in response to gradually learned distortions (i.e., implicit visuomotor adaptation).

While our results cannot directly speak to the magnitude of long-term learning and retention of visuomotor adaptation in PD, our findings suggest that patients do update their sensorimotor mappings to reflect the new association between sensory feedback and movement, at least temporarily. Specifically, we have confirmed that patients are able to adapt to a gradually introduced, relatively small visuomotor rotation, and also to a translated hand cursor, that they are unaware of. This immediate adaptation is comparable to controls and not dependent on PD medication status. Consistent with our original findings in healthy young adults (Cressman and Henriques 2009), reach aftereffects produced by the older controls and patients in the current study were somewhat larger following adaptation to translated hand cursor (70% of the distortion) compared to a rotated cursor (50% of distortion). Importantly, the comparable level of learning and aftereffects observed between patients and healthy controls subsequently allowed us to directly investigate changes in proprioceptive sense of hand position.

Proprioceptive recalibration in PD

Our main, novel, finding in this study was that following visuomotor adaptation, PD patients demonstrated recalibration of their proprioceptive estimates of hand position. Specifically, following reaches with altered visual feedback (either rotated or translated) of hand position, patients recalibrated their sense of felt hand position (i.e., hand-reference marker alignment) more leftwards, in the direction opposite

the distortion and consistent with their reach adaptation. For adaptation to a rotated cursor, this shift was roughly 7° or 25% of the induced 30° distortion; for a translated cursor, this shift was roughly 1.3 cm or 34% of the induced 4 cm distortion. Moreover, the magnitude of this change was comparable to controls. From previous work described earlier suggesting that proprioception is impaired in PD (e.g., see Konczak et al. 2009 for a review), we expected that patients would recalibrate their proprioceptive sense of hand position to a greater extent than healthy adults. This increased recalibration was expected to arise due to an overreliance on visual information resulting in patients perceiving their hand to feel as though it had shifted in the direction they saw it (Simani et al. 2007; van Beers et al. 2002). This was not the case. Indeed, patients recalibrated proprioception to an extent comparable with control participants, during both rotated and translated feedback paradigms. The recalibration that was observed in both paradigms further supports the robustness of this process in visuomotor adaptation. Given that patients did not recalibrate proprioception to match visual estimates of hand position, much beyond 30% of the visual distortion in this task suggests that PD patients do not rely on past visual experience any more than healthy adults.

We assume that the observed shifts in felt hand position arise implicitly. In accordance with this suggestion, Modchalingam and colleagues (2019), have recently demonstrated that proprioceptive recalibration is not modulated based on awareness of the visuomotor distortion and instructions provided on how to counteract it. As well, we have shown that proprioceptive recalibration is similar in magnitude regardless of whether a small cursor distortion is introduced gradually or abruptly (Salomonczyk et al. 2012). While these implicit shifts in hand position may contribute to reach adaptation (Cressman and Henriques, 2010), the lack of relationship between reach aftereffects and proprioceptive recalibration observed in the current study and our previous work (Cressman and Henriques 2009; Cressman et al. 2010; Salomonczyk et al. 2011, 2012) suggest that these processes are served by separate underlying mechanisms. We have previously proposed that a cross-sensory error signal derived from the discrepancy between visual and proprioceptive feedback drives proprioceptive recalibration, while reach adaptation is driven by a sensorimotor error signal, indicating a mismatch between the predicted and actual sensory consequences of the movement (Salomonczyk et al. 2013).

The current finding that proprioceptive recalibration is preserved in PD when reach adaptation arises implicitly suggests that the processes associated with recalibration (and implicit visuomotor adaptation) do not require input from striatal dopaminergic pathways. We propose that the parietal cortex may drive proprioceptive recalibration. Specifically, proprioceptive recalibration could be occurring within the parietal cortex (along with the somatosensory cortex and premotor cortical areas). This proposal is supported by Shadmehr and Krakauer (2008), who in their review suggest that a possible function of the parietal cortex is to update and integrate actual and predicted sensory feedback of the limb for state estimation. Block and Bastian (2012) have also proposed that sensory realignment depends on regions of the posterior parietal cortex after demonstrating that individuals with cerebellar damage recalibrated proprioception despite impaired motor adaptation. Furthermore, Clower and colleagues (1996) interpreted their neuroimaging results to directly implicate the posterior parietal cortex in sensory recalibration. In addition to processes related to proprioceptive recalibration occurring in the parietal cortex, Vahdat and colleagues (2011) have demonstrated the engagement of a cortical network, involving the second somatosensory cortex, ventral premotor cortex, and supplementary motor cortex, in sensory plasticity after reach training in a velocity-dependent force field.

Proprioception in PD

Our paradigm enabled us to rigorously measure patients' proprioceptive acuity at the effector endpoint (i.e., the hand). Following reach training with an aligned cursor (baseline conditions), patients perceived their hand as being aligned with a reference marker when it was slightly biased to the left. This leftward bias was consistent with control participants' estimates of hand-reference marker alignment, as well as with previous work that suggests estimates made with the right hand are naturally biased towards the left (Jones et al. 2010; Salomonczyk et al. 2012); that is, individuals feel their right hand is more rightwards than it actually is. We found that this effect was not modulated by dopaminergic medication.

Previously, the sense of felt limb position in PD has for the most part been measured using single-joint matching tasks. Specifically, patients were asked to match a remembered target joint angle (the elbow) in the absence of vision with the previously displaced limb or by matching a concurrently held limb position with the opposite limb (O'Suilleabhain et al. 2001; Zia et al. 2000, 2002). These studies revealed impairments, such that patients made greater errors in angle matching than controls regardless of active or passive limb placement. The difference between these results and present findings could be due to possible differences in the manner that the CNS processes joint-angle proprioception compared with proprioception of the end-effector. Fuentes and Bastian (2010) have shown that end-effector proprioception is more precise than proprioception of a joint angle (i.e., the elbow), possibly due to CNS optimization resulting from the greater need for estimating hand position in daily activities. Given that the present results did

not indicate impairment in end-effector position estimation, this discrepancy could be due to potential CNS optimization in estimating end-effector position.

Alternatively, another plausible explanation to explain contradictory findings is the cognitive demands associated with the different tasks employed. In contrast to our findings, end-effector (fingertip) proprioception has been shown to be impaired in PD patients (O'Suilleabhain et al. 2001, see also Lee et al. 2013), though these authors employed a task that required matching the position to a remembered spatial location. The relative deterioration found in PD patients in this delayed reproduction task was only half of that produced when the same patients had to discriminate or match the angle of their elbow joint (11% vs 31% and 27%). Matching a remembered joint angle using the ipsilateral limb requires working memory resources that have been shown to be impaired in PD (Lewis et al. 2005; Owen et al. 1997). Conversely, contralateral matching tasks require the transfer of information across the corpus callosum. While the corpus callosum has been shown to remain structurally intact in early-to-moderate PD (Wiltshire et al.2005), functional deficits including interlimb coordination are present (Swinnen et al. 1997; Verschueren et al. 1997). More recently, Isaias and colleagues (2011) demonstrated impaired interlimb transfer of visuomotor adaptation in PD patients that directly related to DAT binding in the caudate and putamen, directly implicating the basal ganglia in tasks requiring interlimb transfer and attention/memory. Together, these findings may implicate memory or central processing impairments in joint-angle matching deficits previously observed. Our present proprioceptive task does not place demands on proprioceptive memory or hemispheric communication of interlimb information, thus providing an accurate assessment of one's ability to localize the endpoint position of the limb without additional interference from cognitive demands.

Finally, differences between previously reported findings and our present results may be due to the modality of the reference around which proprioception is assessed. In elbow matching studies, the reference (elbow joint angle) was proprioceptive. In our paradigm, patients had to match their hand to an external, visual reference marker. While it remains unknown whether PD patients are differentially impaired at spatial encoding around visual or proprioceptive spatial locations, indirect evidence supporting impaired egocentric processing in PD comes from findings of disrupted representations of body size relative to space (Lee et al. 2001). Previous work in our lab revealed no differences in proprioceptive acuity or precision between visual and egocentrically encoded proprioceptive (i.e., body midline) markers (Cressman and Henriques 2009) in healthy control participants. However, evidence suggests that perception of body midline is impaired in PD (Davidsdottir et al. 2008), which could subsequently affect judgements of effector position around this type of reference marker. To explore this further, proprioceptive acuity around both visual and proprioceptive markers should be explored. From the present study, we can only conclude that multi-joint, end-effector proprioceptive acuity around visual markers is retained in PD.

Summary

In summary, this study represents the first attempt at examining sensory recalibration in Parkinson's disease. The results indicate that PD patients are able to recalibrate their proprioceptive sense of hand position to a similar extent as healthy age-matched control participants after adapting their reaches implicitly. Moreover, dopaminergic therapy was not shown to improve (or worsen) proprioceptive acuity or recalibration, indicating that dopaminergic input to the basal ganglia does not play a role in proprioceptive recalibration.

In earlier work, we have also ruled out the possible role of the cerebellum in proprioceptive recalibration. Using a similar task, we found that patients suffering from local ischemic lesions in the cerebellum also showed equivalent changes in hand proprioception following successful adaptation to a gradual-introduced 30° cursor rotation (Henriques et al. 2014). Together, these results suggest that the integration and recalibration of cross-sensory signals for state estimation may be occurring in the cortex, rather than sub-cortical structures, perhaps in the posterior parietal cortex (Shadmehr et al. 2010). Future work remains to be done to further elucidate the neural substrates involved in visuomotor adaptation and proprioceptive recalibration.

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