Longitudinal changes in movement-related functional MRI activity in Parkinson's disease patients

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Abstract

Introduction. Functional brain imaging has shown alterations in the basal ganglia, cortex and cerebellum in Parkinson's disease patients. However, few functional imaging studies have tested how these changes evolve over time. Our study aimed to test the longitudinal progression of movement-related functional activity in Parkinson's disease patients.

Methods. At baseline, 48 Parkinson's disease patients and 16 healthy controls underwent structural and functional magnetic resonance imaging during a joystick motor task. Patients had repeated imaging after 18-months (n=42) and 36-months (n=32). T-tests compared functional responses between Parkinson's disease patients and controls, and linear mixed effects models examined longitudinal differences within Parkinson's disease. Correlations of motor-activity with bradykinesia, rigidity and tremor were undertaken. All contrasts used whole-brain analyses, thresholded at $Z>3.1$ with a cluster-wise $P<0.05$.

Results. Baseline activation was significantly greater in patients than controls across contralateral parietal and occipital regions, ipsilateral precentral gyrus and thalamus. Longitudinally, patients showed significant increases in cerebellar activity at successive visits following baseline. Task-related activity also increased in the contralateral motor, parietal and temporal areas at 36 months compared to baseline, however this was reduced when controlling for motor task performance.

Conclusion. We have shown that there are changes over time in the blood-activation level dependent response of patients with Parkinson's disease undertaking a simple motor task. These changes are observed primarily in the ipsilateral cerebellum and may be compensatory in nature.

Keywords: functional MRI, Parkinson's disease, movement disorders

1. Introduction

Parkinson's disease (PD) is characterised by, but not restricted to, degeneration of dopaminergic cells in the substantia nigra pars compacta [1]. To further understand neural changes underlying impaired motor performance in PD, methods adjunct to dopaminergic imaging, such as functional MRI (fMRI) are necessary. Relative to healthy controls (HC), PD patients show altered cortical and subcortical functional activity [2]. Most fMRI studies report decreased basal ganglia and contralateral motor cortex activation during movements [3]. However, findings are less consistent within other cortical areas and the cerebellum [2, 3, 4] and this may relate to differences between studies in disease stage along with the heterogeneous nature of PD.

The few longitudinal investigations conducted to date have typically used small cohorts. In one study, regional cerebral blood flow in 13 PD patients increased within the basal ganglia and cortical motor areas 2.3 years following baseline imaging, alongside decreases within parietal and temporal cortices [5]. Conversely, an fMRI study in 5 patients found increased cerebellar activity, but no basal ganglia or motor cortex changes over a similar timespan [6].

Our study significantly extends this existing literature. We employed a joystick task during fMRI and performed follow-up scans over 36-months, with the objective to evaluate effects of disease progression on cortical and subcortical regions and the functional correlates of clinical symptoms in PD. It was hypothesised that motor-related brain activity in the basal ganglia-thalamo-cortical loop would be decreased for PD compared to HC at baseline and would be associated with bradykinesia and rigidity symptoms. Group differences at baseline were also predicted in the cerebellar-thalamo-cortical-loop. Longitudinally, it was hypothesised that activity in both basal ganglia and cerebellar motor loops would differ between visits; however, previous research provided no clear prediction about the directionality of results.

2. Materials and methods

2.1 Participants

At baseline, 48 patients with idiopathic PD were recruited from a larger observational cohort [7] Of these, 42 had repeated imaging 20.16±3.52 months later and 32 returned for a third visit, 38.18±4.15 months after baseline. All PD patients satisfied Queen Square Brain Bank criteria for the diagnosis of idiopathic PD, and were on no- or standard- PD medication at baseline [8]. The diagnosis of PD remained the same throughout the study, with no participants showing symptoms consistent with atypical parkinsonism. No participants reported significant motor fluctuations. 16 HC were scanned at baseline only. All volunteers were right-handed, free from significant cognitive impairment (Mini-Mental State Examination >26) and other ongoing neurological or psychiatric disorders. For more detailed information about the inclusion/exclusion criteria see Barker *et al.* (2019) [7]. Data were collected under funding from the FP7 EC Transeuro research project. All participants gave informed consent and research was carried out in accordance with the declaration of Helsinki. Appropriate approvals were obtained by the local National Research Ethics Service Committee and the Joint Research Compliance Office of Imperial College London.

2.2 Clinical Data

At each visit, patients were asked to withdraw from standard release dopaminergic medication for 24 hours and/or 48 hours for controlled release medications. This was defined as the OFF-medication state and motor features were assessed in this state at each visit, using the motor sub-score of the Unified Parkinson's Disease Rating Scale (UPDRS-III) [9]. At each visit, participants also completed a battery of cognitive tests, including the

Addenbrookes Cognitive Examination – Revised (ACE-R) and Mini mental state examination (MMSE).

2.3 fMRI scanning procedure

Data were acquired using a 3T Siemens Magnetom Trio system (Erlangen, Germany) with a 32-channel phased-array head-coil, at Imanova (Hammersmith Hospital, London). Patients were scanned in the OFF-medication state. Structural T1-weighted scans were acquired using a 3D sagittal magnetization-prepared rapid-acquisition gradient-echo sequence (MPRAGE; TR=2300ms, TE=2.98ms, flip angle=9°, time to inversion=900ms, GRAPPA acceleration factor PE=2, slice thickness=1mm, FoV=240*256mm, matrix size=240*256, TA=503s, 160 slices). Whole-brain functional scans were acquired using a T2*-weighted single-shot gradient-echo echo-planar imaging sequence (GE-EPI; TR=2500ms, TE=31ms, FA=80°, bandwidth=2298Hz/Px, GRAPPA acceleration factor PE=2, slice thickness=3mm, FoV=192*192mm, matrix size=64*64, TA=628s). 248 volumes were obtained per run, each consisting of 45 interleaved axial slices acquired parallel to the anterior commissure-posterior commissure line. Rapid visual screening was conducted following the scanning session and patients exhibiting severe white matter hyperintensities (Fazekas scale ≥ 2) or severe atrophy were excluded from further analysis.

2.4 Functional task

The functional imaging paradigm consisted of joystick movements in response to visual cues, Similar joystick tasks used in previous investigations have shown comparable reaction times between PD and controls, thus minimising any effect of task performance or differences in motor impairment on functional neuroimaging findings [10, 11]. Joystick tasks also contain greater depth of information than other simple motor tasks, such as finger tapping, by providing multiple measures of performance. Participants were presented with a central black

circle and four black arrows indicating north, east, south and west directions on a grey background. An MRI-compatible analogue joystick [12] was moved from a central neutral position in the relevant direction when cued (Fig. 1A). Patients made joystick movements using the arm on their clinically most affected side (MAS), as established by clinical history and lateralised UPDRS-III items. HC used their right arm. The task was written by JH in Delphi 7.0 and performance recorded using Chart 5, run on Windows XP. At baseline and 18-months, all participants completed both runs. At 36-months, three participants completed one run whilst the remaining patients completed all runs.

2.5 Statistical analysis

2.5.1 Behavioural analysis

Behavioural measures of movement time and amplitude were computed for each trial and a mean value calculated for each participant. Peak amplitude was defined as the difference between the starting joystick position and the furthest point from this position. Movement time was defined as the time taken to reach peak amplitude. Behavioural analyses were conducted within IBM SPSS, v24 (Armonk, NY: IBM Corp). Due to non-normal distributions, group differences were tested using Mann-Whitney U tests and within-group differences in cognitive measures using Wilcoxon tests. Linear mixed effects (LME) models tested for longitudinal differences in UPDRS-III motor scores, movement time and amplitude within PD. For UPDRS-III derived scores and for movement time, residuals were normally distributed. For movement amplitude, residuals were leptokurtic and negatively skewed. After applying a transformation ((1/k-x), k=300), residuals were not skewed, but remained leptokurtic. However, for repeated measures main effects, LME models remain robust to kurtosis [13]. For all LME models, visit (baseline/18-month/36-month), gender, baseline age, baseline disease duration and time between visits were modelled as fixed effects. A random

intercept was specified for subject identity and a random slope for time between visits. Pairwise comparisons tested changes between baseline:18-month, baseline:36-month and 18-month:36-month visits.

2.5.2 fMRI analysis

Data were analysed within the FMRIB Software Library (FSL; https://fsl.fmrib.ox.ac.uk/fsl/fslwiki) and the Analysis of Functional Neuroimages software package (AFNI) [14]. First level analysis was executed using the fMRI expert analysis tool (FEAT) v6.0 within FSL. Functional images were linearly co-registered with the corresponding MPRAGE and transformed to MNI space using parameters derived from the affine registration (12 dof) between the MPRAGE and Montreal Neurological Institute (MNI) 152 standard brain within FLIRT [15]. Statistical analysis was performed using FMRIB's Improved Linear Model with local autocorrelation correction and pre-whitening [16]. Pre-processing included motion correction, brain-extraction, spatial smoothing using a Gaussian kernel of 8mm FWHM, grand-mean intensity normalisation by a single multiplicative factor and a high-pass temporal filter of 200s. Explanatory variables were included in an event-related design modelling the central cue, movement in each direction (North/South/East/West) and the no-movement condition. Variables were modelled as a boxcar function (central cue-2s duration, movement/no-movement-4s duration) convolved with the haemodynamic response. Rotation/translation motion parameters were added to the GLM as nuisance covariates. A contrast representing the effect of all movements compared to no-movement was calculated for each participant and used in subsequent analyses.

For PD patients with a left MAS, images were flipped, such that brain hemispheres contralateral and ipsilateral to movements were consistent across all participants. A two-sample t-test was conducted on the first level analyses from the baseline visit to compare

patients with a right MAS versus (flipped) left MAS. As no significant differences were shown, these groups were combined for all future comparisons.

All higher level contrasts were thresholded at $Z>3.1$ and a corrected cluster significance of $P<.05$ to correct for multiple comparisons, using the cluster function within FSL [17]. Significant clusters were labelled using Harvard-Oxford cortical and subcortical atlases, probabilistic cerebellar atlas [18, 19] and Human Motor Area Template [20]. A one-sample t-test was executed for each group and visit using FMRIB's Local Analysis of Mixed Effects stage one (FLAME1), within FEAT [21, 22]. A two-sample t-test (FLAME1) examined baseline differences between PD and HC.

For longitudinal analyses, a LME model was selected to allow inclusion of individuals with missing data. An LME model was implemented using 3dLME within AFNI [14, 23]. Visit (baseline/18-months/36-months), gender, baseline age and baseline disease duration were modelled as between-subjects fixed effects, and time between visits as within-subject fixed effect. A random intercept was specified for subject identity and a random slope for the time between visits. Planned contrasts were defined for differences in movement-related activation between baseline:18-month, baseline:36-month and 18-month:36-month visits. Two further LME models were defined including all of the above between- and within- subject factors. In the first model UPDRS-III was added as an additional between-subjects fixed effect and the second model included the two fMRI joystick task performance measures, response time and peak amplitude.

Finally, within-subject analyses tested relationships between task-based activation and UPDRS-III sub-scores using scans from all visits. UPDRS-III sub-scores for MAS bradykinesia (items 4-8), rigidity (item 3) and tremor (items 15-17) were calculated. Whole

brain correlations were tested between each sub-score and movement-related functional activity, using FLAME1 within FSL.

3. Results

3.1 Behavioural data

Clinical and demographic data are displayed in Table 1; with no significant difference in age between PD and HC at baseline (Welch-corrected, $t(18.98)=1.24$, $p=0.23$). The relationship between gender and group was significant ($\chi2(1)=4.22$, $p=0.04$) with a higher ratio of males to females in PD than controls (as expected given the sex distribution in PD). Differences in UPDRS-III sub-scores between visits are indicated in Table 1. No volunteers developed significant cognitive impairment during the course of the 3 visits; there were no significant differences in MMSE or ACE-R scores between visits.

There were no significant differences in baseline movement time (U=373, Z=-0.17, p=0.87) or peak movement amplitude (U=352, Z=-0.50, p=0.62) between PD and controls (Fig 1B). Within PD patients, there was a significant effect of visit on movement time ($F(2, 71)=6.42$, $p=0.003$). Pairwise comparisons showed quicker movements at baseline than 18-months ($p=0.001$) but no significant difference between 18- and 36-months ($p=0.134$) or from baseline to 36-months ($p=0.093$). There was a main effect of visit on transformed movement amplitude ($F(2, 71)=60.45$, $p<0.001$). Movement amplitude decreased from baseline to 18-months ($p<.001$), from 18- to 36-months ($p<.001$) and from baseline to 36-months ($p<0.001$) (Fig 1C). Neither response time nor peak movement amplitude were correlated with UPDRS score at any visit nor with MMSE or ACE-R total scores ($p>.05$; Supplementary Table 1). There was a positive relationship between peak amplitude and ACE-R language sub-score at 18-months only, but this did not remain after correcting for multiple comparisons. There were no other significant relationships between performance measures and any ACE-R sub-scores.

3.2 fMRI analysis

In HC, movements elicited greater activation than the no-movement condition in the contralateral SMA, primary motor (M1) and primary sensory (S1) cortices, as expected. For the same contrast, the PD group at baseline showed bilateral cortical, subcortical and cerebellar activation (Fig. 2A). PD patients had greater activity than HC, peaking in the thalamus, contralateral parietal and occipital regions and ipsilateral M1 (Fig. 2B). Significant clusters extended into the ipsilateral cerebellum and SMA. No region was significantly more activated in HC than PD.

PD patients showed motor task-related activation at all visits, including the putamen, bilateral cortical motor areas and cerebellum (Fig. 2A). From baseline to 18-months activation increased within the ipsilateral cerebellum and occipital pole (Fig. 2C). Between 18- and 36-months, further increases occurred, with peaks bilaterally in the cerebellum extending into the intracalcarine cortex, lingual and parahippocampal gyri, contralateral SMA, M1 and dorsal pre-motor area (PMd) (Fig. 2C). Increased activation was shown from baseline to 36-months, with a maximal effect in the ipsilateral cerebellum (Fig. 2C). This represented a large cluster, including the bilateral cerebellum, SMA, hippocampus, parahippocampal and lingual gyri and the contralateral superior frontal gyrus, pre- and post-central gyri, superior parietal lobule, putamen, supramarginal gyrus, and temporal pole. No regions showed decreased activation between any visits in this model.

When including UPDRS-III as a factor in the LME model, there were no regions where BOLD activation during the motor task was significantly associated with the UPDRS score. As with the initial model, increased motor-related brain activity was shown at 18-months from baseline in the ipsilateral cerebellum and occipital pole (Fig. 3A), with further increases from 18- to 36- months including the bilateral cerebellum, intracalcarine cortex, lingual and

parahippocampal gyri (Fig. 3A). Comparing baseline to 36-months showed a large cluster of increased task-related activity peaking in the cerebellum (Fig. 3A). The within-subject correlation analysis did not show any regions significantly associated with UPDRS-III sub-scores of the most affected side.

The final LME model included factors to represent task performance. As shown in Figure 3B, increased response time (i.e. poorer performance) was associated with greater bilateral motor-related brain activation in the pre- and post- central gyri, as well as the ipsilateral SMA. Smaller peak amplitude (i.e. poorer performance) was associated with clusters of increased functional activity contralaterally in the cerebellum, postcentral gyrus, hippocampus, precuneus, posterior putamen, lingual gyrus, insula, superior parietal, occipital, inferior temporal and fusiform cortices, as well as the bilateral caudate nucleus and thalamus (Fig. 3B). When controlling for task performance, increased activation was observed between baseline and 18-months in the right cerebellum and bilateral occipital pole. Between 18- and 36- months, activation further increased bilaterally in the cerebellum, and occipital pole, as well as in the ipsilateral parahippocampal, inferior temporal and fusiform gyri and the contralateral lingual gyrus. For the overall change between baseline and 36- months, there was increased movement-related activation bilaterally in the cerebellum and occipital pole as well as the contralateral lingual gyrus and ipsilateral cuneus. Decreased task-based activation was observed between baseline and 18-months in regions including the bilateral pre-central gyrus, contralateral postcentral gyrus, precuneus, superior parietal cortex and ipsilateral frontal pole.

Whole-brain correlation analysis within PD revealed a positive relationship between MAS rigidity score and motor-related brain activation across a large distributed cluster including the bilateral cerebellum, brainstem, hippocampus, pre-cuneus, parahippocampal and lingual

gyri, intracalcarine and occipital cortices, and ipsilateral thalamus. There was no significant relation between task-related motor activity and MAS bradykinesia or MAS tremor.

4. Discussion

Our study evaluated movement-related functional activity and its change during disease progression in PD. Relative to HC, PD patients showed hyperactivation in parietal regions and the ipsilateral precentral gyrus, together with equivalent motor performance. Longitudinally, motor performance worsened in PD, accompanied by increased motor-activity, initially in the ipsilateral cerebellum and later in the bilateral cerebellum, SMA and contralateral precentral gyrus. No decreases in motor-related brain activity were found between visits.

When including UPDRS-III scores in the model, there was little change to the observed results. Motor scores were not associated with either measure of task performance, and as such regressing out their effect left a qualitatively similar pattern of activation changes between visits. Conversely, when controlling for measures of task performance, there were differences in the longitudinal pattern of fMRI activation between visits. In this analysis the increase in cerebellar recruitment over time (holding performance constant) was shown predominantly in the ipsilateral cerebellum, with cerebral and sub-cortical differences between visits also reduced. It has been proposed in previous studies that activity of the ipsilateral cerebellum is compensatory in an attempt to preserve motor performance [2, 24, 25]. This compensation may comprise both motor as well as cognitive functions, as these cannot be easily separated within motor tasks [25]. Despite increased cerebellar activation over time, a decrease in task performance was still observed; we suggest that although compensatory mechanisms may be present, that they may not be sufficient to restore or preserve motor function in its entirety.

The current study extends previous findings in PD patients by showing increased cerebellar recruitment over time, which was consistent across all models. Our study population was larger and follow-up period longer than previous studies using similar paradigms. One study, examining newly diagnosed patients, showed increased activation over time within a region of interest comprising the ipsilateral cerebellum, premotor cortex and S1 using externally-generated tasks movements of the MAS [6]. In the same study, a region comprising the contralateral basal ganglia, thalamus, SMA and M1 showed increased functional activity for internally-generated tasks. Our participants performed an externally-generated task with the MAS, demonstrating increased functional activity in ipsilateral cerebellar regions. Further increases were later observed in contralateral motor areas, although these were reduced when controlling for task performance. These regions may be relevant to the performance of externally-generated tasks but with a slower or nonlinear progression that is not apparent in early disease. Supporting this interpretation, Carbon *et al.* (2007) [5] tested mild PD patients at a later disease stage using an externally-generated task. They observed increased cerebral blood flow in the contralateral cerebellum, basal ganglia and motor areas, medial temporal and parahippocampal cortices, together with decreased performance. The increased parahippocampal activation, also observed when controlling for task performance in our study, may imply decreased selectivity in visuospatial processing, as in HCs this region is associated with visuospatial navigation [5, 26].

Contrary to what might be expected, basal ganglia and motor cortex were not hypoactive in PD, but together with the precentral gyrus showed longitudinally increased BOLD activation in the initial analysis, which was associated with poorer task performance. Previous research has typically demonstrated decreased functional activity; a meta-analysis showed hypoactivity of putamen and M1 in PD [3]. However, in other joystick tasks, hypoactivity of the putamen has not been shown [10, 23]. Furthermore, some studies found hyperactivation

within these regions, using methodologies where PD and HC have comparable performance, as they did at our baseline visit [27]. These changes were interpreted as modulatory, as they were not associated with group differences in motor performance but varied with the complexity and context of motor tasks [27, 28]. However, despite increasing activation in these regions over time in our PD patients, there were still longitudinal decreases in task-performance, suggesting that any modulation may not necessarily be advantageous and/or may not be adequate to restore motor function.

The greater motor-related brain activity in PD compared to controls in parietal regions concurs with a recent meta-analysis, which indicated parietal hyperactivation during externally-generated motor tasks [3]. In our study, increased activation of the superior parietal lobule within the PD group was associated with poorer performance. Parietal activation may represent integration across sensory modalities and thus reflect PD patients' increased reliance on external cues to facilitate movement. Additional regions associated with poorer performance included the pre- and post- central gyrus for increased response time, while reduced peak amplitude was associated with a more distributed set of regions.

When testing correlations between UPDRS-III sub-scores and movement-related activity, MAS rigidity was found to positively correlate predominantly with cerebellar and occipital activity. Whilst cerebellar recruitment is implicated as part of the underlying pathophysiology of tremor-dominant PD, current evidence in favour of a compensatory role of the cerebellum appears stronger and more consistent for the akinetic-rigid form, which could potentially be due to the relatively faster rate of disease progression and greater severity of illness characteristic of the latter subtype [29]. Indeed, the current results would indicate that the severity of tremor symptomology is not associated with motor-related brain activation levels in the either the cerebellum or across the whole brain. It remains possible however that the lack of such correlation may relate to the use of an active task in the present study, meaning

that in contrast to action or postural tremor, resting tremor, which is typically representative of the tremor-dominant subtype, is unlikely to be effectively captured. Additionally, no correlations were observed between motor-related brain activity and bradykinesia symptomology, which in the current context suggests that compensatory changes, particularly within the cerebellum as previously discussed [29], may have more relevance to clinical rigidity. An alternative explanation may lie in the distinction between akinesia as an impairment for initiating movements and bradykinesia as a slowness or reduced velocity of ongoing movements [28, 30]. As such, bradykinesia symptomology as evaluated by the prolonged repeated movement sequences within UPDRS-III might not be synonymous with the relatively discrete movements carried out within the scanner.

The presence of longitudinal cerebellar functional activation in our cohort of patients with PD may have therapeutic implications. The use of non-invasive transcranial stimulation mainly of the motor (M1 and SMA) or prefrontal sites has been associated with significant improvement of motor symptoms in PD in one meta-analysis [31]. In a sham-controlled study, the use of low frequency cerebellar repetitive transcranial stimulation displayed divergent voluntary movement effects in the upper limb with improvement and worsening of gross and fine motor skills respectively [32]. Furthermore, cerebellar continuous theta burst stimulation [33] and anodal transcranial direct current stimulation [34] prompted a decrease in levodopa-induced dyskinesia that lasted more than four weeks, likely due to modulation of cerebellothalamocortical pathways. Despite this, further longitudinal multi-center studies are needed to elucidate whether the cerebellum could be a viable stimulation target to relieve PD symptoms.

Some additional methodological limitations of our study should be noted. We acknowledge that the small sample size of healthy control participants is a major limitation of this study and may potentially contribute to the differences observed between PD and HC groups.

Although we have controlled for age, gender, disease duration, motor symptomology, task performance and cognition in our analyses, we cannot exclude the possibility of other influences on observed task-related brain activation within the PD group, such as comorbid disorders, non-motor symptomology, or pain during scanning. Additionally, whilst PD patients showed longitudinal differences in functional activity, controls were tested only once. Although age, clinical measures and time between visits were included as regressors, differences in the patient group over time could reflect age-related changes that may also occur in HC. For example, Sen and colleagues [19] found that changes in neuronal activity in PD did not significantly differ from longitudinal changes in controls. Conversely, greater decreases in bilateral putamen and contralateral M1 activity were found for PD than HC over time, whilst longitudinal changes in the PD group alone were not significant [4]. Thus, in future research, it would be worthwhile following-up both PD and HC groups longitudinally.

5. Conclusion

Disease progression in PD appears to be characterised by changes in functional activity that varies between regions and with duration of illness, providing new insight into motor changes in PD and their clinical correlates. Greater movement-related functional activity was seen in a distributed set of regions in patients as compared to healthy individuals. Within PD, increases were consistently demonstrated in the ipsilateral cerebellum as the disease progressed, including after controlling for motor symptomology or task performance. Increased activity was also observed bilaterally in the cerebellum and contralateral motor regions at the latest time-point, but these were linked to variable performance of the task. The ipsilateral cerebellum may be increasingly recruited during prompted movement in PD patients in an attempt to partially restore motor function.

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Author Contributions

Conception and design of the study – JH, MBW, CL, RAB, PP. Acquisition of data – NPLK, AMB, AAR, CL. Analysis and interpretation of data – NH, NPLK, AMB. Drafting the article – NH. Revising article for intellectual content – NPLK, AMB, AAR, JH, MBW, CL, RAB, PP. Final approval of the version to be submitted – all authors

Conflicts of interest

The authors report no conflicts of interest

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Figure 1. Details of the fMRI motor paradigm, showing sequence and timings of trials for the fMRI motor task (A), and differences in movement time (B) and amplitude (C) between visits and between PD and HC at baseline. *p < .05, **p < .001. Each trial began when the central circle changed to green for 2s, cueing participants to prepare to move. In 80% of trials, one of the surrounding arrows changed to green for 4s. Participants were instructed to move the joystick in the direction corresponding to the green arrow. The circles and arrows then reverted to black for a 3-10s variable inter-stimulus interval (whole integer values, Mean = 6s), and participants returned the joystick to the central position. An equal number of trials was presented for each direction. In 20% of trials, the preparation stimulus continued for an additional 4s and no movement was made. Trials were presented in a pseudo-random order, with two runs of 50 trials, lasting approximately ten minutes each.

Figure 2. Results of one-sample t-tests for each group and visit, for movement > no-movement (A), significant differences between PD and HC (B) as well as within subjects differences between baseline, 18-month and 36-month visits (C) in PD patients ($Z > 3.1$, corrected $p < .05$). Colour bars represent the z-statistic, overlaid on the MNI152 1mm template. Co-ordinates for each axial slice are given in MNI space. IL, ipsilateral; CL, contralateral.

Figure 3. Results of linear-mixed effects modelling with additional factors, including within subjects differences between baseline, 18-month and 36-month visits when controlling for UPDRS-III scores (A) and when controlling for response time and movement amplitude measures of task performance (B) in PD patients ($Z > 3.1$, corrected $p < .05$). Colour bars represent the z-statistic, overlaid on the MNI152 1mm template. Co-ordinates for each axial slice are given in MNI space. IL, ipsilateral; CL, contralateral.

Figure 4. Correlations between movement-related activity and UPDRS-III scores for the most affected side (MAS) in Parkinson's disease patients ($Z > 3.1$, corrected $p < .05$). Colour bars represent the z-statistic, overlaid on the MNI152 1mm template. Co-ordinates for each axial slice are given in MNI space. IL, ipsilateral; CL, contralateral.