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Parkinson's disease accelerates age-related decline in haptic perception by altering somatosensory integration

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This study investigated how Parkinson's disease alters haptic perception and the underlying mechanisms of somatosensory and sensorimotor integration. Changes in haptic sensitivity and acuity (the abilities to detect and to discriminate between haptic stimuli) due to Parkinson's disease were systematically quantified and contrasted to the performance of healthy older and young adults. Using a robotic force environment, virtual contours of various curvatures were presented. Participants explored these contours with their hands and indicated verbally whether they could detect or discriminate between two contours. To understand what aspects of sensory or sensorimotor integration are altered by ageing and disease, we manipulated the sensorimotor aspect of the task: the robot either guided the hand along the contour or the participant actively moved the hand. Active exploration relies on multimodal sensory and sensorimotor integration, while passive guidance only requires sensory integration of proprioceptive and tactile information. The main findings of the study are as follows: first, a decline in haptic precision can already be observed in adults before the age of 70 years. Parkinson's disease may lead to an additional decrease in haptic sensitivity well beyond the levels typically seen in middle-aged and older adults. Second, the haptic deficit in Parkinson's disease is general in nature. It becomes manifest as a decrease in sensitivity and acuity (i.e. a smaller perceivable range and a diminished ability to discriminate between two perceivable haptic stimuli). Third, thresholds during both active and passive exploration are elevated, but not significantly different from each other. That is, active exploration did not enhance the haptic deficit when compared to passive hand motion. This implies that Parkinson's disease affects early stages of somatosensory integration that ultimately have an impact on processes of sensorimotor integration. Our results suggest that the known motor problems in Parkinson's disease that are generally characterized as a failure of sensorimotor integration may, in fact, have a sensory origin.

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Abbreviation: UPDRS = Unified Parkinson's Disease Rating Scale

Introduction

Haptics, also called 'active touch', refers to one's ability to extract object features such as shape, orientation and texture by moving the hands or other body surfaces around it (Gibson, 1966). It relies on the integration of proprioceptive, tactile and pressure cues (i.e., somatosensory external feedback) in conjunction with internal feedback in the form of predicted sensory feedback derived from efferent motor commands that give rise to the exploratory movements (Evarts, 1971; Kawato, 1999). Given that haptic perception requires multimodal sensory and sensorimotor integration, studying haptics allows for the investigation of these integration mechanisms and how they are affected by ageing and neurological disease.

Ageing is associated with sensory loss in multiple modalities, negatively impacting on perceptual precision and on motor systems that rely on sensory information to control balance or the fine-motor actions of the hands (Ducic *et al*., 2004; Wallhagen *et al*., 2006; Whiteside *et al*., 2006; Shaffer and Harrison, 2007). The time course for age-related sensory loss has been well mapped for vision and audition. In contrast, the effects of ageing on proprioception and haptics have received far less attention. There is evidence that proprioceptive acuity declines with age and that this decline is associated with delayed and weaker postural reflexes leading to well-documented postural problems and an increased risk of falls (Horak, 2006). There is less agreement on the extent of age-related decline in haptic perception with studies suggesting that haptic acuity does not decline significantly with old age (Norman *et al*., 2011). (For clarity, we use the term 'acuity' to refer to the sharpness of a sense as quantified by discrimination thresholds. In contrast, 'sensitivity' refers to the smallest detectable stimulus as quantified by detection thresholds. We use the term 'haptic precision' when referring to both aspects.)

There is further evidence documenting that diseases affecting cerebrobasal ganglia circuits, such as Parkinson's disease and dystonia, are associated with impairments in kinaesthesia, tactile discrimination and weight perception (Schneider *et al*., 1987; Sathian *et al*., 1997; Zia *et al*., 2003; Maschke *et al*., 2006; Putzki *et al*., 2006). For example, patients with Parkinson's disease perform poorly in tasks requiring matching, estimation or memorization of joint positions (Demirci *et al*., 1997; Adamovich *et al*., 2001; O'Suilleabhain *et al*., 2001). In addition, psychophysical studies determining detection thresholds (i.e. the smallest detectable stimulus size) have demonstrated that patients with Parkinson's disease experience deficits in limb position and passive motion sense even in the early stages of the disease (O'Suilleabhain *et al*., 2001; Maschke *et al*., 2003; Konczak *et al*., 2008). There is also initial evidence from our group that haptic perception is affected by Parkinson's disease (Konczak *et al*., 2008). In this study, mild to moderately impaired patients with Parkinson's disease judged the roundness of a virtual curved contour that was precisely controlled by a robot manipulandum. The threshold for detecting convex curvatures was elevated in 82% of patients with Parkinson's disease. The respective median threshold for the Parkinson's disease group was increased by 343% when compared with a group of healthy controls. A follow-up study showed that dopamine replacement therapy restores some of the loss in haptic precision (Li *et al*., 2010). While these studies convincingly showed that Parkinson's disease may lead to a decrease in haptic sensitivity, they left several questions unanswered that are important for understanding the effects of the disease on perceptual function and the underlying mechanisms for integrating sensory information.

First, previous work only tested for detection thresholds (i.e. sensitivity). We have no knowledge, whether haptic sensing above the detection threshold is intact. The impairment could only manifest itself as an increased detection threshold (i.e. a decrease in sensitivity), while the ability to discriminate between two detectable haptic stimuli remains unimpaired. By testing for the smallest perceivable difference between two detectable haptic stimuli one obtains a measure of acuity, which would provide an answer to the above question. Finding that haptic sensitivity is impaired while acuity remains intact would indicate that the neurodegenerative process of Parkinson's disease only restricts the range of somatosensory sensing. In contrast, an impairment of sensitivity and acuity would indicate that Parkinson's disease is associated with a general loss of haptic function.

Second, previous research contrasted haptic sensitivity in patients with Parkinson's disease against age-matched older adults, without having a clear understanding of the effect of ageing on haptic function. We lack data that clearly delineate the age-related from the disease-related processes affecting haptic perception. Such delineation requires an independent reference group not affected by ageing and Parkinson's disease. We therefore determined haptic sensitivity and acuity by measuring detection as well as discrimination thresholds in a sample of young healthy adults, a group of middle-aged and older adults without a neurological disease and a group of middle-aged and older adults with Parkinson's disease. This design allowed for mapping haptic precision across the adult lifespan and for distinguishing age from disease-related effects.

Third, while there is evidence that sensorimotor integration is affected by Parkinson's disease (Abbruzzese and Berardelli, 2003), there is little understanding of what aspects of the integration process become dysfunctional in the course of the disease. To gain insights into these processes, it is necessary to dissociate the act of sensing from the act of moving the sensors. We employed a robotic manipulandum to create curved 'virtual walls' in free space that participants explored by moving a handle attached to the end of the robotic arm. Recording participants' judgments of curvature while actively moving the handle versus their hand passively being moved by the robot allowed us understand if the disease affected the processing of external or internal feedback or both.

Materials and methods

Subjects

Twelve right-handed patients with Parkinson's disease (mean ± SD age: 67.3 ± 8.3 years; 10 males and two females; six had initial right-side onset of disease, five had initial left-side onset and one was bilaterally affected), 12 right-handed age-matched healthy middle-aged and older adults between 49 and 77 years without neurological disease or upper limb pathologies (mean ± SD age: 63.3 ± 8.2 years, six males and six females) and 12 right-handed young adults (mean ± SD age: 28.1 ± 1.9; six males and six females) participated in this study. They were naïve to the device and to the task. All participants gave their informed consent prior to testing. The study was approved by the local ethics committee.

Patients with Parkinson's disease were referred from the Department of Neurology at the University of Genoa. Actual testing was performed in the Department of Robotics, Brain and Cognitive Sciences of the Italian Institute of Technology. Prior to the testing, all patients with Parkinson's disease underwent a clinical examination and the disease severity was rated using the Unified Parkinson's Disease Rating Scale (UPDRS) and the Hoehn and Yahr Scale in their ON medication state. All patients were in the mild or moderate stages of the disease. Mean UPDRS total score was 19.4 (SD = ± 8). Daily doses of medication were standardized by using the following established formula: 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 (Fahn, 1999). Inclusion criteria for both the healthy participants and subjects with Parkinson's disease were as follows: (i) a Mini-Mental Status Examination score (Folstein *et al*., 1975) of at least 26 points and (ii) no previous diagnosis of peripheral nerve disorders or other neurological conditions known to affect touch, proprioception and/or motor control. A full description of the clinical data of the patients with Parkinson's disease is provided in Table 1. In all but one subject with Parkinson's disease, the more affected arm was tested, while in healthy participants the test was performed on the dominant hand.

Apparatus

The robotic manipulandum was a two-degrees-of-freedom planar manipulandum with a large elliptical workspace (80 × 40 cm). See online Supplementary material for a detailed technical description of the robot.

Procedure

Subjects sat comfortably on a chair in front of the robot manipulandum (Fig. 1A). Their right shoulder (acromion) was aligned with the neutral position of the manipulandum (i.e. its horizontal position). To restrict upper body motion, the trunk was strapped to the seat by belts. The centre of the robot workspace was adjusted so that subjects assumed initial sagittal joint angles of ∼90° for the elbow and ∼45° for the shoulder. Seat position with respect to the manipulandum was adjusted in such a way that the maximal arm displacement in the sagittal plane during testing did not exceed 85% of the individual's arm length.

The task required subjects to hold the handle and haptically sense a virtual curved contour (Fig. 1C), as if exploring the smooth surface of a round object with their hand. During testing, vision was occluded, so the contour could only be sensed haptically. To discern the possible effects of predictive sensory feedback, two experimental conditions were employed: subjects either moved the handle actively along the virtual contour or the hand was moved passively by the manipulandum along the virtual shape.

During each trial, participants were randomly presented with a sequence of two haptic stimuli in a two-interval forced-choice procedure separated by a 500 ms interstimulus interval. Subjects were required to discriminate between the presentation of one fixed (standard) and one variable curvature (comparison). After each trial, the participant indicated verbally which stimulus (contour) was more curved. Based on this judgment, the curvature of the virtual wall was adjusted in the subsequent trial using an adaptive procedure (QUEST algorithm; see Watson and Pelli, 1983). The adaptive procedure assured that the sequence of curvature values converged to the threshold almost monotonically for all conditions. Each trial was initiated by the

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

No.	Age (years)	Gender	More affected side	Hoehn and Yahr[a]	Disease duration (years)	UPDRS-III ON state	MMSE	Levodopa equivalent dose
1	73	M	R	3	7	18	28	600
2	73	M	L	2.5	6	12	26.2	550
3	65	M	B	3	9	16	29.5	1100
4	60	M	R	3	9	21	29.8	700
5	59	M	L	2.5	3	23	27	800
6	73	F	L	1	2	9	29	Rasagiline
7	68	M	R	2	3	17	27	400
8	69	F	R	3	15	31	30	1050
9	79	M	L	1	2.5	8	30	–
10	48	M	R	1.5	1.5	19	30	Rasagiline
11	71	M	R	3	3	34	28	400
12	70	M	R	2.5	1	25	29	350

a Hoehn and Yahr staging system (stages from 1 to 5, a higher score reflects more severe symptoms).
M = male; F = female; R = right; L = left; B = bilateral; UPDRS-III = Unified Parkinson's Disease Rating Scale, Motor Score (range from 0 to 56, a higher score reflects more severe disease state); MMSE = Mini-Mental State Examination (score from 0 to 30, a lower score reflects a more severe cognitive impairment and a score ⩾25 reflects normal cognition). Rasagiline indicates that this monoamine oxidase inhibitor was taken as monotherapy.

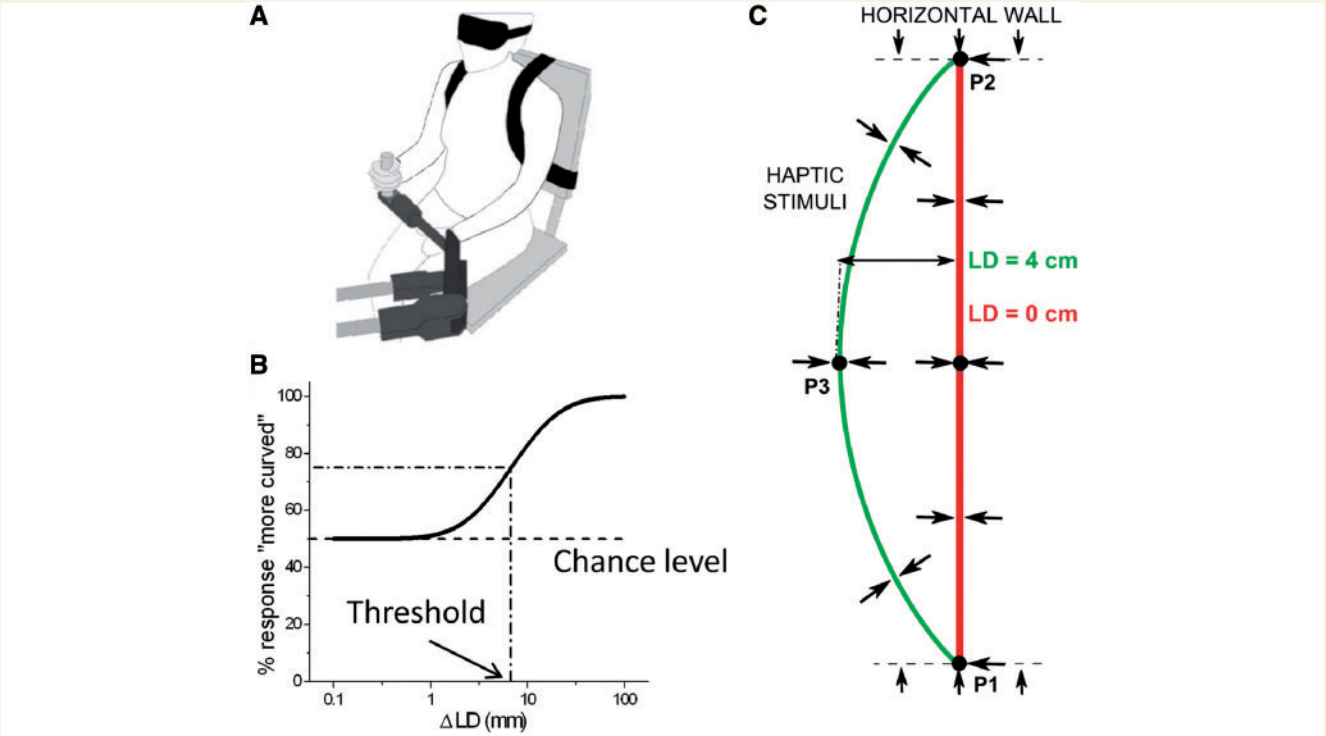

Figure 1 Setup and haptic stimuli. (**A**) Experimental setup depicting the participants and the two-degrees-of-freedom planar robot manipulandum. (**B**) Example of a psychometric function for haptic curvature perception. The ordinate values indicate the percentage of trials where the probe was judged as more curved than the standard, the abscissa represents the differences in lateral deviation between probe and standard. The threshold corresponds to the lateral deviation yielding a 75% correct response level. (**C**) Dimensions of the curved virtual contours. The standard curvatures are expressed in terms of maximum lateral deviation from a straight line (LDs: 0 and 4 cm). The hand path during active exploration was constrained by a set of virtual barriers indicated by the arrows: two radial force fields, two horizontal barriers as stops and a vertical wall that was activated when subjects attempted to move beyond $x = 0$. LD = lateral deviation.

experimenter by pressing a button. Time between trials was kept variable (~4–10 s), so that subjects could not predict the onset of the subsequent trial. Two different standard stimuli were randomly presented (lateral deviations were 0 and 4 cm, corresponding to a straight line and to a curvature of 6.9 m^{-1}; see Fig. 1C; for details see 'Design and measurements' section). The linear path distance for all stimuli was 20 cm. The starting position of the manipulandum was identical for all trials. Before data collection, participants underwent a familiarization phase, in which they experienced the haptic forces during active and passive motion, by performing 15 curvature explorations in each of the two conditions. The end effector moved along an arc starting from point P1, passing through P3 and ending at P2 and then returning to P1 (Fig. 1C).

In the passive condition, the robot delivered a two-component force field to the hand: an attractor force that smoothly moved the hand along the virtual surface and a viscous force field for the stabilization of the subject's arm while interacting with the device. The control scheme allowed for the generation of a stereotyped biological speed profile, characterized by a symmetric shape with a single bell-shaped velocity peak and an acceleration and deceleration phase, which mimicked the profiles seen during active motion in humans. The complete exploration of each curvature lasted $t = 3$ s and consisted of forward motion along the curved surface followed by a motion backward along the same path.

In the active condition, the range of curvatures and the dimensions of the hand paths were identical to the passive condition. Participants actively moved their hand along a virtual contour at a speed similar to the passive condition. To assure that the time to experience the virtual contour was comparable between the active and passive condition, subjects were trained and instructed to perform the active exploration in the same time as during passive motion (3 s). When subjects moved shorter than 2.4 s they were notified by the experimenter and reminded to maintain the target movement time of 3 s (see 'Results' section for details). Knowing that speed cues are not a major contributor in the haptic sensing of shape (Soechting and Poizner, 2005), we refrained from imposing further constraints in the active motion condition.

Design and measurements

In each condition (active/passive), subjects were exposed to one of the two standard values (lateral deviations = 0 and 4 cm). Each standard was presented together with a comparison stimulus in blocks of 60 trials, yielding a total of 240 trials per subject. The order of presentation of the standard and the comparison stimuli in each trial was random and, thus, not predictable for the subject. For determining sensitivity (i.e. detection thresholds), the standard value was a straight line (lateral deviation = 0 cm) and the comparison stimulus had a convex curvature. For determining acuity (i.e. discrimination thresholds) the standard was a curved line (lateral deviation = 4 cm). The curved comparison stimulus was variable, but always larger than the standard.

To assure that mental fatigue or lack of attention did not confound data collection, frequent small breaks were interspersed throughout testing (~20–40 trials). Total testing time was ~60–75 min.

The percentage of trials where the probe was judged as more curved than the standard was computed for each of the four experimental conditions and was fitted with a cumulative Gaussian function, yielding four psychometric sensitivity functions for each subject (for an example, see Fig. 1B). Based on these sensitivity functions, we derived four haptic thresholds (2 conditions × 2 standards). The threshold was defined as the lateral deviation for which the comparison value was correctly perceived as more curved than the standard at the 75% correct response level. Standard errors of the thresholds were computed using a bootstrap simulation (Efron and Tibshirani, 1993).

To discern differences between groups and conditions we performed two-sample *t*-tests (assuming unequal variances) and corrected for multiple testing using the Bonferroni–Holm method. Initial significance level was set to $\alpha = 0.05$.

Results

Based on the obtained sensitivity functions of each participant (Fig. 2A), individual detection and discrimination thresholds were derived for the active and passive exploration condition. To assure that the curvature judgments during active and passive exploration were not biased by large systematic differences in exploration time, we assessed the movement times between conditions. Movement time during passive guidance was fixed to 3.0 s by the robot. Movement times during active exploration were necessarily more variable. Mean active movement time was 2.82 s (±0.1 s) for the young control group, 3.03 s (±0.15 s) for the ageing group and 3.88 s (±0.21 s) for the Parkinson's disease group. The movement time differences for active versus passive exploration were not significant for both control groups ($P > 0.1$), but reached significance for the Parkinson's disease group ($P = 0.003$).

Two of the twelve patients presented with resting tremor. We verified that tremor did not modify the active exploration movement by means of a Fourier analysis. The spectrum did not show any relevant peak at a frequency higher than ≅0.67 Hz, corresponding to the explorative movement frequency, thus excluding an effect of tremor on the movement path.

Age-related changes in haptic precision

To determine effect of age on haptic perception, we compared detection and discrimination thresholds for the healthy young and older adult groups. Analysis of individual data highlight that ageing was associated with an increase in haptic thresholds. Five out of twelve older adults (42%) exhibited thresholds outside the range of the younger adult data, while 9 out of 12 older adults (75%) showed at least one threshold above the respective third quartile of the younger adult group (see Fig. 2B for respective detection threshold data). When compared with young adults the mean detection threshold for the older adult group increased by 33% (young: 7.2 ± 0.5 mm SEM, old: 9.6 ± 1.1 mm SEM; $P = 0.029$). However, after the Bonferroni–Holm correction this difference failed to reach statistical significance (Fig. 3). Significant ageing differences for haptic discrimination thresholds were also not observed (young: 8.0 ± 0.8 mm SEM, old: 8.6 ± 0.8 mm SEM; $P = 0.3$). In relative terms, the mean discrimination threshold of the ageing group increased by 8% during active exploration with respect to the young adult (Fig. 3).

Haptic detection and discrimination thresholds were elevated in Parkinson's disease

To determine if Parkinson's disease is associated with a general impairment in haptic sensing, i.e. a decrease in haptic sensitivity

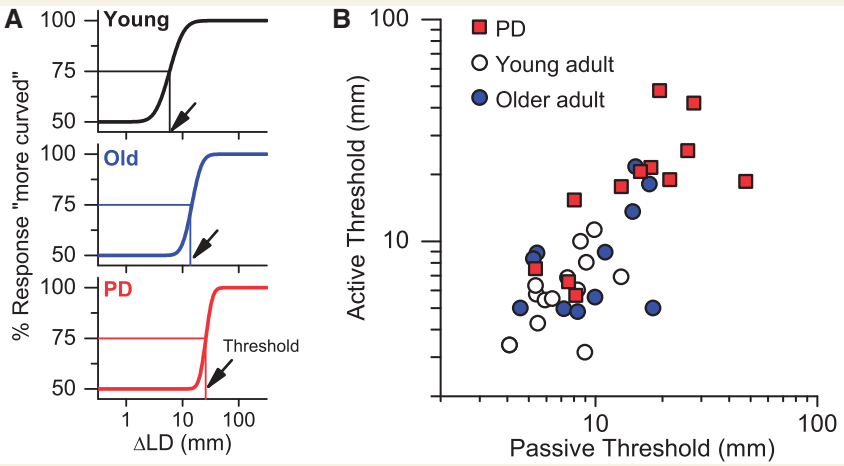

Figure 2 Individual threshold data. (**A**) Exemplar haptic sensitivity functions for passive exploration for a representative subject of each of group. The thin lines indicate 75% correct response level thresholds. A higher ΔLD value indicates a higher threshold. (**B**) Active versus passive curvature detection thresholds for each subject. Note the tight clustering of the young adults, while several older adults performed outside the range of young adults. Several patients with Parkinson's disease exhibited normal thresholds, while others exceeded the performance range of older adults. Axes scales are log10. LD = lateral deviation; PD = Parkinson's disease.

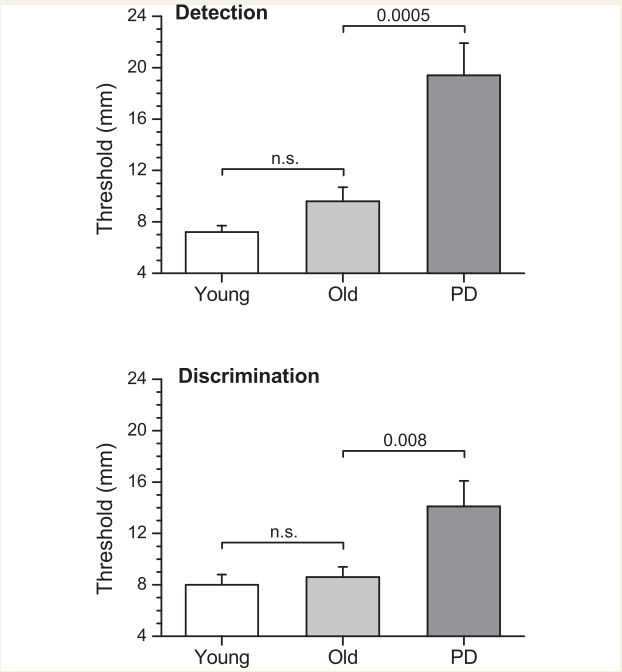

Figure 3 Mean haptic thresholds for detection and discrimination. Bars indicate the mean thresholds for each group. Error bars represent standard errors. n.s. = not significant.

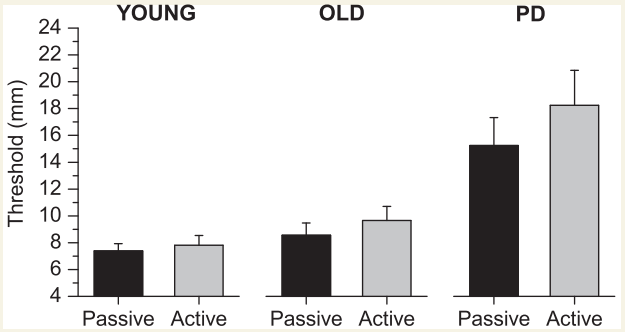

Figure 4 Active versus passive haptic sensing within each group. Bars indicate the mean thresholds. Values for detection and discrimination thresholds were collapsed for each group for each condition. Error bars represent standard errors. Note that the difference between active and passive thresholds increased with age. However, none of the within-group comparisons of active versus passive thresholds reached statistical significance. PD = Parkinson's disease.

and acuity, both detection and discrimination thresholds were computed. With respect to the older adult group, a subset of patients with Parkinson's disease presented with elevated thresholds for detection and discrimination (Fig. 2). When considering the complete patient sample, mean detection threshold for the Parkinson's disease group was 19.4 ± 2.5 mm which corresponded to a 103% increase with respect to the older adult group ($P < 0.0005$). Mean discrimination threshold for the Parkinson's disease group was 14.1 ± 2.0 mm, corresponding to a 63% increase with respect to the older adult group ($P = 0.008$, see Fig. 3).

Active versus passive haptic sensing

To discern the processing of external somatosensory from internal feedback processing (i.e. predicted sensory feedback), the differences in active and passive haptic sensing were analysed within each group. Within the young group, mean thresholds were computed as 7.4 ± 0.6 mm SEM (passive) and 7.8 ± 0.7 mm SEM (active), a 5.9% difference. For the ageing group this difference increased to 12.9% (passive: 8.5 ± 0.9 mm SEM; active: 9.7 ± 1.05 mm SEM), and to 19.7% in the Parkinson's disease group (passive: 15.3 ± 2.0 mm SEM; active: 18.3 ± 2.5 mm SEM). However, none of the within-group comparisons yielded significance ($P > 0.14$) (Fig. 4).

Furthermore, using the young group as a reference allowed for an independent evaluation of how active and passive haptic precision was affected by ageing and Parkinson's disease. With respect to the young adult group, the mean threshold increase of the Parkinson's disease group was ~2–2.5 times larger than the age-matched control group (increase in passive thresholds: 105% Parkinson's disease versus 15% old; active: 144% Parkinson's disease versus 25% old).

Finally, no significant correlation between the daily levodopa equivalent dose and detection or discrimination thresholds for passive and active sensing was observed (detection: $r_{passive} = 0.186$, $r_{active} = -0.005$; discrimination: $r_{passive} = 0.196$, $r_{active} = 0.024$; all $P > 0.05$). In addition, haptic threshold levels were not significantly correlated with the UPDRS motor score (detection: $r_{passive} = 0.260$, $r_{active} = 0.372$; discrimination: $r_{passive} = -0.059$, $r_{active} = -0.301$; all $P > 0.05$) or disease duration (detection: $r_{passive} = -0.004$, $r_{active} = 0.072$; discrimination: $r_{passive} = 0.040$, $r_{active} = -0.115$; all $P > 0.05$).

Discussion

This study sought to accomplish the following goals. First, to determine to what extent aging is associated with a decline in haptic precision, in order to delineate such age-related changes from changes due to Parkinson's disease. Second, to quantify the degree of the somatosensory processing deficit in Parkinson's disease. Specifically, we determined if the neurodegenerative processes underlying Parkinson's disease cause a general impairment in haptic function (i.e. a decline in sensitivity and acuity). Third, to understand what aspects of sensorimotor integration are mostly affected by the disease, the processing of afferent feedback or the generation of internal feedback in the form of predicted sensory feedback. The main findings of the study are the following: First, we provide evidence showing ageing is associated with a decline in haptic precision. Based on our middle-aged to older adult sample, such decline is mild (21% mean decrease) and more pronounced for haptic sensitivity. Parkinson's disease can lead to an additional decrease in haptic sensitivity well beyond the levels typically seen in middle-aged and older adults. Second, the haptic deficit in Parkinson's disease is general. That

is, it becomes manifest as a decrease in perceivable range (i.e. decline in sensitivity), and in the ability to discriminate between two perceivable haptic stimuli (i.e. decline in acuity). Third, thresholds during both active and passive exploration are elevated, but not significantly different from each other, indicating that somatosensory processing is impaired in Parkinson's disease.

Parkinson's disease leads to a general decline in haptic acuity

Previous research documented that haptic sensitivity can be affected in Parkinson's disease (Konczak *et al*., 2008). The current study documented that patients with Parkinson's disease showed elevated haptic detection and discrimination thresholds (Fig. 3). That is, patients with Parkinson's disease not only had a reduced sensitivity to detect small haptic stimuli, they also lost precision in differentiating between two haptic stimuli that they both could clearly detect. In other words, Parkinson's disease not only led to a decrease in sensitivity, but also to a decrease in acuity. This result implies that Parkinson's disease is associated with a general decline in haptic function. To our knowledge, this is the first study to document the extent of the haptic deficit in Parkinson's disease. The observed decline in haptic precision can be regarded as perceptual manifestation of altered processing of somatosensory signals (Seiss *et al*., 2003).

Are there alternative explanations that could account for the above finding? It is known that at the later stages of the disease mechanoreceptor density might decrease (Nolano *et al*., 2008), indicating peripheral deafferentation in Parkinson's disease likely plays a role in the pathogenesis of the haptic dysfunction in more severe forms of Parkinson's disease. Yet, we tested patients with mild and moderate Parkinson's disease who had no signs of a peripheral neuropathy. In addition, there are no reports indicating that changes in muscle or tactile receptor density are a universal feature of early Parkinson's disease. That is, although we cannot fully exclude this possibility, the haptic deficits in our study are unlikely the sole manifestation of a peripheral nervous system deficit.

Moreover, our finding is in line with a growing list of studies documenting somatosensory deficits in Parkinson's disease such as reduced sensitivity to touch (Sathian *et al*., 1997; Prätorius *et al*., 2003), elevated proprioceptive thresholds for limb position and limb motion sense (Maschke *et al*., 2003, 2006; Konczak *et al*., 2007) or joint position matching (Zia *et al*., 2000, 2003; O'Suilleabhain *et al*., 2001). The majority of these studies examined patients with mild to moderate disease states, which indicates that the decline in processing of somatosensory signals is not a sign of advanced Parkinson's disease. In fact, the results suggest that the decline in somatosensory processing may precede motor signs. Currently, we lack data on patients with presymptomatic Parkinson's disease. However, a recent study characterizing somatosensory function in symptomatic and asymptomatic PINK1 mutation carriers found elevated thresholds for mechanical detection, mechanical and pressure pain when compared with controls (Gierthmuhlen *et al*., 2009), a finding consistent with the notion that somatosensory deficits are a very early manifestation of Parkinson's disease. A possible pathomechanism is the early degeneration of areas in the reticular formation known as the 'gain setting' system which acts as a neural gate-control mechanism for ascending somatic sensations (Hawkes *et al*., 2009). That is, the observed early stage somatosensory deficits in Parkinson's disease may actually reflect brainstem degeneration that is subsequently enhanced by basal ganglia degeneration.

Another caveat to consider is whether the elevated thresholds were induced by anti-parkinsonian medication. It is a limitation of the study that patients were only examined ON medication. Thus, we are not able to discriminate a possible role of dopamine replacement therapy. However, a previous study using a similar paradigm (Li *et al*., 2010) found that dopamine replacement did not deteriorate haptic sensitivity but instead slightly improved haptic detection thresholds by ~15%. Also, the present study found no significant correlation between levodopa equivalent dosage and haptic thresholds. Taken together, these findings make it very unlikely that levodopa administration alone can account for the observed haptic deficits in our Parkinson's disease sample.

Finally, are the differences in haptic sensitivity between patients and controls explained by differences in movement times, i.e. by allowing one group for systematically more exploration time? This argument cannot be true for passive motion as exploration time was fixed to 3 s by the robot. For active exploration for the Parkinson's disease group the mean movement time was ~0.9 s longer when compared to the ageing cohort (3.9 versus 3.03 s), yet the thresholds of the Parkinson's disease groups were elevated with respect to the ageing group. Normally, longer exploration time should aid haptic perception. However, despite the added 900 ms exploration time for the Parkinson's disease group, patients still performed poorer than the ageing control group. Thus, it is not plausible that differences in exploration time can convincingly account for group differences in haptic acuity.

What mechanisms of sensory or sensorimotor processing are affected by Parkinson's disease?

A substantial body of theoretical and animal research indicates that the corticobasal ganglia loop is involved in sensory processing (Lidsky *et al*., 1985), and that Parkinson's disease is associated with altered processes of sensorimotor integration (Lewis and Byblow, 2002; Abbruzzese and Berardelli, 2003). In addition, a picture emerges that patients with Parkinson's disease also have perceptual deficits that are not explained by the motor symptoms. Yet, it remains unclear what sensory mechanisms are affected. Is it integration of multimodal sensory information, i.e. combining proprioceptive and touch information for haptic perception, or lies the problem in combining external with internal feedback (Fig. 5)? In order to understand this, we investigated haptic sensing during active and passive motion. During passive motion no internal feedback is available. That is, any deficits seen are due to the problems at the level of sensory processing, either the alteration of a sensory signal or a failure of sensory integration. Our results clearly add to the notion that the processing of afferent somatosensory signals is

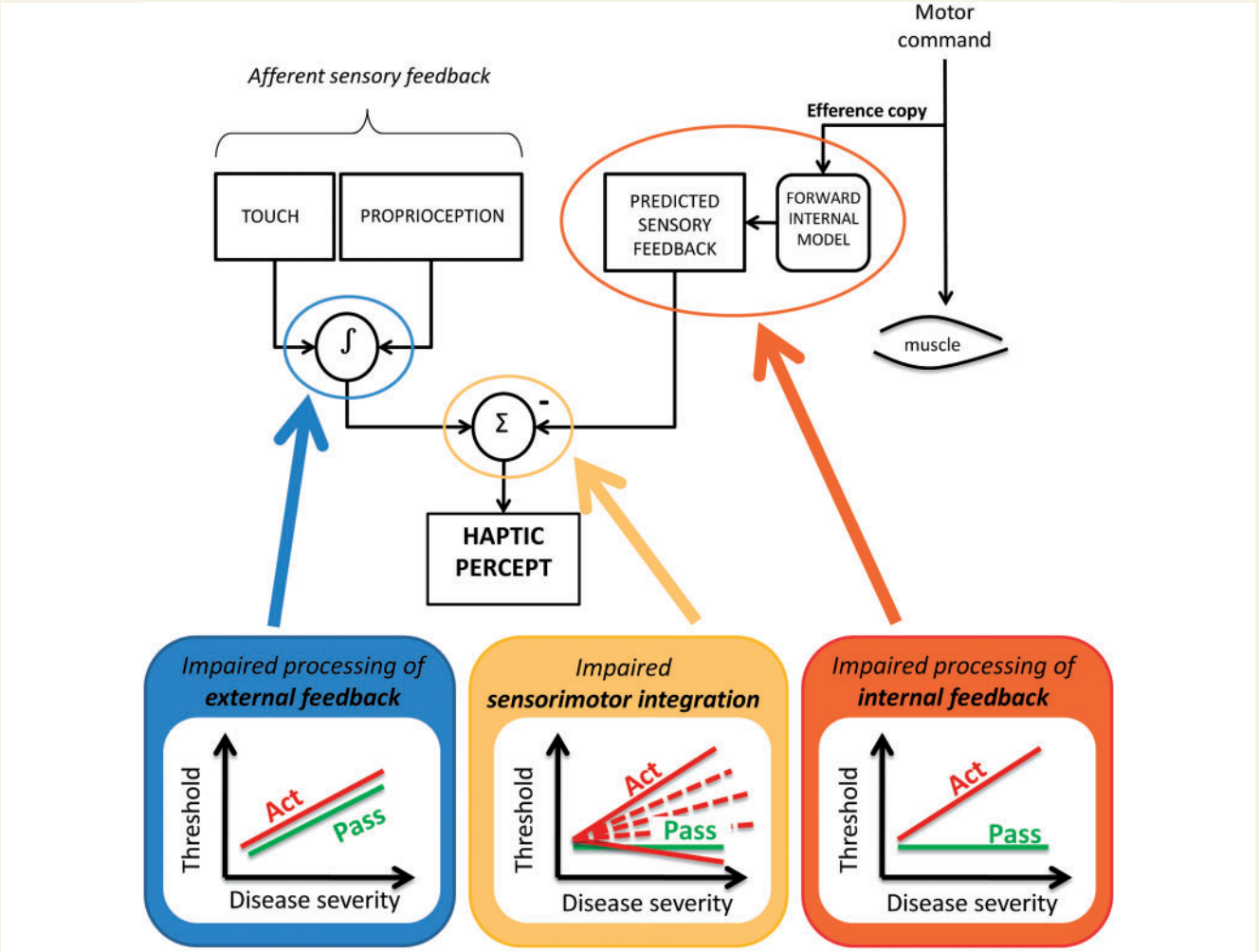

Figure 5 Computational view of the effect of failed processes underlying haptic perception due to Parkinson's disease (PD). Haptic perception is the result of the combination of afferent and efferent signals. The afferent input is based on the integration of touch and proprioceptive information, while efferent signals are generated by a forward dynamic model on the basis of the issued exploratory motor command. Parkinson's disease could be associated to a damage at each processing level of this mechanism: (i) loss in the sensitivity of afferent external feedback or the failure of multisensory integration would predict that thresholds would increase for passive and active exploration, as predicted sensory feedback alone is not sufficient for haptic perception (see blue box); (ii) failure to produce accurate predicted sensory feedback would imply additional noise during active exploration. Consequently, thresholds during passive exploration (no predicted sensory feedback necessary) would result in normal thresholds (red box); and (iii) failure to integrate external with internal feedback (predicted sensory feedback) would imply that the system can no longer cancel the effect of ego-motion on haptic perception. This would induce a difference between active and passive haptic perception, varying as a function of the relative weight given to the two input signals (yellow box). Our data support i, found no evidence for ii, but cannot exclude iii.

impaired, because thresholds during passive motion were elevated in our Parkinson's disease group. This implies that Parkinson's disease already affects relatively early levels of somatosensory processing, not just 'later' processes of sensorimotor integration that make use of such sensory information. However, the growing differences between active and passive haptic sensing indicate that with ageing and during later stages of the disease processes of sensorimotor integration also become affected. In other words, as the disease progresses successive stages of sensory and sensorimotor processing become dysfunctional. Our data cannot speak decisively to the notion whether Parkinson's disease is only associated with impaired processing of external, afferent feedback or whether it also alters internal feedback processes (i.e. predicted sensory feedback, Fig. 5). However, we can state convincingly that a scenario where internal feedback processing is impaired, but external feedback processing is intact, is not compatible with our data. Such failure would imply altered active exploration thresholds and normal passive motion thresholds. However, we found elevated thresholds for both active and passive exploration.

Conclusion

This is the first study to systematically evaluate the decline of haptic function in Parkinson's disease. Our data document that

Parkinson's disease leads to a general impairment of haptic precision. That is, not only the sensitivity to detect haptic stimuli declines, but also the ability to discriminate haptic stimuli within the still detectable range. The finding that thresholds are increased both during active and passive haptic exploration indicates that the haptic deficit in Parkinson's disease must be understood as a sensory integration problem. We found no evidence suggesting that internal feedback mechanisms involving sensorimotor integration are affected by Parkinson's disease. This is not to say, sensorimotor integration *per se* is not affected. However, our results suggest that the known motor problems in Parkinson's disease that are generally associated as a failure of sensorimotor integration may, in fact, have a sensory origin.

Supplementary material

Supplementary material is available at *Brain* online.

References

Abbruzzese G, Berardelli A. Sensorimotor integration in movement disorders. Mov Disord 2003; 18: 231–40.

Adamovich SV, Berkinblit MB, Hening W, Sage J, Poizner H. The interaction of visual and proprioceptive inputs in pointing to actual and remembered targets in Parkinson's disease. Neuroscience 2001; 104: 1027–41.

Demirci M, Grill S, McShane L, Hallett M. A mismatch between kinesthetic and visual perception in Parkinson's disease. Ann Neurol 1997; 41: 781–8.

Ducic I, Short KW, Dellon AL. Relationship between loss of pedal sensibility, balance, and falls in patients with peripheral neuropathy. Ann Plast Surg 2004; 52: 535–40.

Efron B, Tibshirani RJ. An introduction to the bootstrap. New York, NY: Chapman and Hall; 1993.

Evarts EV. Central control of movement. V. Feedback and corollary discharge: a merging of the concepts. Neurosci Res Program Bull 1971; 9: 86–112.

Fahn S. Parkinson disease, the effect of levodopa, and the ELLDOPA trial. Earlier vs later L-dopa. Arch Neurol 1999; 56: 529–35.

Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; 12: 189–98.

Gibson JJ. The senses considered as perceptual systems. Oxford, UK: Houghton Mifflin; 1966.

Gierthmuhlen J, Lienau F, Maag R, Hagenah JM, Deuschl G, Fritzer E, et al. Somatosensory processing in a German family with PINK1 mutations: its potential role in Parkinson disease. J Neurol Neurosurg Psychiatry 2009; 80: 571–4.

Hawkes CH, Del Tredici K, Braak H. A timeline for Parkinson's disease. Parkinsonism Relat Disord 2009; 16: 79–84.

Horak FB. Postural orientation and equilibrium: what do we need to know about neural control of balance to prevent falls? Age Ageing 2006; 35 (Suppl 2): ii7–11.

Kawato M. Internal models for motor control and trajectory planning. Curr Opin Neurobiol 1999; 9: 718–27.

Konczak J, Krawczewski K, Tuite P, Maschke M. The perception of passive motion in Parkinson's disease. J Neurol 2007; 254: 655–63.

Konczak J, Li K-Y, Tuite PJ, Poizner H. Haptic perception of object curvature in Parkinson's disease. PLoS One 2008; 3: e2625.

Lewis GN, Byblow WD. Altered sensorimotor integration in Parkinson's disease. Brain 2002; 125: 2089–99.

Li KY, Pickett K, Nestrasil I, Tuite P, Konczak J. The effect of dopamine replacement therapy on haptic sensitivity in Parkinson's disease. J Neurol 2010; 257: 1992–8.

Lidsky TI, Manetto C, Schneider JS. A consideration of sensory factors involved in motor functions of the basal ganglia. Brain Res 1985; 356: 133–46.

Maschke M, Gomez CM, Tuite PJ, Konczak J. Dysfunction of the basal ganglia, but not the cerebellum, impairs kinaesthesia. Brain 2003; 126: 2312–22.

Maschke M, Tuite PJ, Krawczewski K, Pickett K, Konczak J. The perception of heaviness in Parkinson's disease. Mov Disord 2006; 21: 1013–8.

Nolano M, Provitera V, Estraneo A, Selim MM, Caporaso G, Stancanelli A, et al. Sensory deficit in Parkinson's disease: evidence of a cutaneous denervation. Brain 2008; 131: 1903–11.

Norman JF, Kappers AM, Beers AM, Scott AK, Norman HF, Koenderink JJ. Aging and the haptic perception of 3D surface shape. Atten Percept Psychophys 2011; 73: 908–18.

O'Suilleabhain P, Bullard J, Dewey RB. Proprioception in Parkinson's disease is acutely depressed by dopaminergic medications. J Neurol Neurosurg Psychiatry 2001; 71: 607–10.

Prätorius B, Kimmeskamp S, Milani TL. The sensitivity of the sole of the foot in patients with Morbus Parkinson. Neurosci Lett 2003; 346: 173–6.

Putzki N, Stude P, Konczak J, Graf K, Diener HC, Maschke M. Kinesthesia is impaired in focal dystonia. Mov Disord 2006; 21: 754–60.

Sathian K, Zangaladze A, Green J, Vitek JL, DeLong MR. Tactile spatial acuity and roughness discrimination: impairments due to aging and Parkinson's disease. Neurology 1997; 49: 168–77.

Schneider JS, Diamond SG, Markham CH. Parkinson's disease: sensory and motor problems in arms and hands. Neurology 1987; 37: 951–6.

Seiss E, Praamstra P, Hesse CW, Rickards H. Proprioceptive sensory function in Parkinson's disease and Huntington's disease: evidence from proprioception-related EEG potentials. Exp Brain Res 2003; 148: 308–19.

Shaffer SW, Harrison AL. Aging of the somatosensory system: a translational perspective. Phys Ther 2007; 87: 193–207.

Soechting JF, Poizner H. The use of motion cues in the haptic sense of circularity. Exp Brain Res 2005; 165: 413–21.

Wallhagen MI, Pettengill E, Whiteside M. Sensory impairment in older adults: part 1: hearing loss. Am J Nurs 2006; 106: 40–8; quiz 48–9.

Watson AB, Pelli DG. QUEST: a Bayesian adaptive psychometric method. Percept Psychophys 1983; 33: 113–20.

Whiteside MM, Wallhagen MI, Pettengill E. Sensory impairment in older adults: part 2: vision loss. Am J Nurs 2006; 106: 52–61; quiz 61–2.

Zia S, Cody F, O'Boyle DJ. Joint position sense is impaired by Parkinson's disease. Ann Neurol 2000; 47: 218–28.

Zia S, Cody FW, O'Boyle DJ. Discrimination of bilateral differences in the loci of tactile stimulation is impaired in subjects with Parkinson's disease. Clin Anat 2003; 16: 241–7.