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ORIGINAL COMMUNICATION

The effect of dopamine replacement therapy on haptic sensitivity in Parkinson's disease

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Abstract Increasing evidence indicates that processing of proprioceptive information is altered in Parkinson's disease (PD), leading to reduced kinaesthetic and haptic sensitivity. However, there is inconclusive evidence whether dopamine replacement therapy (DRT) ameliorates or worsens kinaesthetic and haptic function in PD. For assessing perceptual function, we employed a task that did not require active motion or stressed working memory function, which may become impaired in PD. A group of mild to moderate stage PD patients ($n = 9$) and a group of age-matched healthy controls participated in this study. Without vision, a subject's hand was moved by a robotic manipulandum along the contours of a small "virtual box" (5×15 cm). At the end of each trial, they indicated whether the contour was "curved" or "straight". PD patients were tested ON and OFF antiparkinsonian medication. Psychophysical detection thresholds were determined (curvature at which subjects correctly perceived a curved contour at the 75% level). Compared to the control group, thresholds were elevated by 55% in the PD patient group. During the ON medication state, the mean detection threshold of the patient group was reduced by 15% (ON: 4.71 m^{-1}; OFF: 5.42 m^{-1}). Increases in curvature sensitivity were highly correlated with improved clinical scores of motor function ($r = 0.74$) with more affected patients showing higher gains in sensitivity as the result of DRT ($r = 0.80$). This report documents that DRT can ameliorate haptic and kinaesthetic function in patients with mild to moderate PD, suggesting that DRT can have beneficial effects on perceptual function.

Keywords Basal ganglia · Proprioception · Perception · Sensory integration

Introduction

There is increasing evidence that basal-ganglia-related diseases such as dystonia or Parkinson's disease (PD) are associated with perceptual deficits, such as a loss of smell, tactile discrimination, or kinaesthetic and haptic deficits [9, 14, 19, 24, 30, 33, 36]. These perceptual deficits become understandable knowing that many basal ganglia neurons respond to multimodal sensory afferents [27], and underline the notion that the basal ganglia-thalamo-cortical system is involved in perception. Kinaesthetic impairments such as reduced sensitivity in limb position sense and passive motion sense have been documented in early stages of PD and in de novo patients, suggesting that problems in kinaesthesia may be considered an early marker of the disease [18, 21, 23]. In addition, haptic perception such as exploring objects with the hands is also compromised in PD with patients showing elevated thresholds in detecting object contours [19].

Haptic percepts are based on the integration of tactile and proprioceptive stimuli. Knowing that both kinaesthesia and haptics rely on proprioceptive information indicates

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that the processing of proprioceptive information becomes impaired during the disease process of PD (we here refer to *kinaesthesia* as the conscious perception of limb and body motion, and *proprioception* as the unconscious processing of proprioceptive signals used for reflexive and postural motor control). Given that intact processing of proprioceptive information is essential for voluntary motor control and planning, numerous accounts have documented that impaired kinesthesia directly contributes to the observed movement deficits of PD [2, 16, 17].

Dopamine replacement therapy (DRT) is highly effective in ameliorating the majority of motor symptoms especially in early PD. It is well known to improve movement speed in simple tasks [3, 26, 35] and complex skills [3, 5, 31, 34]. Yet, available information about the effect of levodopa on perception, in general, and on kinaesthetic or haptic processes, in particular, is inconclusive. It has been concluded that levodopa does not improve kinaesthetic deficits in PD after finding that blindfolded PD patients did not improve their sensitivity to perceive differences in movement amplitudes made to a target away from the body their ON medication [15]. Other studies conclude that DRT may actually have a detrimental effect on proprioceptive function in PD [25, 28]. For example, PD patients who were asked to match elbow positions of both arms increased their elbow position error by 31% 1 h after levodopa administration [28]. Problematic with the above studies is that they inferred kinaesthetic dysfunction by assessing the ability to match joint positions of different limbs or by analyzing kinematic movement parameters during reaching tasks. That is, their tasks involved active voluntary motion, which is known to be compromised in PD. Thus, it becomes difficult to discern problems in motor function or sensorimotor integration from perceptual function. None of these studies actually measured psychophysical thresholds for detecting or discriminating proprioceptive stimuli to determine the loss in kinaesthetic acuity in these patients. Those studies that determined perceptual thresholds often failed to find significant correlations between levodopa dosage and kinaesthetic or haptic sensitivity [19, 21–23]. However, these studies did not systematically compare patients during their ON and OFF medication states, making it impossible to discern the effect of anti-parkinsonian medication on kinaesthetic sensitivity.

To overcome the methodological problems associated with earlier studies, the current study determined psychophysical thresholds for detecting changes in hand trajectory curvature during the exploration of a virtual curved object in PD patients during their ON and OFF medication state. The paradigm evaluated kinaesthetic sensitivity without relying extensively on motor or memory abilities in non-demented patients with mild to moderate PD.

Method

Subjects

Nine patients with idiopathic PD participated in this study (mean ± SD age: 51.3 ± 7.4 years; range 51–72; seven males and two females; seven were right-handed with initial right-side onset of disease except one; and two were left-handed with initial left-side onset of disease). Nine age-matched healthy control subjects between 46 and 71 years without neurological disease or upper limb pathologies served as controls (mean ± SD age: 61.0 ± 9.4 years; seven males and two females; eight right-handed). Handedness was evaluated using the Edinburgh Handedness Inventory [29]. All participants gave their informed consent prior to entering the study. The study was approved by the Institutional Review Board of the University of Minnesota.

PD patients were recruited from the movement disorders outpatient clinic of the University of Minnesota. Nine patients were diagnosed as having idiopathic Parkinson's disease with late disease onset (>40 years). Prior to the testing, all PD patients underwent a clinical examination and the disease severity was rated using the Unified Parkinson's Disease Rating Scale (UPDRS). All patients were evaluated twice, once during the OFF medication state (after a minimum 12 h of withdrawal) and again 1.5 h after taking and obtaining an optimal response from their routine antiparkinsonian medications (ON medication state). All patients were in the mild or moderate stages of the disease. UPDRS total score during the OFF medication state was mean ± SD: 41.9 ± 10. Daily doses of medication were standardized by using the following established formula [10]: 100 mg standard levodopa = 125 mg sustained-release levodopa, or 1.5 mg pramipexole, or 6 mg ropinirole, or 10 mg bromocriptine, or 1 mg pergolide. None of the patients took long-lasting dopaminergic agents such as pergolide and cabergoline. Inclusion criteria for both the healthy and PD participants included a Mini-Mental Status Examination (MMSE) score [13] of at least 24 points as well as no diagnosed peripheral nerve disorders or other neurological conditions. A full description of the clinical data of the PD patients is provided in Table 1. The more affected arm was tested in the PD group and the matched arm was tested in the control group.

Apparatus and procedure

Participants moved the handle of a two-joint robotic manipulandum (*Interactive Motion Technologies, InMotion2*, see Fig. 1). The participant sat facing the robot holding the handle that was positioned midline with respect to the trunk and just below shoulder joint level. Vision was

Table 1 Clinical characteristics and basic demographics of Parkinson's disease patients

n	Age	Gender	Handed -ness	Disease duration (years)	UPDRS				Levodopa equivalent dose	Medication
					Total score		Motor score			
					OFF	ON	OFF	ON		
1	72	M	R	6	32	29	23	20	267	P
2	66	M	R	6	40	25	27	12	500	L
3	65	M	R	11	61	44	41	24	400	L
4	65	M	L	2	41	27	29	15	1,000	L
5	65	M	L	9	29	23	18	12	350	L, P
6	51	M	R	3	43	36	36	29	200	P
7	65	M	R	5	46	35	32	21	425	L, P
8	51	F	R	11	51	44	33	26	600	L, P
9	71	F	R	6	34	24	21	11	950	L, P

Gender: *M* male; *F* female; Handedness: based on Edinburgh Handedness Inventory [range from 20 (right-handed) to −20 (left-handed)] [23]; *UPDRS* Unified Parkinson's Disease Rating Scale (range from 0 to 192, the higher the score, the severe the disease)

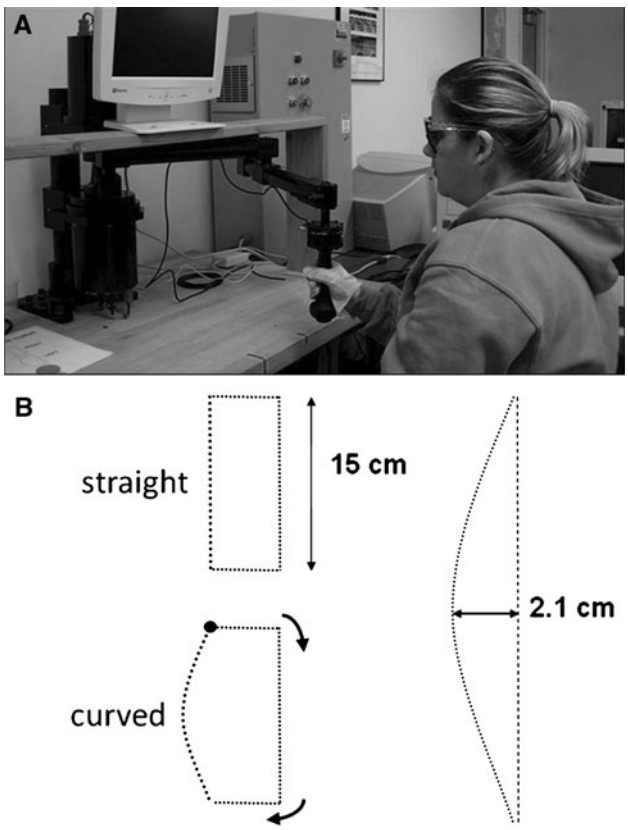

Fig. 1 **a** Experimental setup. Vision was occluded and haptic information from gripping the handle was reduced by wearing a glove made of low-friction material. **b** Movements were made along the boundaries of a 15 × 5 cm box, where its left side was either curved or straight. The MIT Manus robot manipulandum generated necessary forces to passively move the hand along the virtual contours of the box. Maximum curvature translated to a 2.1-cm deviation from a straight path

occluded via opaque glasses. Participants wore a synthetic gauze glove to reduce friction between the skin of the hand and the handle and thus, minimizing tactile cues. In addition, all participants were told to hold the handle and allow it to move them around the space, not to squeeze the handle. The robotic device passively moved a participant's hand around the edges of a virtual box (5 × 15 cm) that had a curved left wall. Curvature of the left side of the box was either convex or straight with curvature values ranging from 7 to 0 m^{-1}. A curvature of 7 translates to a 2.1 cm deviation from the straight path (see Fig. 1). Stimuli were presented at intervals of 0.5 m^{-1} resulting in 15 different curvature values. In each trial, either a straight line (curvature = 0 m^{-1}) or a curved contour (curvature > 0 m^{-1}) was presented. Using a forced-choice paradigm, participants were then required to indicate whether the hand trajectory was "curved" or "straight" at the end of each trial.

Healthy participants were tested once completing four blocks of trials ($n = 60$ trials). Each value of curvature value was tested four times in total. For each trial, we recorded the curvature value of its left wall and the associated perceptual judgment of the participants. PD patients were tested twice and completed eight blocks of trials ($n = 120$) with more affected arm. The first test was clinically defined as "OFF" state, that is, patients were tested in the morning at least 12 h after the previous administration of medication. After completing the first test, all PD patients took their antiparkinsonian medication and were retested 1.5 h after the administration of their regular dose of dopaminergic medication (ON state).

Statistical analysis

Based on the participant's responses a psychometric function was obtained for each individual and group. The fitted Boltzmann functions had the form:

$$r = \frac{A1 - A2}{1 + e^{(c - c_0)}} + A2$$

where r was the correct response rate, c was the experienced curvature of the virtual object, e is Euler's number, and $A1$ and $A2$ were estimated constants. Following established psychophysical methods [11], the detection threshold was defined as the curvature value at the 75% correct response level. The difference in thresholds between the PD patient and the control group was analyzed using a one-way analysis of variance procedure (ANOVA). A correlation analysis was conducted to evaluate the effects of the dose of medication and disease duration on changes in curvature sensitivity.

Results

Detection thresholds were elevated in the PD group

Based on the obtained sensitivity functions, the detection threshold for the healthy control group was computed as 3.39 m^{-1}, while the PD group had a threshold of 5.26 m^{-1} during OFF state (see Fig. 2). The corresponding one-way ANOVA yielded a significant difference in the detection threshold difference between the controls and PD-OFF ($p < 0.05$). This difference translates to a 55% increase in the curvature detection threshold of the PD group when compared to controls, indicating that the PD patient group during their OFF state exhibited a reduced kinaesthetic sensitivity to perceive curved contours with their hands.

Effects of dopamine replacement therapy on hand curvature sensitivity

In the PD group, the detection threshold for perceiving curvature was reduced to 4.45 m^{-1} during the ON-medication state, which corresponds to a 15% improvement in sensitivity with respect to the OFF state. To obtain a clearer picture of the medication effect on curvature sensitivity in each of the PD patients, we computed the individual sensitivity functions of each patient and determined their detection threshold for both ON and OFF state. Six out of nine PD patients exhibited reductions in their thresholds between 13 and 49%, meaning they became more sensitive in detecting curvature after levodopa administration. In the remaining three patients, thresholds increased between 13 and 56%. As expected, levodopa administration did improve motor performance in the patient group, which was reflected by reductions in the UPDRS motor scores (all nine patients showed a reduction in their UPDRS motor scores after DRT—see Table 1). This improvement in motor function highly correlated with lower thresholds in curvature sensitivity ($r = 0.74$), indicating that perceptual performance improved in conjunction with motor performance (see Fig. 3a). In order to understand how disease severity and levodopa affected perceptual thresholds, we correlated the OFF medication UPDRS total score, as an indicator of disease severity, with the change in detection threshold from OFF to ON medication state. The analysis yielded a significant positive correlation of $r = 0.80$, indicating that the more severely affected patients benefited the most from levodopa administration by showing the highest improvements in motor and perceptual function within the patient group (see Fig. 3b).

In contrast, there was no significant correlation between the daily levodopa-equivalent dose and the change in detection threshold. Also, the correlation between the

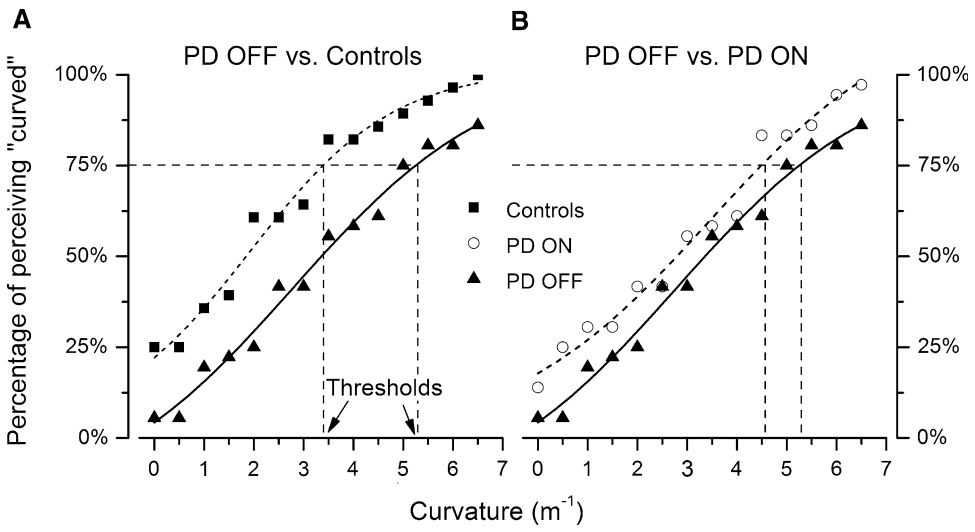

Fig. 2 Curvature sensitivity functions and detection thresholds. The threshold for detecting the contour as being curved corresponds to the curvature value at the 75% correct response level. **a** Control group versus patient group. With respect to the control group the curve of the PD group is shifted to the *right* indicating that haptic sensitivity was decreased in the patient sample. **b** ON versus OFF medication. For the ON medication state, the function shifted *leftwards*, indicating that sensitivity improved with medication

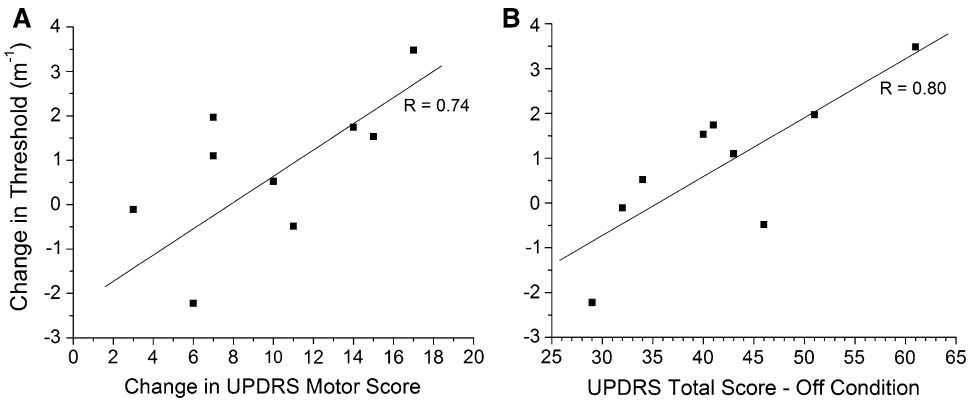

Fig. 3 Effect of DRT on the curvature thresholds of individual patients. **a** Relationship between change in threshold and change in motor ability as measured by the UPDRS motor score. Improvement in haptic and motor function correlated highly ($r = 0.74$). **b** Relationship between change in threshold and disease severity as measured by the UPDRS total score during OFF medication state. More severely affected patients tended to show the largest improvements in haptic function after DRT

disease duration and the change in threshold was not significant ($p > 0.05$).

Discussion

Humans routinely use their hands to actively explore the properties of objects within their environment. This form of haptic perception relies on the availability tactile information from the mechanoreceptors of the hand and the joint proprioceptors of the arm, and is based on the integration of these two sources of afferent information. This study essentially employed a haptic task, although we implemented two important constraints. First, participants did not actively move, but were asked to detect the curvature of a virtual object while their hand was moved passively around it. Thus, possible motor impairments could not confound their perception. Second, participants grasped the handle of the robot manipulandum wearing a synthetic glove, which decreased friction and reduced the acuity of tactile information. Although wearing the glove did not fully remove tactile information, it is reasonable to assume that this haptic task relied mainly on proprioceptive information, thus, had a large kinaesthetic component.

Haptic sensitivity is impaired in PD

This study provides further evidence that the processing of proprioceptive information is impaired in PD, leading to a reduced sensitivity in kinaesthesia and haptic perception. It corroborates previous findings indicating that the ability of PD patients to haptically perceive a curved object contour is diminished [19]. Compared to the control group, the detection thresholds were elevated by 55% in the PD patient group of this study (see Fig. 2a). Given that all patients were in the mild to moderate stage of the disease underlines the notion that haptic and kinaesthetic deficits may become manifest early in the disease process. By testing patients in their OFF medication state, this study shows for the first time that deficits in haptic precision are genuine to PD and cannot be understood as unwanted side effects of anti-parkinsonism medication.

Effects of DRT on haptic sensitivity

Previous research reported that DRT has a detrimental effect on kinaesthetic function [28]. In that study, the precision of PD patients to match joint positions of their more affected with their less affected arm further degraded 1 h after levodopa intake (elbow position error increased by 31%). The results from our experiment could not corroborate this assessment. We found no clear evidence that administration of dopaminergic agents further deteriorated haptic sensitivity in PD. In fact, our results rather suggest that DRT mildly improves haptic sensitivity. Six out of nine patients (66%) revealed lower thresholds and the PD group's perceptual threshold dropped by 15% after intake of dopaminergic agents (see Fig. 2b). Our results further indicate that those patients who responded well motorically to DRT by exhibiting the larger reductions in the UPDRS motor score, also showed the biggest gains in haptic sensitivity (see Fig. 3a). These patients also tended to be in a more advanced stage of the disease (see Fig. 3b).

What are the possible mechanisms that can explain that DRT improves haptic function? There are two possible neural systems that may benefit from DRT. First, many dopaminergic cells in the in the basal ganglia are known to respond to multimodal somatosensory stimulation. Animal studies have long established that many basal ganglia neurons have proprioceptive receptive fields, responding both to passive and active joint motions [6–8] with the vast majority of neurons in the monkey internal globus pallidus

(GPi) responding to passive motion of a single joint [4, 12]. In humans, single cell recordings in PD patients submitted to neurosurgery revealed that a third of the neurons in the nucleus subthalamicus responded to passive or active movements of limbs [32]. It is further known that the rate of inhibited GPi neurons drastically decreases in Parkinsonian monkeys, leading to a loss in response specificity (e.g., firing during flexion and extension movements instead of flexion only) [12]. It is very likely that improved availability of dopamine likely improves the activity of these neuronal circuits, restoring joint and directional specificity and, thus, proprioceptive and haptic sensitivity. Second, DRT is known to improve working memory in PD patients who are in the primary stages of the disease [20]. Haptic perception is *eo ipso* a serial process. It requires processing of somatosensory information over time (on the order of seconds). As DRT improves processing of basal ganglia–frontal lobe circuits, enhanced short-term memory function may also contribute to enhancements in haptic perception.

What are the possible reasons for the seemingly contradictory finding between this study and reports that saw no or a negative effect of levodopa on kinaesthetic function [25, 28]? One likely reason lies in the type of task being previously used to assess kinaesthetic function. The experimental paradigma that yielded negative results were arm position matching or reaching tasks. Both of these tasks involve a substantial motor component and possibly a memory component in the matching task. Thus, they may have tested the intactness of motor and sensorimotor integration processes in addition to examining kinaesthetic sensitivity. There is substantial evidence indicating that certain aspects of sensorimotor integration become abnormal in PD and that these are linked to the observed motor symptoms of PD patients [1]. In contrast, we employed a perceptual task that had no motor component (passive motion) and no extra demands on working memory (patients immediately reported on their sensation at the end of passive motion). In addition, we did not use measures of motor performance to deduct perceptual sensitivity but instead used established psychophysical methods to determine detection thresholds that are known to be indicative of perceptual sensitivity. Thus, we are reasonably confident that our measures closely reflect the perceptual ability of patients to detect haptic stimuli under two different states of medication.

In summary, this study has two main findings. First, it corroborates previous research showing that PD is associated with a decrease in kinaesthetic and haptic function [18, 19, 21, 28, 36]. Second, it demonstrates that the beneficial effects of levodopa on motor function can also extend to perceptual function. This assessment is based on the finding that detection thresholds of the PD group improved by 15% after administration of dopaminergic agents with six out of nine patients showing reductions in their thresholds. The implications of this finding are that DRT may improve haptic precision in PD patients, a function essential for the proper handling and manipulation of objects.

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