

SUPPLEMENTARY MATERIAL

Suppl. Methods - Image processing

First, functional images were spatially realigned using a sinc interpolation algorithm that estimates rigid body transformations (translations, rotations) by minimizing head-movements between each image and the reference image (Friston et al., 1995). Subsequently, the time-series for each voxel was realigned temporally to acquisition of the first slice. Images were normalized to a standard EPI template centered in Talairach space (Ashburner and Friston, 1997) by using 12 linear parameters (translation, rotation, zoom, and shear) and resampled at an isotropic voxel size of 2 mm. The normalized images were smoothed with an isotropic 10 mm full-width-at-half-maximum (FWHM) Gaussian kernel. Anatomical images were spatially coregistered to the mean of the functional images (Ashburner and Friston, 1997) and spatially normalized by using the same transformation matrix applied to the functional images. The ensuing pre-processed fMRI time series was analyzed at the first level using an event-related approach in the context of the General Linear Model (GLM). Then, the contrast images from the first level were entered into a second level random-effect analysis in a within-patient analysis of variance (ANOVA).

Suppl. Methods - Effective connectivity

A psychophysiological interaction (PPI) analysis makes inferences about regionally specific responses caused by the interaction between the psychological factor and the physiological activity in a specified index area (Friston et al., 1997). The analysis was constructed to test for differences in the regression slope of the activity in all remaining brain areas on the activity in the index area (the MFC), as a

function of HAND-ORDER for the most affected hand (SWITCH > REPEAT). In other words, this analysis searches for brain regions showing increased connectivity with the MFC for trials where motor imagery (MI) of most affected hands was preceded by MI of the least affected hands (SWITCH), as compared to trials where MI of least affected hands was preceded by MI of least affected hands (REPEAT). The index area was defined by the first eigentime series of all voxels within a 6 mm radius sphere centered on the regional maxima in the MFC that showed a HAND-ORDER effect for the most affected hand (SWITCH > REPEAT). First, a PPI analysis for each subject was performed at the first level. Then we assessed at the second-level whether these individual connectivity patterns were modulated by subject-by-subject variance in disease severity. This was done by entering individual PPI contrast images (obtained at the first level) into a simple regression (correlation) analysis, using lateralized disease severity for the most affected side (in UPDRS points) as an explanatory variable. Based on our a priori hypothesis, we used four VOIs centered on the bilateral BG (left GP and putamen), using the same images and statistical inference as described above.

Suppl. Methods & Results: Experiment 2.

In this experiment we compared behavioral performance of 10 PD patients (see Table 1) with that of 10 matched, healthy controls. The task involved motor imagery of left and right hands (almost identical to Exp.1, see below). We analyzed the effect of factors GROUP (CONTROLS, PD), HAND (LEFT, RIGHT) and HAND-ORDER (REPEAT, SWITCH) on the RTs.

Experimental task setup: Subjects were seated in front of a computer screen with their left and right big toe on separate response buttons. They were presented with realistic

photos of left and right hands and asked to report as quickly as possible whether they saw a picture of a left or right hand by flexing their left or right big toe, respectively. Reaction time was defined as the time between onset of the visual stimulus and key press. Visual stimuli presentation and behavioral responses recording were controlled with a PC running Presentation software (Neurobehavioral systems, Albany, USA). The photos of left and right hands were identical mirror images, they could be shown rotated from an upright (0°) position until $\pm 100^\circ$ (in 10 steps of 20°), and they could be shown as back- or palm-views, according to a pseudo-randomized trial order. There were 352 stimuli (intertrial interval: 0.5 - 1.5 sec), presented in 44 blocks of 8 trials, with a total measurement time of ~20 minutes. The focus here was on trial order effects in the laterality of imagined hand movements (factor HAND-ORDER), which were calculated in the same way as in Exp.1. The first trial of each of the 44 blocks, incorrect trials, and trials following incorrect trials were excluded from the analyses.

Results: Both patients and controls performed the task accurately, although patients tended to make more errors than controls (PD patients: 8.7 ± 2.1 %; controls: 4.3 ± 1.3 %; mean error rate $\pm$ SEM; main effect of GROUP: $F(1,18)=3.43$; $p=0.080$). PD patients were slower than controls when the task required them to switch from one hand to the other (GROUP x HAND-ORDER interaction: $F(1,18)=14.60$; $p=0.001$; main effect of HAND-ORDER for PD patients: $F(1,9)=20.76$; $p=0.001$; no main effect of HAND-ORDER for controls: $F(1,9)=1.44$; $p=0.26$; Fig. 2 A & B). The effect of HAND-ORDER on the RT was similarly modulated by factor HAND in both groups. In the control group this effect consisted of a relatively smaller switch benefit for the right hand than for the left hand (see Suppl. Fig. 1A), whereas in the PD group this effect consisted of a significantly larger switch cost for the (most affected) right

hand than for the (least affected) left hand (see Suppl. Fig. 1B). Although PD patients appeared to be overall slower than healthy controls, this was not significant ($p > 0.15$). Finally, the subjects were overall faster during trials showing right hand stimuli (main effect of HAND: $F(1,18) = 6.85$; $p = 0.017$), probably due to the generic bias introduced by the right-handedness of the subjects.

Suppl. Methods & Results – Experiment 3

In this experiment we compared the most and least affected hand of 11 PD patients (Table 1) in a within-patients design. The task involved spatially cued movements with either the most or the least affected hand. We investigated the effect of factors HAND-ORDER (REPEAT, SWITCH) and HAND (LEAST AFFECTED, MOST AFFECTED) on RTs.

Experimental procedures: The patients were seated in front of a table with their left and right hand positioned on the table over corresponding buttons (home-keys) on either side of the mid-sagittal plane (30 cm apart – see Suppl. Fig. 2). The table contained also two target buttons (with built-in LEDs) and two speakers, symmetrically positioned along the mid-sagittal plane (4 cm apart and 24 cm. from the corresponding home key). The patients were presented with one of four stimuli: an orange LED was illuminated in either the left or the right target button, or a 1000 Hz. sound from either the left or the right speaker. The patients were asked to leave the home key and move their left or right hand toward the corresponding left or right target button as soon as they saw the left or right LED turned on, or they heard a sound from the left or right loudspeaker. For instance, when they heard a sound coming from the left loudspeaker, or saw the left target button lighting up, they were required to move their left hand from the home key, press the left target button and

then move back to the left home key. The light or the sound remained switched on until the target button was pressed. The factor STIMULUS (2 levels: AUDITORY, VISUAL) was orthogonal to the previous two conditions, and we collapsed over this factor in our analyses. There were 320 trials (intertrial interval 1.5 – 2.5 sec) presented in a single block, with a total measurement time of ~20 minutes. The reaction time was defined as the time between onset of the sensory stimulus and the moment the hand left the home key.

Results: Patients were slower in responding with their most affected hand than with their least affected hand (main effect of HAND: $F(1,10)=5.30$; $p=0.044$). In contrast to the findings of Experiments 1 and 2, there was no significant effect of HAND-ORDER, and no HAND x HAND-ORDER interaction ($F(1,10)=0.19$; $p=0.67$). See also Suppl. Fig. 2.

SUPPLEMENTARY TABLES

Patient	Exp.	Sex	Age	UPDRS						H & Y
				Right hand	Left hand	Right foot	Left foot	other	total	
8	1-3	2	59	10	5	3	2	10	30	2.5
9	1-3	1	68	18	10	5	4	15	52	3
10	1-3	1	65	6	5	5	4	11	31	3
11	1-3	1	56	10	6	4	3	8	31	2.5
12	1-3	1	34	11	4	3	2	4	24	2
13	1-3	1	50	12	8	5	5	11	41	3
14	1-3	1	53	8	4	3	3	6	24	2.5
15	1-3	2	67	4	0	1	0	1	6	1.5
16	1-3	1	65	6	2	2	1	6	17	2
17	1, 3	2	43	16	8	3	2	11	40	2
18	1, 3	2	56	11	3	2	2	5	23	2
Mean		7 men	56.0	10.2	5.0	3.3	2.5	8.0	29.0	2.4
SD			10.6	4.2	2.9	1.3	1.4	4.0	12.5	0.5

Table 1: Clinical characteristics (Exp. 3)

Eleven patients with idiopathic Parkinson's disease were tested in a practically-defined off-state (more than 12 hours after having taken their last medication; (Langston et al., 1992) during Exp. 3. UPDRS: Unified Parkinson's Disease Rating Scale; H&Y: Hoehn and Yahr rating scale.

Anatomical label	Functional label	Hemisphere	cluster statistics		local maximum			
			size (voxels)	p-value	T-value	x	y	z
'Errors > Correct'								
Pre-SMA Middle Cingulate Cortex	Pre-SMA	R / L	2062	<0.001	6.1	-2	18	50
	ACC	R / L			5.36	2	26	36
Insular Cortex	Insula	R	2081	<0.001	6.78	36	26	-4
Caudate Nucleus	Caudate Nucleus	R			5.06	14	10	2
Inferior Frontal Gyrus	BA 45	R			4.79	52	22	22
Insular Cortex	Insula	L	1630	<0.001	5.5	-42	20	-4
Caudate Nucleus	Caudate Nucleus	L			4.24	-12	10	4
Inferior Frontal Gyrus	BA44	L	178	0.015	3.98	-48	8	22
Intraparietal sulcus	PPC	L	835	<0.001	4.57	-38	-40	48

Suppl. Table 2: Error-related cerebral activity

MNI stereotactic coordinates of local maxima for clusters where activity increased more for error trials than for correct trials [contrast: “ERRORS > CORRECT”]. For large clusters spanning several anatomical regions (e.g., the left and right insula), more than one local maximum is given. Cluster size is given in number of voxels. Statistical inference ($p < 0.05$) was performed at the cluster level, correcting for multiple comparisons over the search volume (the whole brain). The intensity threshold necessary to determine the cluster-level threshold was set at $p < 0.001$ uncorrected.

ACC: anterior cingulate cortex; BA: Brodmann Area; PPC: posterior parietal cortex; pre-SMA: pre-supplementary motor area.

SUPPLEMENTARY FIGURE LEGENDS

Suppl. Figure 1: Experiment 2

The bars show the time that subjects used to solve the hand-laterality judgment task (reaction time, RT, in ms; mean $\pm$ SEM). RTs for hand-repeat trials (blue bars) and hand-switch trials (orange bars) are shown separately according to hand laterality (left, right). Panels A and B illustrate RTs from 10 healthy controls and 10 right-lateralized Parkinson's disease patients (PD), respectively.

Suppl. Figure 2: Experiment 3

Task setup (panel A). Patients had their left (least affected) and right (most affected) hand on a home-key (black buttons) and were presented with one of four stimuli: an orange LED was illuminated in either the left or the right target button, or a 1000 Hz. sound from either the left or the right speaker. They were asked to leave the home key and move their left or right hand toward the corresponding left or right target button as soon as they saw the left or right LED turned on, or they heard a sound from the left or right loudspeaker.

Results (panel B). The bars show the average reaction times ($\pm$ SEM) for 11 right-lateralized PD patients. The results are depicted separately for hand-repeat (blue bars) and hand-switch (orange bars) conditions, and separately for the most and least affected hand (see x-axis).

Suppl. Figure 3: Switch-related brain activity

To rule out that the enhanced switch-related activity for the most affected hand (Fig. 3 A) was driven by longer RTs, we ran a second analysis where we modeled trial-by-trial RTs as variable event durations in our first-level model.

Panel A shows the anatomical distribution (in orange) of cerebral activity that increased during hand-switch trials (compared to hand-repeat trials), specifically for the most affected hand (as compared to the least affected hand), superimposed on a sagittal section of a representative brain of the MNI series (at an intensity threshold of $p < 0.001$ uncorrected; cluster-level corrected for multiple comparisons at $p < 0.05$).

Panel B shows the beta values from the CMA local maximum for hand-switch and -repeat trials, separately for the least and most affected hand.

This result is essentially the same as shown in Figure 3A and B, which demonstrates that switch-related activity in the CMA is not merely driven by longer RTs. It is interesting that the pre-SMA activity was not visible at this threshold. This finding, together with the overlap of switch- and error-related activity in the pre-SMA (Fig. 3G-I), indicate that the pre-SMA activity (unlike the CMA) may be related to enhanced response monitoring.

Reference List

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4. Langston JW, Widner H, Goetz CG, Brooks D, Fahn S, Freeman T, Watts R (1992) Core assessment program for intracerebral transplantations (CAPIT). *Mov Disord* 7: 2-13.