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Deep Brain Stimulation for Parkinson's disease changes perception in the Rubber Hand Illusion

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Parkinson's disease (PD) alters cortico-basal ganglia-thalamic circuitry and susceptibility to an illusion of bodily awareness, the Rubber Hand Illusion (RHI). Bodily awareness is thought to result from multisensory integration in a predominantly cortical network; the role of subcortical connections is unknown. We studied the effect of modulating cortico-subcortical circuitry on multisensory integration for bodily awareness in 24 PD patients treated with subthalamic nucleus (STN) deep brain stimulation (DBS), in comparison to 21 healthy volunteers, using the RHI experiment. Typically, synchronous visuo-tactile cues induce a false perception of touch on the rubber hand as if it were the subject's hand, whereas asynchronous visuo-tactile cues do not. However, we found that in the asynchronous condition, patients in the off-stimulation state did not reject the RHI as strongly as healthy controls; patients' rejection of the RHI strengthened when STN-DBS was switched on, although it remained weaker than that of controls. Patients in the off-stimulation state also misjudged the position of their hand, indicating it to be closer to the rubber hand than controls. However, STN-DBS did not affect proprioceptive judgements or subsequent arm movements altered by the perceptual effects of the illusion. Our findings support the idea that the STN and subcortical connections have a key role in multisensory integration for bodily awareness. Decision-making in multisensory bodily illusions is discussed.

Bodily awareness is thought to result from the integration of multiple sensory cues with an internal sense of time and body image¹. Much of the evidence for this theory comes from Rubber Hand Illusion (RHI). In the classic RHI experiment, synchronous visual and tactile cues (from stroking the subject's hidden hand and a visible rubber hand) typically induce a false perception of touch on the rubber hand as if it were the subject's hand, whereas asynchronous visual and tactile cues do not elicit this illusion (measured by questionnaire)². Also, subjects mislocalize their unseen hand closer to the position of the rubber hand in the synchronous condition compared with the asynchronous condition (measured as "proprioceptive drift"). fMRI studies of the RHI have implicated prefrontal, premotor and intraparietal cortices and the cerebellum in a neural network for multisensory integration in body awareness³⁻⁵. However, little is known about the subcortical structures that may underpin this network.

People with Parkinson's disease (PD) have a similar RHI experience to healthy controls in the synchronous condition but fail to reject the RHI experience as strongly in the asynchronous condition⁶. PD patients also have increased proprioceptive drift towards the rubber hand independent of visual-tactile synchrony⁶. The pathophysiological basis of PD is striatal dopaminergic degeneration resulting in altered cortico-basal ganglia-thalamic circuitry⁷. PD is treated with dopaminergic drugs and high-frequency deep brain stimulation (DBS) of the subthalamic nucleus (STN) or globus pallidus interna (GPI), which is thought to work by modulating cortico-basal

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ganglia-thalamic circuitry⁸. Previously, we found that dopaminergic drugs did not affect RHI experience or proprioceptive drift⁶. This study aims to explore possible subcortical involvement in bodily awareness by examining the effect of STN-DBS on the RHI in people with PD.

Based on our previous findings in PD patients without STN-DBS⁶, we hypothesized that STN-DBS treated patients would also have: first, higher illusion scores on the RHI questionnaire than controls in the asynchronous condition, with no differences in the synchronous condition, and second, greater proprioceptive drift than controls in both stroking conditions.

Our third hypothesis was that when STN-DBS is switched on, patients will have lower illusion scores in the asynchronous condition compared with when STN-DBS is switched off. Rather than being all-or-nothing, the subjective RHI experience exists on a spectrum—it is strongest when temporal mismatch between visual and tactile cues is less than 300 ms, weakens with increasing mismatch, and is eliminated when mismatch is greater than 600 ms⁹. Therefore, noisy or inaccurate temporal processing of visual and tactile cues in PD could weaken the asynchronous signal, resulting in the higher illusion scores reported in our previous study. PD patients have well-characterised temporal deficits, including increased somatosensory temporal discrimination thresholds¹⁰ and inaccurate estimation of temporal inter-stimulus intervals^{11,12}. STN-DBS improves temporal estimation of auditory intervals in PD^{13,14}. Extrapolating from these studies, STN-DBS could potentially improve perception of the asynchronous signal and hence “normalize” illusion scores in the asynchronous condition.

Our fourth hypothesis was that switching STN-DBS on would decrease proprioceptive drift in both synchronous and asynchronous conditions. Although proprioceptive drift was initially considered a behavioural correlate of subjective experience², the two phenomena can be dissociated; just viewing a rubber hand in peri-personal space produces proprioceptive drift similar to that of the synchronous stroking condition, without evoking the subjective RHI¹⁵. Rohde *et al.*¹⁵ proposed that ‘visual capture of proprioception’ (visuo-proprioceptive integration and spatial recalibration) produces proprioceptive drift and is attenuated by asynchronous visuo-tactile cues. PD patients have well-characterised proprioceptive deficits^{16,17} and increased dependence on vision^{18,19}, which may make them more susceptible to visual capture, resulting in the increased proprioceptive drift reported in our previous study⁶. STN-DBS improves proprioceptive accuracy in kinaesthesia²⁰ and proprioceptive-tactile integration in haptic perception²¹ in PD patients, and may help to “normalize” their proprioceptive drift. To differentiate the effect of STN-DBS implantation surgery on the RHI from that of STN stimulation itself, we tested eligible subjects before and after they underwent implantation surgery.

Lastly, we included a reaching task at the end of each RHI trial to assess the influence of somatic illusions on movement. For healthy subjects, the literature is mixed on whether the RHI affects the trajectory of reaching tasks^{22–24} or pointing accuracy^{25,26}. We had expected the RHI to have a greater influence on the subsequent actions of PD patients than controls because patients have proprioceptive deficits that compromise reaching accuracy²⁷. We found no such effect in either patients or controls in our previous study⁶. However, most of those patients were mildly affected. The STN-DBS-treated PD patients in this study have more advanced disease. Our fifth hypothesis, therefore, was that the reach-to-grasp performance of STN-DBS-treated patients would differ between the synchronous and asynchronous condition, in addition to the expected improvement in motor function from STN-DBS^{27,28}.

Methods

Participants. We recruited 24 patients with idiopathic PD treated with STN-DBS from our Movement Disorders Clinic, excluding those with clinically significant sensory or cognitive deficits. 12 of these patients had only postoperative testing. The other 12 patients had STN-DBS implantation surgery within the time frame of this study and were opportunistically tested pre- and postoperatively. Preoperative data from eight of these 12 patients and data from 21 healthy controls (aged 50–80) in this study has been published as part of a previous study⁶. Participant characteristics are shown in Table 1. Compared with the PD patients in this study, controls were older and showed less symptomatology on the Hospital Anxiety and Depression Scale (HADS) and the Apathy Scale, but Montreal Cognitive Assessment (MoCA) scores were similar. This study was approved by the Monash Health Research Ethics Committee (HREC 12350B) and carried out in accordance with national ethical guidelines. All subjects gave written informed consent.

For the entire patient cohort, the median disease duration from diagnosis was 13.5 years (IQR 10–20 years). The median duration of STN-DBS treatment was 16.5 months (IQR 7–38 months) with a minimum of 5 months. Intraoperative semi-microelectrode recordings were performed to guide placement within the anatomical boundaries of the STN. Postoperatively, all patients had a CT brain scan within 24 hours, which was then fused with their preoperative MRI brain scan to confirm lead placement within the STN (Fig. 1A). A neurologist (CD) assessed motor severity (on- and off-stimulation) using the Movement Disorders Society Unified Parkinson’s Disease Rating Scale Part III (UPDRS).

In the 12 subjects with pre-operative testing, the median interval between pre- and postoperative testing was 12.5 months (IQR 9.75–17.25 months). Although subjects took less dopaminergic medication postoperatively (preoperative levodopa equivalent daily dose (LEDD): Mdn (IQR) = 1350 (1090–1973); postoperative LEDD: Mdn (IQR) = 417 (0–508), $V = 75$, $p = 0.005$), there was no difference in motor severity in respective on-treatment states (preoperative on-medication UPDRS: Mdn (IQR) = 15 (11.5–16); postoperative on-stimulation UPDRS: Mdn (IQR) = 14 (9.25–16.25), $V = 22$, $p = 1$) or off-treatment states (preoperative off-medication UPDRS: Mdn (IQR) = 31.5 (18–28); postoperative off-stimulation UPDRS: Mdn (IQR) = 33 (22.5–41), $V = 25.5$, $p = 0.878$). Implantation surgery did not significantly affect scores on the MoCA, HADS or Apathy Scale (Supplementary Table A).

Experiment design. The RHI set-up used in this study is detailed in our previous paper⁶ and the graphical timeline of a trial is reproduced in Fig. 1B. Briefly, subjects sat in front of a black box with three compartments and a dark glass top that allowed them to view the contents of each compartment only when individually

	Parkinson's disease patients with STN-DBS	Controls	Test Statistic	p value
Number	24	21		
Sex (male)	15	10	$\chi^2 = 1.00$	0.32
Handedness (right)*	17	19	$\chi^2 = 2.70$	0.10
Median Age (IQR)	61 (56–63.75)	66 (61–70)	Wilcoxon rank sum $W = 349$	0.03
Median Montreal Cognitive Assessment score (IQR)	28 (27–28.5)	27 (26–28)	Wilcoxon rank sum $W = 190.5$	0.23
Median Hospital Anxiety and Depression Scale score (IQR)	9.5 (7.25–15)	7 (3–10)	Wilcoxon rank sum $W = 146$	0.04
Median Apathy Scale score (IQR)	15.5 (7.5–18)	7 (4–10)	Wilcoxon rank sum $W = 108$	0.01
Median Parkinson's disease duration in years (IQR)	13.5 (10–20.25)	NA		
Hoehn and Yahr Parkinson's disease stage	2–4	NA		
Side-tested (right hand)**	11	10		
Median STN-DBS duration in months (IQR)	16.5 (7–38)	NA		
Median levodopa equivalent daily dose in mg (IQR)***	416.5 (200–599.2)	NA		
Median UPDRS Part III 'off' (IQR)	35 (27.5–42.75)	NA	Wilcoxon signed rank of 'on' vs. 'off' scores $V = 0$	<0.0001
Median UPDRS Part III 'on' (IQR)	16 (8.5–21)	NA		

Table 1. Demographic and clinical characteristics of all 45 subjects (see text for details). UPDRS: Movement Disorders Society Unified Parkinson's Disease Rating Scale, SD: standard deviation, IQR: interquartile range. *Patients were asked to classify themselves as 'Right-handed' or 'Not right-handed'. **Parkinson's disease patients were tested in the more severely affected hand. In controls, the hand tested was matched to patients. ***Four patients were not taking any dopaminergic drugs postoperatively.

illuminated. In each trial, the hand being tested was placed in the corresponding lateral compartment, while an identically aligned rubber hand was placed in the central compartment. Each trial began with the subject making a 'baseline estimate' of the position of their unseen middle finger. They did this by verbally directing the investigator to move a marker along the length of the box until they were satisfied that the marker was directly in front of their middle finger. Then, the central compartment was illuminated to reveal the rubber hand. The subject was instructed to watch the rubber hand as the investigator stroked it alongside their hidden hand by using two identical paint brushes (brush area 0.5 cm × 2 cm). In the synchronous condition, the experimenter stroked corresponding fingers on the real and rubber hands in unison. In the asynchronous condition, the experimenter alternately stroked non-corresponding fingers on the real and rubber hands (i.e., such that there was both temporal and spatial asynchrony between the seen and felt touch). Using a timer, we varied the temporal interval in the asynchronous condition between 1 and 3 s. After two minutes of stroking, the light was switched off to hide the rubber hand once more. The subject then made a verbal 'post-stroking estimate' of the position of their hidden middle finger. Next, a cylinder in the far corner of the lateral compartment was illuminated, and the subject was instructed to touch the cylinder. Their hand was hidden from view until it neared the cylinder. At the end of each trial, the subject took their hand out of the box and completed a RHI questionnaire that assessed their perceptual experiences during that trial.

A testing session comprised two trials of the synchronous condition and two trials of the asynchronous condition in randomised order. Patients were tested on the more severely affected hand; in controls the hand tested was matched to patients, ensuring each group had the same number of left and right-sided trials. All subjects completed at least two testing sessions Fig. 1C. For STN-DBS patients, one session commenced after stimulation had been switched off for 30 min ('off-stimulation') while the other session commenced after stimulation had been switched on at usual settings for at least 30 min. In a counterbalanced, crossover design, half the STN-DBS patients were tested on-stimulation first, while the other half were tested in the reverse order. Patients took their usual anti-Parkinson medication in the on- and off-stimulation states.

To make a comprehensive comparison of pre- and postoperative on and off-states achieved by medication and STN-DBS respectively, in randomised order, we aimed to test the 12 preoperative patients whilst they were taking their usual dopaminergic drugs ('on-medication') and after all dopaminergic drugs had been withheld for at least 12 hours ('off-medication'). Due to the timing of their operations, two patients could not be tested 'on-medication'.

Measures. We recorded three outcome measures from each trial: (1) questionnaire responses (2) proprioceptive drift, and (3) reach movement metrics.

Questionnaire responses. Subjects completed an 11 statement RHI questionnaire used in previous studies^{6,24}, comprising three critical ('illusion') statements designed to elicit the subjective strength of the RHI, intermixed with eight control ('mock') statements designed to detect response biases (Supplementary Table B). Subjects marked their response on a 14 cm long visual analogue scale with "Strongly disagree" at 0 cm, "Strongly agree" at 14 cm and "Very unsure whether to agree or disagree" in the middle. Thus, higher illusion scores quantitatively capture endorsement of the RHI, while lower illusion scores quantify rejection of the RHI.

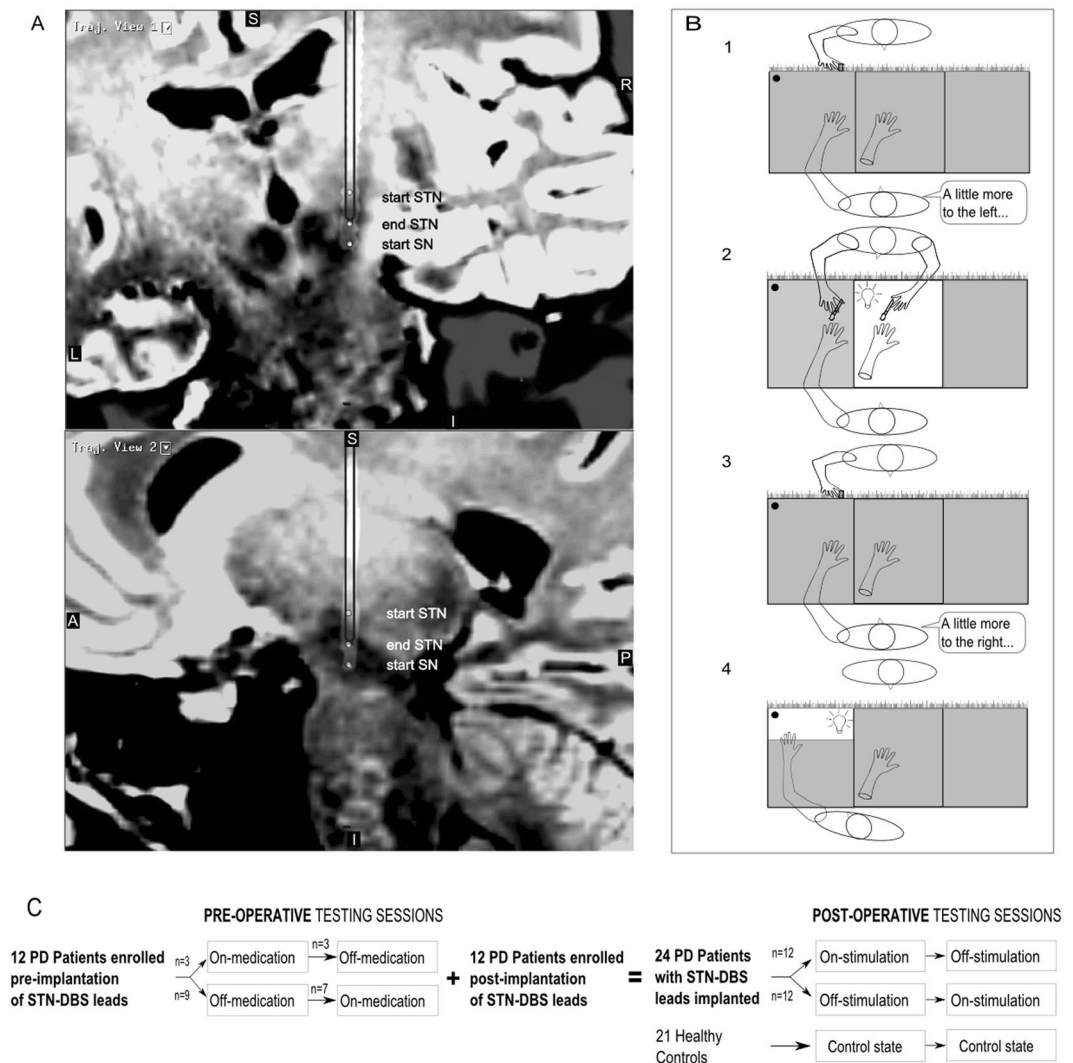


Figure 1. (A) Example postoperative CT fused with the preoperative MRI (sagittal 3D FLAIR sequences with 1 mm slices obtained on a Siemens Verio 3 Tesla unit). Orthogonal planes intersecting through a right Medtronic 3387 lead are shown (S: superior; I: inferior; L: left; R: right; A: anterior; P: posterior). White dots map the subthalamic nucleus (STN) and substantia nigra (SN) according to intraoperative semi-microelectrode recordings. (B) Graphical timeline of a trial: 1. Subject verbally indicates their pre-stroking estimate of middle finger position, 2. Investigator either synchronously or asynchronously (randomised) strokes the subject's hand (shaded = hidden) and a visible rubber hand, 3. Subject verbally indicates their post-stroking estimate of middle finger position, 4. Subject reaches for a cylinder now illuminated in the far corner of the lateral compartment. At the end of each trial, the subject fills in the Rubber Hand Illusion questionnaire (not pictured). (C) Graphical timeline of the study. Pre-DBS implantation surgery, patients were tested in on and off-medication states. Post-DBS implantation surgery, patients were tested in on and off-stimulation states. Controls were also tested twice. (B) is from Ding, C. *et al.*⁶ Parkinson's disease alters multisensory perception: Insights from the Rubber Hand Illusion, *Neuropsychologia* by Elsevier Science Ltd. Reproduced with permission of Elsevier Science Ltd in the format Journal/magazine via Copyright Clearance Center.

Proprioceptive drift. We measured proprioceptive drift as the difference between the subject's 'baseline' and 'post-stroking' estimates of middle finger position. We also assessed proprioceptive (in)accuracy as the difference between the 'baseline' estimate and the actual position of their middle finger. For both proprioceptive drift and baseline proprioceptive inaccuracy, positive measurements indicate the medial direction (towards the position of the rubber hand), whereas negative measurements indicate the lateral direction.

Reach movement metrics. We recorded reach trajectories using a magnetic 3D motion tracker and a sensor attached to the subject's thumbnail. We defined the reaching movement as the period starting from when the velocity of the sensor first exceeded 20 mm/s, to when it finally slowed below 20 mm/s. We then calculated seven reach metrics: 1. duration of movement, 2. mean velocity of movement, 3. peak velocity of movement, 4. time to reach peak velocity, 5. peak lateral displacement, 6. initial angle of movement (the angle of instantaneous velocity

from the midline when 10% of the movement was completed) and 7. integrated jerk (the time derivative of acceleration integrated over the course of the movement).

Statistical analysis. To compare STN-DBS patients in ‘on-stimulation’ and ‘off-stimulation’ states with controls, we estimated mixed-effects regression models for questionnaire responses and proprioceptive drift using fixed effects for ‘subject group’ (controls vs. PD on-stimulation vs. PD off-stimulation), ‘stroking condition’ (synchronous vs. asynchronous) and their interaction. We estimated random effects for ‘stroking condition’ nested within subjects. Questionnaire data (visual analogue scores) was bound between 0 and 14 and thus treated as the odds of a binary response between strongly disagree and strongly agree. We used logistic regression on averaged responses to mock and illusion statements in each trial, estimating additional fixed and random effects for the statement type (‘mock’ vs. ‘illusion’). Linear regression was appropriate for proprioceptive drift data. We applied Bonferroni corrections for multiple comparisons to posthoc contrasts. We controlled for age, sex, cognition (MoCA), mood (HADS) and apathy (Apathy Scale) as potential covariates in both models. We also controlled for baseline proprioceptive inaccuracy in the proprioceptive drift model.

To evaluate the effect of STN-DBS implantation surgery on the RHI, in the subset of patients who had pre-operative testing, we compared their outcome measures in four ‘treatment states’ (pre-op off-medication, pre-op on-medication, post-op off-stimulation, post-op on-stimulation). We estimated additional mixed effects models of questionnaire responses and proprioceptive drift, using the fixed effects of ‘treatment state’, ‘stroking condition’ and their interaction. Random effects for questionnaire response and proprioceptive drift models were as described above. We controlled for the duration of disease, motor severity (UPDRS) and LEDD in both models, as well as baseline proprioceptive inaccuracy in the proprioceptive drift model.

To evaluate the effect of the RHI on movement in the STN-DBS patients, we estimated linear mixed effects models for each of the seven reach movement metrics, using fixed effects of side-of-test, ‘stroking condition’, ‘stimulation state’ (on vs. off), and their interactions. Random effects were estimated for stimulation state nested within subjects. We controlled for motor severity (UPDRS) as a potential covariate. Statistical analysis was performed in R²⁹, using packages ‘lme4’³⁰, ‘nlme’³¹, ‘Effects’^{32,33}, ‘Phia’³⁴, and ‘Stargazer’³⁵.

The datasets for the current study are available in the figshare repository, <https://doi.org/10.6084/m9.figshare.5662219.v1>.

Results

Subject excluded. One PD patient (who was studied preoperatively) had a unique postoperative RHI response wherein he strongly endorsed illusion statements in the asynchronous condition but not in the synchronous condition. When questioned at the conclusion of testing, he stated that in the synchronous trials he was watching his hand being stroked rather than a rubber hand! This response was not seen in any other subjects in our study, and to our knowledge, has not been reported in the RHI literature. Because of doubt over the validity of his questionnaire responses, we excluded him from all analysis.

Questionnaire data. *All subjects.* As expected, all subject groups reported a stronger RHI in the synchronous condition compared with the asynchronous condition, which was reflected in the illusion statements but not the mock statements. Regression analysis of questionnaire responses showed a three-way interaction between ‘statement type’, ‘stroking condition’ and ‘subject group’ ($\chi^2 = 37.35$, $p < 0.0001$). Examination of contrasts revealed that all subject groups were more likely to agree with illusion statements in the synchronous condition than in the asynchronous condition (controls: $\chi^2 = 156.67$, $p < 0.0001$; PD off-stimulation: $\chi^2 = 33.49$, $p < 0.0001$; PD on-stimulation: $\chi^2 = 68.38$, $p < 0.0001$). By contrast, agreement with mock statements did not differ between stroking conditions or amongst subject groups (all $p > 0.05$).

Focusing on the illusion statements (Fig. 2A), PD patients did not reject the RHI in the asynchronous condition as strongly as controls (PD off-stimulation: $\chi^2 = 34.18$, $p < 0.0001$; PD on-stimulation: $\chi^2 = 12.26$, $p < 0.006$), which is consistent with our first hypothesis. In the asynchronous condition, patients had lower illusion scores in the on-stimulation state compared with the off-stimulation state ($\chi^2 = 20.02$, $p < 0.0001$), which is consistent with our third hypothesis that switching on STN-DBS strengthens rejection of the RHI experience in the asynchronous condition. By contrast, in the synchronous condition, endorsement of the RHI was similar between controls and patient on- or off-stimulation (all $p > 0.05$). Age, sex, cognition, mood and apathy were not significant covariates and thus excluded from the final model (Supplementary Table C).

Subset of PD patients studied preoperatively. The preoperative subset of 11 patients had similar results to the larger patient cohort; regression analysis of questionnaire responses showed a three-way interaction between ‘statement type’, ‘stroking condition’ and ‘treatment state’ ($\chi^2 = 19.06$, $p = 0.025$). In all treatment states, patients had higher illusion scores in the synchronous stroking condition than in the asynchronous condition (pre-op off-medication: $\chi^2 = 36.21$, $p < 0.0001$; pre-op on-medication: $\chi^2 = 32.83$, $p < 0.0001$; post-op off-stimulation: $\chi^2 = 36.17$, $p < 0.0001$; post-op on-stimulation: $\chi^2 = 77.44$, $p < 0.0001$). By contrast, agreement with mock statements did not differ between stroking conditions in any treatment state (all $p > 0.05$).

Focussing on illusion statements (Fig. 2B), illusion scores did not differ between pre-op and post-op treatment states (all $p > 0.05$). As with the 23 STN-DBS patients, postoperative illusion scores in the asynchronous condition in this subset were lower when their stimulators were switched on ($\chi^2 = 10.89$, $p = 0.023$). Preoperative illusion scores in the asynchronous condition were similar between on- and off-medication states ($p > 0.05$). Illusion scores in the synchronous condition were similar between all four treatment states (all $p > 0.05$). LEDD was not a significant covariate and although duration of disease was significant ($\log(\text{OR}) = 0.07$, 95% CI [0.02, 0.13], $p = 0.004$), it did not affect the fixed effects of interest (Supplementary Table D).

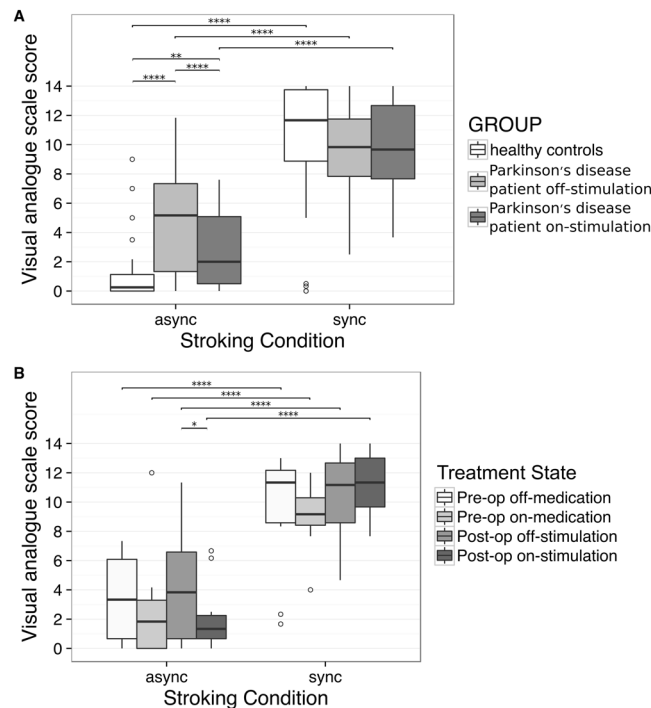


Figure 2. Scoring of critical Rubber Hand Illusion statements in (A) 23 Parkinson's disease patients treated with deep brain stimulation of the subthalamic nucleus (in on-stimulation and off-stimulation states) and 21 healthy controls and (B) a subset of 11 Parkinson's disease patients studied prior to STN-DBS implantation surgery (pre-op) whilst taking their usual anti-Parkinson drugs ('on-medication', $n = 9$), and after withholding all anti-Parkinson drugs ('off-medication', $n = 11$). Thick line: median, hinge: IQR, whisker: hinge ± 1.5 IQR, \circ : outlier, async: asynchronous, sync: synchronous. P-values are based on the regression model, **** $p < 0.0001$, ** $p < 0.01$, * $p < 0.05$. All unlabelled contrasts were not significant.

Proprioceptive drift. *All subjects.* Proprioceptive drift was larger in the synchronous condition than in the asynchronous condition and in PD patients compared with controls (Fig. 3A), which is consistent with our second hypothesis. However, in STN-DBS treated patients, proprioceptive drift depended on baseline proprioceptive inaccuracy (the difference between the baseline estimate and the actual position of their middle finger); regression analysis showed an effect of stroking condition and an interaction between group and baseline proprioceptive inaccuracy ($\chi^2 = 15.75$, $p < 0.001$). Although baseline proprioceptive inaccuracy did not differ between controls and patients on- or off-stimulation (all $p > 0.05$), patients had less proprioceptive drift when their baseline estimates were closer to the position of rubber hand (interaction plot Fig. 3C). Examination of contrasts showed all subject groups had greater proprioceptive drift in the synchronous condition than in the asynchronous condition ($\chi^2 = 44.91$, $p < 0.0001$). Patients in the off-stimulation state had greater proprioceptive drift than controls in both stroking conditions (both $\chi^2 = 7.95$, $p = 0.029$). The difference between patients in the on-stimulation state and controls was not significant in either stroking condition (both $p > 0.05$). Contrary to our fourth hypothesis that switching STN-DBS on improves the precision of somatosensory perception and thus decreases proprioceptive drift, proprioceptive drift did not differ between on- and off-stimulation states in either stroking condition (both $p > 0.05$). Age, sex, cognition, mood and apathy were not significant covariates and thus excluded from the final model (Supplementary Table E).

Subset of PD patients studied preoperatively. The preoperative subset of 11 patients had similar results to the larger patient cohort (Fig. 3B). Proprioceptive drift was greater in the synchronous condition than in the asynchronous condition, and patients had less proprioceptive drift when their baseline estimates were closer to the position of rubber hand; regression analysis showed an effect of stroking condition ($b = 20.93$, 95% CI [0.53, 24.36], $p = 0.016$) and baseline proprioceptive inaccuracy ($b = -0.17$, 95% CI [-0.27, -0.07], $p = 0.004$). Examination of contrasts revealed no differences amongst the preoperative and postoperative treatments states (all $p > 0.05$). Duration of disease, motor severity and LEDD were not significant covariates and thus were not included in the final model (Supplementary Table F).

Reach movement metrics. Patients had a larger peak lateral displacement in the synchronous condition than in the asynchronous condition; regression analysis showed an effect of stroking condition ($b = 11.32$, 95% CI [3.60, 17.87], $p = 0.004$) and side-of-test ($b = -45.91$, 95% CI [-69.90, -13.08], $p = 0.005$) but not stimulation state ($b = 0.59$, 95% CI [-15.06, 15.80], $p = 0.944$). The effect of stroking condition was explained only by proprioceptive drift ($b = 2.15$, 95% CI [0.17, 4.31], $p = 0.053$), not post-stroking estimate ($b = -0.47$, 95% CI [-2.01, 1.21], $p = 0.571$) or motor severity ($b = 0.03$, 95% CI [-0.89, 1.07], $p = 0.951$). That is to say, when patients tried to touch the laterally

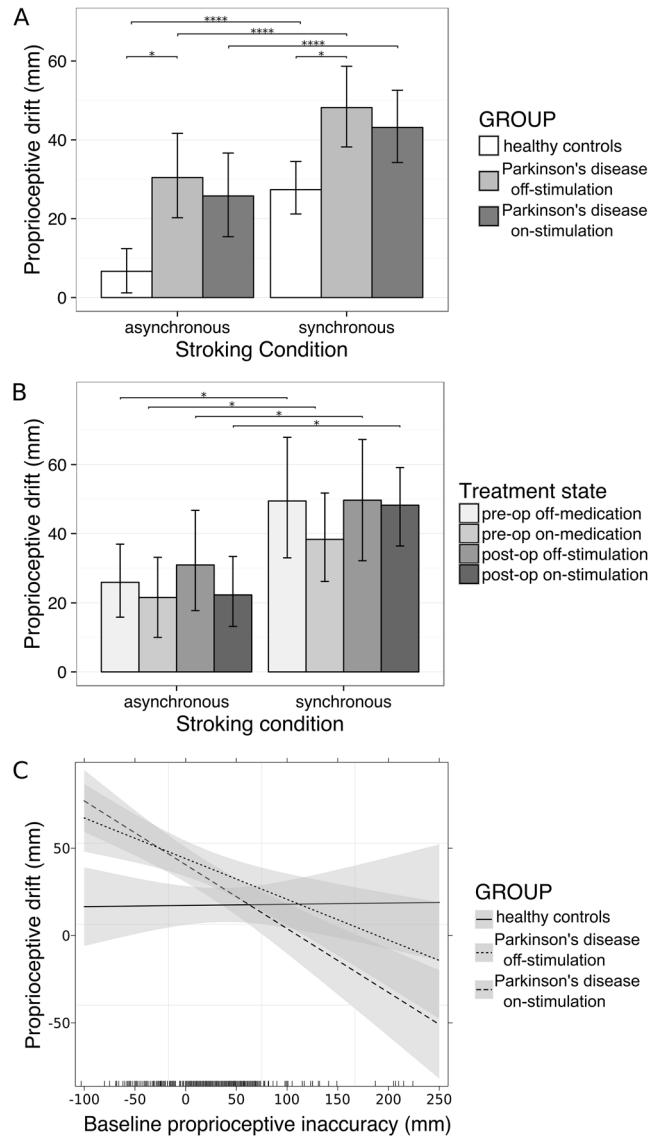


Figure 3. Mean and 95% CI (error bars) of proprioceptive drift in (A) 23 Parkinson's disease patients treated with deep brain stimulation of the subthalamic nucleus (STN-DBS) and 21 controls, and (B) a subset of 11 Parkinson's disease patients tested prior to STN-DBS implantation surgery (pre-op) whilst taking their usual anti-Parkinson drugs ('on-medication', $n = 9$), and after withholding all anti-Parkinson drugs ('off-medication', $n = 11$). Patients had greater proprioceptive drift than controls only in the off-stimulation state. Amongst the subset of patients studied preoperatively, there was no difference in proprioceptive drift between the four treatment states. P-values are based on the regression model. **** $p < 0.0001$, * $p < 0.05$. All unlabelled contrasts were not significant. (C) Interaction plot showing that in the 23 patients, proprioceptive drift (i.e. the difference between their baseline and post-stroking estimates of finger position) decreased as baseline estimates became more inaccurate towards the direction of the rubber hand. Shading: 95% CI.

positioned target, they made larger lateral movements in the synchronous condition than in the asynchronous condition because proprioceptive drift towards the medially placed rubber hand was greater in the synchronous condition.

No other movement metric was affected by stroking condition (Supplementary Tables H–J). As expected, patients were faster in the on-stimulation state than in the off-stimulation state (mean velocity: $b = 42.47$, 95% CI [23.54, 69.22], $p = 0.001$; movement duration: $b = -0.56$, 95% CI [-0.91, -0.23], $p = 0.006$). The effects of stimulation on mean velocity and movement duration were explained by the improvement in motor severity (UPDRS) (Supplementary Tables H–I).

Discussion

PD and STN-DBS affect illusory perception in multisensory bodily awareness. Firstly, we replicated our previous findings⁶—that people with PD do not reject the RHI as strongly as controls in the asynchronous condition, and have greater proprioceptive drift in both synchronous and asynchronous conditions—in a cohort of STN-DBS treated patients with more advanced disease. In the present study, we also modulated cortico-basal

ganglia-thalamic circuitry by switching STN-DBS on and off. We found that switching STN-DBS on strengthens patients' rejection of the RHI in the asynchronous condition, although it remains weaker than that of controls. By contrast, STN-DBS had no effect on proprioceptive drift. Surgical implantation of the STN-DBS electrodes alone, in the absence of electrical stimulation, had no effect on the RHI.

RHI responses in PD are novel in two ways: 1) dissociation between the subjective RHI questionnaire and proprioceptive drift, and 2) in the RHI questionnaire, dissociation between the asynchronous condition and synchronous conditions. These findings suggest that the two RHI phenomena measure different things with different neural substrates that are affected in different ways by PD.

Our finding that PD increases proprioceptive drift independent of visuo-tactile synchrony is consistent with the 'visual capture' model of proprioceptive drift, where visuo-proprioceptive integration is sufficient for spatial recalibration and asynchronous stroking attenuates visual capture¹⁵. PD patients have well-characterised proprioceptive deficits^{16,17} and increased visual dependence^{18,19} that may make them more susceptible to visual capture and thus proprioceptive drift. We hypothesised that STN-DBS would reduce proprioceptive drift because it has been reported to improve proprioceptive deficits in kinesthesia²⁰ and haptic perception²¹ in PD. However, in our study, STN-DBS did not improve baseline or post-stroking estimates of finger position. Neuroanatomically, proprioceptive drift has been attributed to the inferior parietal lobe because disrupting its function in healthy subjects using repetitive transcranial magnetic stimulation attenuates proprioceptive drift whilst preserving illusionary experience³⁶. STN-DBS did not affect this network.

The mechanisms for feeling touch on a rubber hand as if it were your own hand is theorized to involve multisensory integration of visual, tactile and proprioceptive cues with an internal sense of time and body image¹. The temporal and spatial coherence of the visuo-tactile cues is critical, as synchronicity typically evokes the RHI whereas asynchronous cues do not^{2,9}. So why do PD patients have consistently higher illusion scores than controls in the asynchronous but not the synchronous condition? We cannot exclude a ceiling effect because the distribution of illusion scores in the synchronous condition skews towards the upper limit of 14; however, the finding that STN-DBS alters illusion scores only in the asynchronous conditions adds weight to the idea that PD (and STN-DBS) differentially affect the asynchronous condition. By extension, PD must either affect temporal processing of multisensory cues or the evaluation of temporally incongruent multisensory cues.

PD patients have well-characterised temporal deficits including increased somatosensory temporal discrimination thresholds¹⁰ and inaccurate estimation of temporal inter-stimulus intervals^{11,12}. STN-DBS improves discrimination of auditory inter-stimulus intervals in PD¹³. It is possible that STN-DBS improves temporal discrimination in the RHI to strengthen perception of the asynchronous signal and hence rejection of RHI in the asynchronous condition. In this study, STN-DBS affected only the subjective questionnaire responses and did not strengthen the asynchronous signal sufficiently to reduce proprioceptive drift. Precise temporal processing may be of greater importance in RHI judgements than in proprioceptive drift. However, dopaminergic drugs, like STN-DBS, also improve estimation of auditory inter-stimulus intervals^{11,13} but do not affect the RHI⁶.

STN-DBS, but not dopaminergic medication, is known to affect complex cognitive³⁷ and perceptual decisions³⁸; simple cognitive and perceptual decisions are not affected by STN-DBS. For example, Green *et al.* (2013) found that as visual stimulus complexity increased, the reaction times of STN-DBS treated patients did not increase as much as that of controls. This is also consistent with our study in (onset) binocular rivalry in which DBS, but not dopaminergic drugs, facilitated perceptual decisions³⁹. Moreover, this facilitation effect was seen in perceptual decisions during complex binocular rivalry, but not in simpler non-rivalrous situations³⁹. In some perceptual tasks, this facilitation effect lead to increased errors³⁸, however in the current study, switching stimulation on made perceptual inference in the asynchronous condition closer to that of controls. There are similarities between our results and olfactory studies in PD, where STN-DBS improves odour recognition but not odour detection thresholds—suggesting that STN-DBS enhances higher-order perceptual inference by modulating connectivity between the basal ganglia and sensory association cortices^{40,41}. Body perception is a complex task requiring integration of possibly incongruent multisensory cues with an internal sense of time to generate a momentary perception of the body that is then evaluated against higher-order notions of body image¹. Estimating auditory intervals (temporal processing of a single sensory modality) and limb localisation (visuo-proprioceptive integration without decisions about body image) may be comparatively simpler and thus not affected by STN-DBS.

Anatomically, the subjective RHI experience is attributed to ventral premotor³⁴, ventromedial prefrontal and lateral occipitotemporal cortices⁵ because fMRI activity in these areas correlate with illusion scores. Activity in ipsilateral premotor cortices also correlates with the temporal synchronicity of the stimuli⁴². The medial prefrontal cortex is part of the associative loop of the STN⁷, and this connection is one potential pathway for STN-DBS to affect illusion scores. The STN is hypothesised to act as a brake in the cortical-striatal network, increasing the threshold of evidence required to make a complex decision when there are conflicting cues—a process thought to be disrupted by STN-DBS³⁷. How STN-DBS does this is not fully understood. Evidence from experiments in cognitive tasks points to modulation of brain network activity: EEG studies show that increased theta power in the medial prefrontal cortex associated with high-conflict tasks predicts increased time to decision, while STN-DBS reverses mediofrontal influence on decision thresholds¹⁴. Furthermore, intraoperative intracranial recordings in the STN show corresponding changes in low-frequency power during high-conflict tasks, suggesting communication with the medial prefrontal cortex¹⁴.

Consistent with our final hypothesis that certain movement metrics would be affected by stroking condition, we found that when PD patients tried to touch the laterally positioned target, they made larger lateral movements in the synchronous condition than in the asynchronous condition. It is important to note that this was explained by proprioceptive drift (away from the reach target) rather than by their post-stroking estimate (i.e., how far away they perceived their hand to be from the target) or their motor severity (UPDRS). This was not found in our previous study of PD patients without STN-DBS⁶, but they may have been too mildly affected for such an effect to manifest. The STN-DBS treated patients in this study had longer disease durations, greater

motor severity (UPDRS off-treatment) and more proprioceptive drift. Taken together, our findings indicate that illusionary misperception of hand position can alter subsequent bodily movement in people with advanced PD. Our results are consistent with other studies that found somatic misperceptions influenced actions in PD. In these studies, sensory scaling errors reduced movement amplitude (hypokinesia)⁴³, and teaching patients to make actions “too big” and vocalisations “too loud” overcame hypokinetic movement and speech that they perceive to be normal^{43,44}.

The duration of stimulation “washout” in this study (30 min) was sufficient to invoke the effects that we report here and to elicit a significant change in UPDRS scores (Table 1), which is consistent with reports that 75% of the effect of STN-DBS on the signs of PD wears off within 15–30 minutes of discontinuation⁴⁵. Moreover, questionnaire responses and proprioceptive drift in the postoperative off-stimulation state did not differ from preoperative values, which suggests no chronic effects of stimulation on the RHI.

Despite postoperative confirmation that the DBS electrodes were situated in the STN, the precise location and active terminals were not uniform across patients, and we cannot predict individual differences in the spread of local electrical current. Hence we are unable to discern whether the effect of stimulation results from modulation of the STN or more wider cortico-basal ganglia-thalamic circuitry. Another effective target for DBS in PD is the GPi. In the future, it may be informative to compare the effects of DBS on the RHI in PD based on the exact site of stimulation (e.g., STN vs GPi).

In conclusion, illusionary misperception of arm position was greater in patients with severe PD than healthy subjects, and altered their subsequent movements. Stimulation of the STN had no effect on proprioceptive drift. However, not only have we confirmed that PD patients reject illusionary experience less than healthy subjects in a typically unambiguous condition, we discovered that STN-DBS strengthens their rejection of the RHI, although it remains weaker than in those without the disease. Our findings implicate the STN and subcortical connections in the network for multisensory integration in bodily awareness and pave the way for future research into the perceptual effects of DBS.

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Author Contributions

Catherine Ding contributed to the design of the project, collected and analysed the data, wrote the first draft, reviewed and edited the manuscript, and prepared the figures. Colin J. Palmer contributed to the design of the project, reviewed and edited the manuscript. Jakob Hohwy contributed to the design of the project, reviewed and edited the manuscript. George J. Youssef contributed to the design of the project, reviewed and edited the manuscript. Bryan Paton contributed to the design of the project, reviewed and edited the manuscript. Naotsugu Tsuchiya contributed to the design of the project, reviewed and edited the manuscript. Julie C. Stout contributed to the design of the project, reviewed and edited the manuscript. Dominic Thyagarajan contributed to the design of the project, reviewed and edited the manuscript.

Additional Information

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