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Cerebral compensation during motor imagery in Parkinson's disease

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Abstract

In neurodegenerative disorders, neural damage can trigger compensatory mechanisms that minimize behavioural impairments. Here, we aimed at characterizing cerebral compensation during motor imagery in Parkinson's disease (PD), while controlling for altered motor execution and sensory feedback. We used a within-patient design to compare the most and least affected hand in 19 right-handed PD patients with markedly right-lateralized symptoms. We used a motor imagery (MI) task in which the patients were required to judge the laterality of hand images, rotated either in a lateral or in a medial orientation with respect to the body sagittal plane. This design allowed us to compare cerebral activity (using fMRI) evoked by MI of each hand separately, while objectively monitoring task performance. Reaction times and parieto-premotor activity increased in a similar manner as a function of stimulus rotation during motor imagery of left and right hands. However, patients were markedly slower when judging images of the affected hand in lateral orientations, and there was a corresponding increase in activity in the right extrastriate body area (EBA) and occipito-parietal cortex during mental rotation of the affected hand. Furthermore, these regions increased their connectivity towards the left PMd for right (affected) hands in a lateral orientation. We infer that, in strongly lateralized PD patients, motor imagery of the most-affected hand exploits additional resources in extrastriate visual areas. These findings characterize the cerebral bases of the increased dependence on visual information processing during the generation of motor plans in PD, pointing to its compensatory role.

Keywords: Functional magnetic resonance imaging; Extrastriate body area; Visual cortex; Mental rotation; Biomechanical constraints; Body schema

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disease characterized by deficits in motor control, which are clinically apparent as bradykinesia, hypokinesia and akinesia (Berardelli, Rothwell, Thompson, & Hallett, 2001). At the neuronal level, the disease is characterized by progressive cell death in the substantia nigra pars compacta, which leads to dopamine depletion in the striatum and indirectly to cortical dysfunction (Marsden, 1982; Braak et al., 2003). The clinical signs are an expression of altered neural processing at one or more stages of movement generation, including motor planning, motor execution and sensory feedback (Marsden, 1982). The motor deficits can be improved when PD patients are provided with external sensory cues (Bloem, Hausdorff, Visser, & Giladi, 2004). This suggests that impaired motor-related cerebral function can be compensated for by additional processing (e.g. enhanced attention or increased reliance on visual features), which implies that cerebral compensatory mechanisms occur in chronically progressive neurodegenerative disorders (Palop, Chin, & Mucke, 2006). These mechanisms may rely on local changes in neuronal properties, like synaptic plasticity (Bezard & Gross, 1998), but they may also arise from system-level changes in cerebral circuits supporting a given cognitive process. In computational terms, compensation within a cerebral circuit is known as degeneracy, namely 'the ability of elements that are structurally different to perform the same function or yield the same output' (Edelman & Gally, 2001). Degeneracy implies that structurally different cerebral circuits are able to contribute to one particular function. If one node or circuit fails, other circuits may take over and prevent deficits in overt behaviour. In PD, degeneracy may explain why so many neurons in the substantia nigra can die before they are missed

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at the clinical level, and why the disease progresses so slowly. Specifically, degeneracy might involve the engagement of additional (compensatory) brain regions in a cerebral circuit, thereby preserving its functional output in behavioural terms. Also, the chronicity of neurodegenerative disorders *allows* the brain to deploy compensatory mechanisms—for example, by increasing neuronal activity in relatively unaffected regions. Thus, within the boundaries set by neuronal loss, the nervous system has a notable capacity to maintain neurological functions (Palop et al., 2006; Price & Friston, 2002). This may have important implications, since it shifts the focus of therapeutic intervention from neurons that are lost to those that survive.

Several neuroimaging studies have been performed to investigate changes in functional networks in PD, finding decreased activity in mesial frontal regions and increased activity in cerebellum, lateral premotor and parietal regions (Haslinger et al., 2001; Sabatini et al., 2000; Samuel et al., 1997). A similar pattern of increased activity in the right rostral cingulate motor area and left dorsal premotor cortex (PMd) was found in presymptomatic gene-carriers at risk for developing PD (Buhmann et al., 2005), confirming that compensatory changes at the network level are very early adaptations of the brain to maintain behavioural functions, even before a neurodegenerative disease becomes visible to the clinical eye.

These studies have used motor execution tasks, and their results indicate that degeneracy may occur at the level of motor planning, motor execution, or even be related to abnormal sensory feedback (Boecker et al., 1999; Seiss, Praamstra, Hesse, & Rickards, 2003). To resolve this ambiguity, other studies have used motor imagery (MI) paradigms in PD patients (Cunnington et al., 2001; Samuel, Ceballos-Baumann, Boecker, & Brooks, 2001; Thobois et al., 2000), where patients were asked to *imagine* performing movements while brain activity was recorded. These studies excluded that the altered cerebral activity during MI in PD could be due to altered motor output or sensory feedback, but it remains unclear to what extent these results reflect the inability of PD patients to solve a task, i.e. to select appropriate motor circuits and inhibit inappropriate ones. It has been argued that to reliably attribute cerebral activation patterns to compensatory mechanisms, it is necessary to use tasks that the patient can perform (Price & Friston, 2002), while allowing for objective measures of patients' performance and strategies.

Here, we have quantified performance of PD patients during a motor imagery task, while measuring cerebral activity with event-related fMRI. When asked to judge the laterality of a rotated image of a hand, human subjects solve the task by mentally moving their own hand from its current position into the stimulus orientation for comparison (Parsons, 1987). A direct comparison between mental rotation of hands (motor imagery) and mental rotation of letters (visual imagery) has revealed that MI is supported by a specific parieto-premotor network (de Lange, Hagoort, & Toni, 2005) that closely resembles the cerebral network activated during motor preparation (Thoenissen, Zilles, & Toni, 2002) and partially overlaps with structures involved during movement execution (Decety, 1996; Hanakawa et al., 2003), showing the same somatotopical distribution (Michelon, Vettel, & Zacks, 2006). Psychophysical studies in healthy controls have documented that making hand laterality judgements and executing a movement to match the hand position depicted on the screen follow the same temporal profile and the same hand-specific joint-constraints (Parsons, 1987, 1994; Sekiyama, 1982). Furthermore, the position of the subjects' own hand has been found to affect both behavioural performance (Shenton, Schwoebel, & Coslett, 2004) and cerebral activity (de Lange, Helmich, & Toni, 2006) during the hand laterality judgement task in a hand-specific manner. This underlines that the hand laterality judgment task implies first-person motor imagery. Using a different task involving third-person motor imagery, no such effect of body posture was found (Fischer, 2005). Accordingly, the hand laterality judgement task allows one to assess behavioural and neural correlates of motor imagery separately for the left and right hand. We have exploited this task feature and tested PD patients with *lateralized* symptoms during performance of hand laterality judgements, comparing behavioural and neural performance between the most and least affected hand in a within-patient design. By quantifying motor imagery performance and its supporting cerebral activity, it becomes possible to distinguish whether differences in cerebral activity during motor imagery of the two hands were related to altered task performance or to compensatory mechanisms.

2. Methods

2.1. Patients and controls

2.1.1. Main experiment

Nineteen right-handed idiopathic Parkinson's disease patients (13 men, 53.2 ± 9.1 years, mean $\pm$ S.D.) participated after giving written informed consent according to institutional guidelines of the local ethics committee (CMO region Arnhem-Nijmegen, The Netherlands). Before scanning, the patients' disease severity was assessed by one examiner (RCH) using the Hoehn and Yahr stages and the Unified Parkinson's Disease Rating Scale (UPDRS; see Table 1). Patients were included when they had idiopathic Parkinson's disease, diagnosed according to the UK Brain Bank criteria by an experienced movement disorders specialist (BRB), with clearly right-lateralized symptoms. Exclusion criteria were: moderate-severe tremor, cognitive dysfunction (i.e. mini mental state examination <24), other neurological diseases (such as severe head trauma or stroke), and general exclusion criteria for MRI scanning (such as claustrophobia, pace-maker, and implanted metal parts). Six patients did not yet use any anti-Parkinson medication; the others used dopaminergic medication (levodopa or dopamine-agonists). The experiments were carried out in the morning, and the patients were asked not to take their medication the evening before the experiment. Thus, they were all off-medication for at least 12 h during the experiment (i.e. in a practically defined off-condition; Langston et al., 1992).

2.1.2. Control experiment

In a second behavioural (control) experiment, we compared 12 of the PD patients mentioned above (8 men, 56.4 ± 10.0 years, mean $\pm$ S.D.) with two groups of right-handed, healthy control subjects: 10 age- and sex-matched elderly volunteers (6 men, 57.0 ± 6.2 years, mean $\pm$ S.D.) and 15 young volunteers (7 men, age 26.7 ± 3.3, mean $\pm$ S.D.).

2.2. Stimuli, time course and procedures

2.2.1. Main experiment

We used line drawings of left and right hands, with either the back or the palm of the hand in view. The left and right hands drawings were identical

Table 1
Clinical characteristics

Patient	Sex	Age (years)	H&Y	UPDRS-L	UPDRS-R
1	m	39	2	3	17
2	m	48	2.5	4	18
3	f	51	2	7	12
4	m	48	3	3	15
5	m	53	2	2	10
6	m	50	1.5	2	10
7	f	54	1	2	1
8	m	51	3	9	24
9	f	59	2	6	15
10	m	68	2	8	15
11	m	65	2	3	8
12	m	56	2	7	16
13	m	34	1.5	0	14
14	m	50	3	7	14
15	m	53	2	5	17
16	f	67	2	6	14
17	m	65	1.5	0	6
18	f	43	2	9	16
19	f	56	2	4	14
Mean	13 males	53	2.1	4.6	13.5
S.D.		9	0.5	2.8	5.0

Nineteen patients (13 men; age 53.2 ± 9.1 years, mean ± S.D.) with idiopathic Parkinson's disease were tested in a practically defined off-state (i.e. more than 12 h after having taken their last medication). All patients were consistent right-handers. Patients had markedly asymmetric symptoms lateralized to the right side of their body. UPDRS: Unified Parkinson's Disease Rating Scale; H&Y: Hoehn and Yahr Rating Scale.

mirror images. The hand drawing could be shown rotated from its upright (0°) position in either a counter-clockwise (CCW) or a clockwise (CW) orientation, or turned upside down (180°). For both orientations, three different rotations from 45° to 135° in steps of 45° were used. This yielded eight different rotations (Fig. 1). These stimuli were presented through a PC running Presentation software (Neurobehavioural systems, Albany, USA). They were projected via a mirror above the patients' heads onto a screen. The stimuli subtended a visual angle of ∼10°. The patients' task was to report whether the hand drawing on display represented a left or a right hand (regardless of its rotation) by pressing one of two buttons attached to their left and right big toe. The stimuli were serially presented in a random order. During scanning, reaction times and error rates were measured for subsequent behavioural analysis. The imaging session consisted of 30 task blocks (duration ∼60 s per block) intermixed with 30 baseline periods (duration 10 s). Each block consisted of 16 trials, which started with a fixation cross, displayed for a variable interval (1.5–2.5 s), followed by the presentation of a hand drawing. When a response was provided, the stimulus was replaced by the fixation cross till the presentation of the next hand drawing. Rotation and laterality of the hand drawings were randomized from trial to trial. On the basis of pilot data, the reaction time cut-off was set at 5.0 s. In total, subjects performed 480 trials, leading to a total scanning time of ∼40 min. During the experiment, the posture of the patients' left and right arm was manipulated. At the beginning of each block, a cartoon instructed the patients to position their arms in one of three postures: (1) both arms extended; (2) the left forearm flexed, right arm extended; (3) the right forearm flexed, right arm extended. The period during which the cartoon was displayed and the instruction for postural adjustment took place (duration 7 s) was followed by a baseline period during which a fixation cross was displayed on the screen. Each posture change was followed by a block of 16 trials. During the whole experiment, the patients were lying supine in the scanner, facing the bore of the magnet, unable to see their hands. Before the start of the scanning session, patients were trained until they could perform the task with an accuracy of at least 90% correct responses. All patients were able to perform the task after the training. Furthermore, after being positioned in the MR-scanner, but before the start of the MR measurements, the patients performed a simple stimulus-response task to assess possible differences in response times between the left and the right foot. During this test, the patients saw 20 pictures of a red circle and 20 pictures of a green square, in randomized order, and responded with either their left or right foot to either visual stimulus according to a pre-defined mapping. This control task served to assess whether differences in reaction times were due to differences in the foot response.

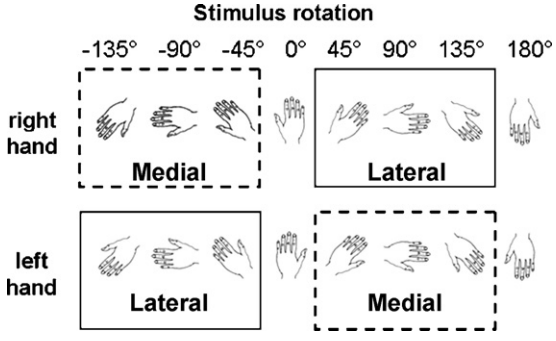

Fig. 1. Task setup (main experiment). Subjects had to judge whether the stimulus was a left or right hand, irrespective of its rotation (from 0° to 315° in 8 steps of 45°). The stimulus could be orientated either laterally or medially with respect to the body axis. Counter-clockwise rotations (−135°, −90° and −45°) were averaged and coded as a lateral orientation for left hands and a medial orientation for right hands (lateral: rotations in continuous squares). Clockwise rotations (135°, 90° and 45°) were averaged and coded as a medial orientation for left hands and a lateral orientation for right hands (medial: rotations in dashed squares). In our analyses, we focused on two effects: (1) brain activity that increased as a function of stimulus rotation for one hand but not the other (HAND × ROTATION interaction) and (2) brain activity that changed as a function of stimulus orientation (clockwise or counter-clockwise rotations) for one hand but not the other (HAND × ORIENTATION interaction).

2.2.2. Control experiment

We used realistic photos of left and right hands, with either the back or the palm of the hand in view. The left and right hands stimuli were identical mirror images. The picture of the hand could be shown rotated from its upright (0°) position in either a counter-clockwise (CCW) or a clockwise (CW) orientation. For both orientations, five different rotations from 20° to 100° in steps of 20° were used. These stimuli were presented through a PC running Presentation software (Neurobehavioural systems). The subjects (both patients and controls) were seated in front of a computer screen with their left and right big toe on a response button. Their task was the same as in the main experiment: they had to respond with their left or right foot when they saw a picture of a left or right hand, respectively. The laterality and rotation of the stimuli were randomized. In total, the subjects saw 352 stimuli, leading to a measurement time of ∼20 min. The stimuli were presented in 44 blocks of 8 trials. At the beginning of each block, the subjects were asked to adopt one of four possible body postures: both hands palm-up, both hands palm-down, left hand palm-up and right hand palm-down, right hand palm-up and left hand palm-down. A plate positioned over their hands prevented vision of their body posture. When the subjects' own hand posture matched the view of the stimulus on the screen (e.g. the subject saw a picture of a left hand with the palm in view, and at the same time his own hand was positioned with the palm upwards), the body posture for this trial was coded as "matching". When the subjects' hand did not match the view of the stimulus on the screen (e.g. the subject saw a picture of a left hand with the palm in view, and at the same time his own hand was positioned with the palm downwards), the body posture for this trial was coded as "non-matching".

2.3. Behavioural analysis

2.3.1. Main experiment

First, we analysed the influence of the factors ROTATION (8 levels: from 0° to 345° in steps of 45°) and HAND (2 levels: LEFT or RIGHT) by means of a

repeated measures ANOVA on reaction times collected during scanning. Then, we proceeded to test the effect of biomechanical constraints and body posture on the behavioural performance. The term "biomechanical constraints" refers to the reaction time difference in mentally rotating a hand towards a lateral, as compared to a medial orientation with respect to the body axis. Lateral and medial orientations were coded as follows: CCW rotations (−135°, −90° and −45°) were averaged and recoded as a lateral orientation for left hands and a medial orientation for right hands; CW rotations (135°, 90° and 45°) were averaged and recoded as a medial orientation for left hands and a lateral orientation for right hands. The effect of factors HAND (2 levels: LEFT or RIGHT), stimulus ORIENTATION (2 levels: LATERAL, MEDIAL) and body POSTURE (2 levels: EXTENDED, FLEXED) on the reaction times was calculated in a repeated-measures ANOVA. The Greenhouse–Geisser method was used to correct for non-sphericity. Alpha-level was set at $p = 0.05$.

2.3.2. Control experiment

We analysed the influence of the factors HAND (2 levels: LEFT or RIGHT), ORIENTATION (2 levels: LATERAL or MEDIAL) and body POSTURE (MATCHING, NON-MATCHING) by means of a three-way repeated measures ANOVA on reaction times. GROUP (PATIENTS, ELDERLY CONTROLS, YOUNG CONTROLS) was used as a between-subjects factor. Lateral and medial orientations were calculated in the same way as mentioned above for the main experiment. The Greenhouse–Geisser method was used to correct for non-sphericity. Alpha-level was set at $p = 0.05$.

2.4. Image acquisition

Functional images were acquired on a Siemens SONATA 1.5 T MRI system (Siemens, Erlangen, Germany) equipped with echo planar imaging (EPI) capabilities, using the standard head coil for radio frequency transmission and signal reception. Blood oxygenation level-dependent (BOLD) sensitive functional images were acquired using a single shot gradient EPI-sequence [TE/TR = 40 ms/2560 ms; 32 axial slices, voxel size = 3.5 mm × 3.5 mm × 3.5 mm; field of view (FOV) = 224 mm]. High-resolution anatomical images were acquired using an MP-RAGE sequence (TE/TR = 3.39 ms/2250 ms; voxel size = 1.0 mm × 1.0 mm × 1.0 mm, 176 sagittal slices; FOV = 256 mm).

2.5. Image analysis

Functional data were pre-processed and analysed with SPM2 (Statistical Parametric Mapping, http://www.fil.ion.ucl.ac.uk/spm). 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 centred in Talairach space (Ashburner & Friston, 1999) 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 & Friston, 1997) and spatially normalized by using the same transformation matrix applied to the functional images. The ensuing pre-processed fMRI time series was analysed 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 the second level in a within-patients analysis of variance (ANOVA).

2.6. General linear models

We used two different GLMs to analyse two different effects in our data. The first model (GLM-1) was aimed at finding regions where activity changed as a function of stimulus rotation for either hand. This model considered the laterality of the hand drawing on display (factor HAND, 2 levels: LEFT, RIGHT), and its ROTATION (5 levels: 0°, 45°, 90°, 135°, 180°; clock-wise and counter-clockwise rotations were collapsed) as independent explanatory variables. We used a linear basis function for the modulation of cerebral activity by stimulus rotation (parametric modulation). This gave rise to a model with two different conditions (left hands, right hands), each with a linear parametric modulation of stimulus rotation.

The second model (GLM-2) was aimed at finding regions where activity changed as a function of stimulus ORIENTATION (lateral or medial) for either hand. Additionally, we investigated how activity in those regions was modulated by the patients' own body POSTURE. This model considered the laterality of the hand drawing on display (factor HAND, 2 levels: LEFT, RIGHT), its ORIENTATION (4 levels: LATERAL, MEDIAL, UPRIGHT (0°), DOWN (180°)) and the patients' own body POSTURE (2 levels: FLEXED, EXTENDED). This gave rise to a model with 16 different conditions.

Finally, both models included separate regressors of no interest, modelling posture changes, incorrect and missed responses, residual head movement-related effects, signal of segmented white matter and cerebral spinal fluid (Verhagen, Grol, Dijkerman, & Toni, 2006), and low-frequency signal drifts over time. Parameter estimates for all regressors were obtained by maximum-likelihood estimation, while using a temporal high-pass filter (cut-off 60 s), and modelling temporal autocorrelation as an AR(1) process. Linear contrasts pertaining to the main effects and interactions of the factorial design were calculated. Consistent effects across patients were tested using two different random effects analyses. In GLM-1, for each patient two contrast images (rotation-related activity for left hands and for right hands) were entered into a within-patient ANOVA. In GLM-2, for each patient, eight contrast images (resulting from the 2 × 2 × 2 interaction: HAND (left, right) × ORIENTATION (lateral, medial) × POSTURE (flexed, extended)) were entered into a within-patient ANOVA.

2.7. Contrasts

We tested for two different effects in our data, namely the effect of factor HAND on ROTATION-related activity (GLM-1) and the effect of factor HAND on ORIENTATION-related activity (GLM-2).

First, we looked for differences in rotation-related activity between hands. This refers to cerebral activity that increased linearly as a function of stimulus rotation. Brain regions that show this activity pattern are thought to be specifically involved in mental rotation. We searched for regions where BOLD response changed as a function of HAND, ROTATION or an interaction of these factors. When testing the interaction, we always confined our search to regions that also showed a main effect of rotation for that hand using inclusive masking. For instance, the contrast "RH-rotation > LH-rotation" was masked by the contrast "RH-rotation", and the contrast "LH-rotation > RH-rotation" was masked by the contrast "LH-rotation".

Second, we looked for differences in orientation-related activity between hands, following the behavioural effect. We looked for regions where activity changed as a function of HAND, ORIENTATION or an interaction of these factors. When looking into the biomechanical constraints of each hand, we confined our search to regions that were specifically involved in mental rotation of that hand, using inclusive masking. For instance, when assessing the biomechanical constraints of right hands, we masked the contrast "RH-lateral > RH-medial" with the contrast "RH-rotation" (from GLM-1). For left hands, we masked the contrast "LH-lateral > LH-medial" with the contrast "LH-rotation" (from GLM-1). This approach was based on the idea that a modulation of activity by stimulus rotation is necessary to label a region as being involved in the task (e.g. mental rotation). Post hoc, we further characterized orientation-related activity specific for the right hand by investigating the effect of the patients' own (right) arm posture on activity in those regions. It should be emphasized that this analysis served only to better describe the role of those regions. Hence, we restricted our analysis to the right hand, and did not test for between-hand differences. We expected the difference between lateral and medial orientations to increase when the patients' own arm was positioned in a medial orientation (i.e. flexed arm posture). Therefore, we investigated whether orientation-related activity in those regions increased as a function of body posture (i.e. POSTURE (flexed versus extended) × ORIENTATION (lateral > medial). Second, we tested which of those brain regions showed similar orientation-related activity for both postures (conjunction analysis of "extended posture; lateral > medial" and "flexed posture; lateral > medial") (Nichols, Brett, Andersson, Wager, & Poline, 2005). All

contrasts were masked by the rotation-related network for the right hand (i.e. "RH-rotation").

2.8. Statistical inference

Statistical inference ($p < 0.05$) was performed at the cluster-level, correcting for multiple comparisons over the search volume (i.e. the whole brain). The intensity threshold (i.e. at the voxel level) was set at $p < 0.01$ family-wise error corrected (to identify the general, rotation-related network; see Fig. 3 and Table 2), or $p < 0.01$ uncorrected (all other analyses). Additionally, we focused our analysis on four a priori regions, previously shown to be specifically involved in motor imagery of hand movements (left and right posterior parietal cortex, PPC [−18 −66 +48] and [+20 −66 +52]; left and right dorsal premotor cortex, PMd [−24 −8 +54] and [+30 −8 +56]; de Lange et al., 2006). More specifically, we drew four spherical volumes of interest (VOIs) centered at these coordinates with a radius of 10 mm. Within these regions, statistical inference was performed as described above. Last, as described above, we post hoc tested the effect of right hand posture on orientation-related activity for that hand. Hence, we took the peak coordinates of regions specifically involved in simulating movements of the right hand towards a lateral orientation (i.e. "right hand > left hand; lateral > medial"; Table 4), drew spheres (with a 10 mm radius) around these coordinates and looked into these volumes of interest (VOI) for increases in cerebral activity as a function of right hand body posture. We also expanded this search to the whole brain.

2.9. Effective connectivity analysis

After having identified regions in the right occipito-parietal cortex that were specifically involved in mental rotation of right hands (GLM-1), and moreover in mental rotation of right hands towards a biomechanically difficult orientation (GLM-2), we hypothesized a change in connectivity between those regions and the parieto-premotor network. More specifically, we hypothesized an increased connectivity between these regions (right V6 and EBA) and the left or right PPC/PMd (de Lange et al., 2006) during mental rotation of right hands towards a lateral (as compared to a medial) orientation.

For connectivity analysis, we employed the psychophysiological interaction (PPI) method described by Friston et al. (1997). A 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. 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 (e.g. right V6 or EBA), depending on the orientation of the right hand stimulus (LATERAL or MEDIAL). Connectivity analyses used right area V6 and the right EBA as index areas, because these areas showed increased activity during mental rotation of right hand stimuli towards a lateral (as compared to a medial) orientation (Table 4). The index area was defined by the first eigentime series of all voxels within a 6 mm radius sphere centred on the regional maxima in the right V6 and EBA that showed a relative increase in BOLD signal during mental rotation of right hands stimuli towards a lateral orientation (RH-lateral > baseline; $p < 0.05$ uncorrected). In two patients, no significant voxels in area V6 were found for that contrast, so their data could not be included in the analysis. First, separately for V6 and for EBA, a PPI analysis for each subject was performed at the first level. Then, individual PPI contrast images were entered into a two-sample *t*-test at the second level (random effects analysis). Based on our a priori hypothesis, we considered only those voxels in our four regions of interest. The SVC procedure included all voxels within a 10 mm radius sphere centred on the maxima of those regions. The statistical inference ($p < 0.05$) was performed at the voxel-level, using family-wise-error correction for multiple comparisons over the search volume (i.e. the VOI).

2.10. Anatomical inference

Anatomical details of significant signal changes were obtained by superimposing the SPMs on the structural images of each subject. The atlas of Duvernoy, Cabanis, and Vannson (1991) was used to identify relevant anatomical landmarks. The Anatomy Toolbox (Eickhoff et al., 2005) was used for regions where cytoarchitectonic maps were available.

3. Results

3.1. Patients

All patients had markedly lateralized symptoms: UPDRS-left: 4.6 ± 2.8; UPDRS-right: 13.5 ± 5.9; $t = 9.73$; $p < 0.001$ in a paired-samples *t*-test.

3.2. Behavioural results (main experiment)

3.2.1. General performance

Patients performed the task accurately, with mean error rates and reaction times that were comparable across hands (error rates: left hand $7 \pm 1\%$, right hand $8 \pm 1\%$; reaction times: left hand, 1549 ± 102 ms; right hand, 1527 ± 97 ms; mean ± S.E.M.). Importantly, patients responded equally fast with their left and right foot on a simple stimulus-response task (left foot, 804 ± 50 ms; right foot, 818 ± 59 ms; mean ± S.E.M.; no significant differences in a paired-samples *t*-test: $t = 0.40$, $p = 0.69$). *Reaction times:* the reaction times changed as a function of the rotation of the hand drawing (main effect of ROTATION: $F(7,126) = 32.12$; $p < 0.001$). This was the case for each hand (left hand, ROTATION: $F(7,126) = 29.22$; $p < 0.001$; right hand, ROTATION: $F(7,126) = 18.05$; $p < 0.001$), indicating that patients used mental rotation to solve the task for both hands. However, the effect of stimulus rotation on the reaction times differed between hands (HAND × ROTATION interaction: $F(7,126) = 6.91$; $p < 0.001$). This interaction reflects the influence of biomechanical constraints on the task: for counter-clockwise (CCW) angles, patients were faster for right hands, whereas for clockwise (CW) angles they were faster for left hands (Fig. 2A). We then proceeded to test the effects of factors ORIENTATION (lateral, medial), POSTURE (flexed, extended) and HAND (left, right) on the reaction times in a three-way ANOVA. There was a large effect of stimulus orientation for right hands (ORIENTATION: $F(1,18) = 28.13$; $p < 0.001$), but not for left hands (ORIENTATION: $F(1,18) = 2.72$; $p = 0.12$) (Fig. 2B). This gave rise to a HAND × ORIENTATION interaction (HAND × ORIENTATION: $F(1,18) = 6.39$; $p < 0.021$), which indicates that patients had specific difficulty in mentally rotating their right hand towards a lateral orientation (i.e. away from the body). When patients had their own hand in a medial position (i.e. flexed arm posture), they experienced a larger effect of biomechanical constraints (i.e. mentally rotating their hand towards a lateral, compared to a medial, orientation) than when they had their own hand in a neutral position (i.e. extended arm posture) (POSTURE × ORIENTATION: $F(1,18) = 12.63$; $p = 0.002$). This effect was similar for both hands (no HAND × POSTURE × ORIENTATION interaction; $F(1,18) = 0.43$; $p = 0.52$). This indicates that patients mentally rotated their own hands to solve the task (i.e. first-person motor imagery).

3.2.2. Error rates

The number of errors increased as a function of rotation for both left and right hands (ROTATION: $F(7,126) = 12.82$; $p < 0.001$). There was no difference in the number of errors for

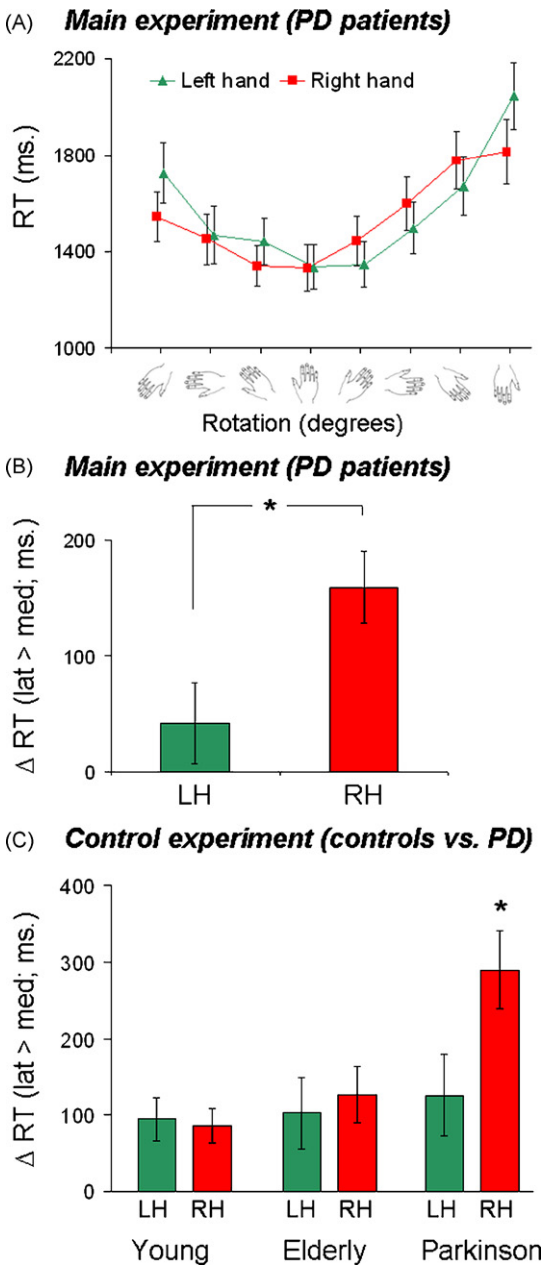

Fig. 2. Behavioural performance. *Main experiment*. (A) Reaction times (mean ± S.E.M.) as a function of hand (left or right hand) and stimulus rotation (−135° to 180° in 8 steps of 45°). Reaction times increased as a function of stimulus rotation for both hands. Patients were faster for right hands (RH) when the stimulus was presented in a counter-clockwise orientation, and for left hands (LH) when the stimulus was presented in a clockwise orientation. (B) Reaction times (mean ± S.E.M.) as a function of stimulus laterality (left or right hand) and stimulus orientation (medial or lateral with respect to the body axis; see Fig. 1). For each hand, the reaction time differences between lateral and medial orientations reflect differences in the biomechanical constraints associated with actual lateral and medial hand movements. The right-lateralized PD patients revealed stronger effects of biomechanical constraints following presentation of right hands than left hands. *Control experiment.* (C) Reaction times (mean ± S.E.M.) as a function of stimulus laterality (left or right hand) and stimulus orientation (medial or lateral with respect to the body axis) for 12 PD patients, 10 age- and sex-matched controls, and 15 young controls. It can be seen that the asymmetric effect of biomechanical constraints on motor imagery is specific to the group of PD patients (asterisk indicates significantly larger biomechanical constraints for the right hand in the PD patients as compared to the healthy controls).

the two hands and there was no HAND × ROTATION interaction. We also explicitly tested the influence of factors HAND, ORIENTATION and POSTURE on the error rates, and found no significant effects in any of the factors, or in their interactions.

3.3. Behavioural results (control experiment)

In a behavioural control experiment, we investigated whether the larger effect of stimulus ORIENTATION for right hands than for left hands (see above) was different from controls.

3.3.1. General performance

Parkinson patients made overall more errors (PD: 11 ± 2%; elderly: 4 ± 2; young: 4 ± 1%; GROUP: $F(2,34) = 5.58$; $p = 0.008$) and were slower (PD: 1547 ± 126 ms; elderly: 1178 ± 123 ms; young: 1006 ± 76 ms; GROUP: $F(2,34) = 7.25$; $p = 0.002$) than the healthy control groups.

3.3.2. Reaction times

Stimulus ORIENTATION influenced the reaction times such that subjects responded slower for pictures in a lateral as compared to a medial orientation (ORIENTATION: $F(2,34) = 55.30$; $p < 0.001$). However, this effect was modulated by factors HAND and GROUP (ORIENTATION × HAND × GROUP interaction: $F(2,34) = 3.61$; $p = 0.038$). More specifically, for left hands the effect of stimulus ORIENTATION was equal between groups (ORIENTATION × GROUP: $F(2,34) = 0.14$; $p = 0.87$), but for right hands this effect was larger for PD patients than for controls (ORIENTATION × GROUP: $F(2,34) = 8.50$; $p = 0.001$; post hoc Tukey test: PD versus elderly, $p = 0.042$; PD versus young: $p = 0.001$; young versus elderly: $p = 0.48$). In PD patients, this effect of stimulus ORIENTATION was larger for right hands than for left hands (ORIENTATION × HAND: $F(1,11) = 6.95$; $p = 0.023$), but this asymmetry was lacking in both elderly (ORIENTATION × HAND: $F(1,9) = 0.27$; $p = 0.62$) and young (ORIENTATION × HAND: $F(1,14) = 0.058$; $p = 0.81$) controls. Hence, we show that PD patients were specifically impaired in mentally moving their affected right hand towards a lateral orientation (e.g. away from the body), whereas this effect was not present in young or age-matched controls (Fig. 2C). All three groups were significantly faster for hand stimuli that matched their own hand posture than for stimuli that did not match their own hand posture (POSTURE: $F(2,34) = 28.38$; $p < 0.001$; no interactions with GROUP or HAND). This further emphasizes that all three groups mentally rotated both of their own hands to solve the task, strongly suggesting that they were engaged in first-person motor imagery.

3.4. Imaging data—rotation-related effects

We searched for regions where activity increased with increasing stimulus rotation, for each hand separately (Table 2; Fig. 3). A conjunction analysis of these two contrasts (Nichols et al., 2005) revealed regions that were involved in mental rotation of *both* hands. We found a bilateral parieto-premotor network, confirming its involvement in mental rotation of hands (de Lange

Table 2
Cerebral activity—rotation-related activity as a function of HAND

Anatomical region	Functional region	Hemisphere	Cluster size	*p*-value	Local maximum			*t*-value
Left hand, rotation-related effect								
Dorsal intraparietal sulcus	PPC	L	1547	<0.001	−24	−64	60	22.92
		R	401	<0.001	18	−70	48	16.65
Superior precentral sulcus	PMd	L	321	<0.001	−22	0	58	20.49
		R	239	<0.001	28	−4	52	19.1
Middle and inferior frontal gyrus (BA's 44 and 45)	Broca's area	L	290	<0.001	−46	22	32	13.01
Superior frontal gyrus	SMA	L and R	757	<0.001	−2	16	50	16.15
					6	14	48	14.18
Middle occipital gyrus (BA 18)	V2	R	150	<0.001	30	−94	16	14.45
Inferior occipital gyrus		L	480	<0.001	−46	−70	−10	14.01
Insular cortex	Insula	L	133	<0.001	−40	18	−6	12.47
Right hand, rotation-related effect								
Dorsal intraparietal sulcus	PPC	L	2315	<0.001	−24	−64	60	19.15
Superior occipital gyrus	V6				−26	−74	32	15.08
		R	1520	<0.001	18	−70	48	19.04
					30	−80	38	18.12
Superior precentral sulcus	PMd	L	148	<0.001	−22	0	58	15.84
		R	94	<0.001	28	−4	52	14.97
Middle and inferior frontal gyrus (BA's 44 and 45)	Broca's area	L	333	<0.001	−46	24	32	13.03
Middle frontal gyrus		L	80	<0.001	−38	54	8	12.72
Insular cortex	Insula	L	255	<0.001	−34	28	−4	12.22
		R	97	<0.001	36	20	0	11.81
Superior frontal gyrus	SMA	L and R	102	<0.001	−8	20	44	9.11
					12	16	50	11.67
Left and right hand, rotation-related effect								
Dorsal intraparietal sulcus	PPC	L	1036	<0.001	−24	−64	60	19.15
		R	358	<0.001	18	−70	48	16.45
Superior precentral sulcus	PMd	L	145	<0.001	−22	0	58	15.84
		R	92	<0.001	28	−4	52	14.97
Middle and inferior frontal gyrus (BA's 44 and 45)	Broca's area	L	194	<0.001	−46	22	32	12.67
Superior frontal gyrus	SMA	L and R	99	<0.001	−8	20	44	9.11
					2	18	46	10.51
Insular cortex	Insula	L	117	<0.001	−40	18	−6	11.92

MNI stereotactic coordinates of the local maxima of regions showing activity that increased as a function of stimulus rotation following presentation of left hands, right hands, and across the two hands (conjunction analysis). For large clusters spanning several anatomical regions (e.g. the intraparietal clusters for the right hand), 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 (i.e. the whole brain). The intensity threshold necessary to determine the cluster-level threshold was set at $p < 0.01$, family-wise-error (FWE) corrected. PMd: dorsal premotor cortex; SMA: supplementary motor area; PPC: posterior parietal cortex; V2: visual area 2; V6: visual area 6. See also Fig. 3.

et al., 2006; Johnson et al., 2002). We then tested for differential rotation-related changes in cerebral activity between right and left hands (HAND × ROTATION interaction). Three areas in the left and right occipital cortex were found to be specifically involved in mental rotation of right hands (Table 2; Fig. 4). First, we found activity in the right occipito-temporal cortex. This region was spatially distinct from area hV5/MT+ [only 0.7% of the cluster was located within that region (Eickhoff et al., 2005)], but close (<8 mm) to the extrastriate body area [EBA (Downing, Jiang, Shuman, & Kanwisher, 2001)]. Second, we found activity in the right superior occipital gyrus. This region was spatially distinct from Brodman area 17 (V1) and 18 (V2) [only 1.7 and 0.4% of the cluster was located in those regions, respectively (Eickhoff et al., 2005)], but close (≤8 mm) to area V3A and V6 (Pitzalis et al., 2006). Third, we found activity in the left middle occipital gyrus, partially overlapping with BA 17 and 18 [30.9 and 19.5% of the cluster was located in these areas, respectively (Eickhoff et al., 2005)]. These three regions were specifically involved in mental rotation of the right hand. We then tested for rotation-related activity specific for mental rotation of left hands (HAND × ROTATION interaction) and found activity in the bilateral inferior occipital cortex (right lingual gyrus and left calcarine gyrus). This cluster partly overlapped with BA 17 (V1; 15.1% of the cluster in left BA 17, 9.5% in the right BA 17) and BA 18 (V2; 21.6% in right BA 18) (Eickhoff et al., 2005). There was no differential effect for either hand in the

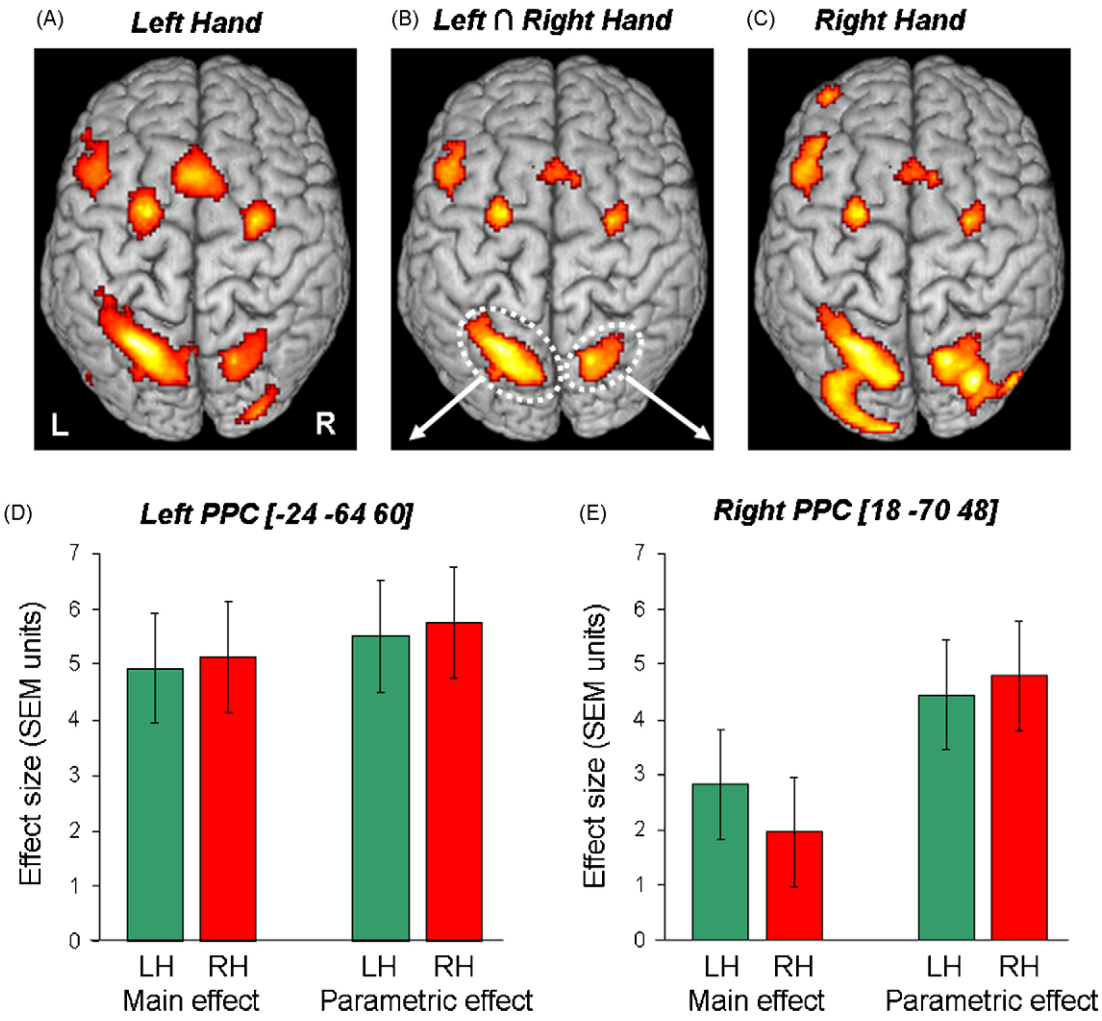

Fig. 3. Cerebral activity related to performance of the motor imagery task—rotation-related effects. (A and C) Spatial distribution of cerebral activity that increased as a function of stimulus rotation following presentation of left and right hands, respectively. In 'B', common rotation-related activity across left and right hands (conjunction analysis; Nichols et al., 2005). The images show the relevant SPM{t}s (in orange, $p < 0.01$ family-wise error corrected over the whole brain, random effect analysis) superimposed on a rendered brain surface. (D and E) Cerebral responses over the left and right posterior parietal cortex (PPC), respectively (numbers in square brackets indicate MNI stereotactic coordinates for the local maxima). The histograms show parameter estimates (in S.E.M. units) for the overall effect of stimulus presentation ("main effect") and for the effect evoked by varying the rotation of the hand drawing ("parametric effect"), separately for trials in which left or right hands were shown (LH, RH, respectively). The main effect describes the relationship between BOLD response and stimulus presentation. The parametric effect describes the relationship between BOLD response and stimulus rotation. In these regions, these effects were comparable across the two hands. The left side in the figure represents the left side of the brain (neurological convention). See also Table 2.

bilateral PPC or PMd. Thus, although behavioural performance indicated a similar strategy for both hands (i.e. mental rotation) and demonstrated an equal amount of errors, patients relied on partly different networks during mental rotation of left and right hands.

3.5. Imaging data—orientation-related effects

Following the behavioural result of larger biomechanical constraints (e.g. longer RTs for lateral than for medial angles) for right hands than for left hands, we searched for areas where cerebral activity followed the same pattern. Specifically, we looked for regions that showed a HAND (LEFT, RIGHT) × ORIENTATION (LATERAL, MEDIAL) interaction. This revealed three significant clusters (Table 4; Fig. 5). The first was centred on the right middle occipital gyrus (EBA). Only a fraction of this cluster (2.9%) overlapped with the human motion area MT/V5, which lies more superior and anterior (Eickhoff et al., 2005). The second cluster was located in the right superior occipital gyrus, extending into the dorsal intraparietal sulcus (V3A, V6, PPC). Last, we found a cluster in the left inferior occipital cortex, centred on the calcarine gyrus. Large parts of this cluster overlapped with BA 17 (25.1%) and BA 18 (25.7%). In these three regions, activity was larger for right (but not left) hand stimuli in a lateral (but not a medial) orientation. Hence, activity in these regions was specifically associated with biomechanical constraints of the right hand. The simple main effect of right hand stimuli in a lateral compared to a medial orientation revealed approximately the same regions as found in the interaction, with the addition of the left PMd (Table 4).

Next, we looked for regions where ORIENTATION-related activity (i.e. (LATERAL > MEDIAL) was present for

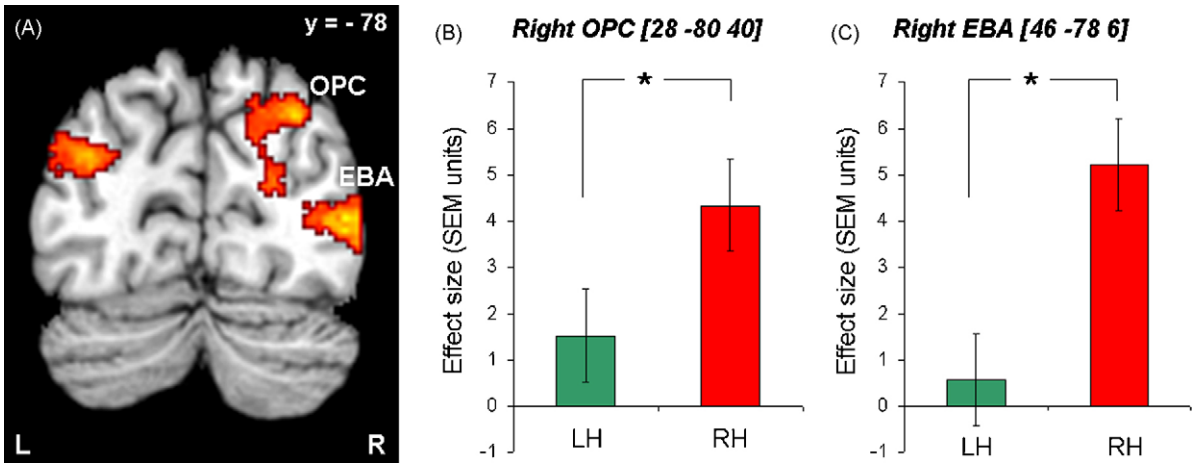

Fig. 4. Cerebral activity related to performance of the motor imagery task—between-hands differences in rotation-related effects. (A) Spatial distribution of cerebral activity that increased as a function of stimulus rotation, with stronger increases following presentation of right hands than left hands. The image shows the relevant SPM{t} (in orange, $p < 0.01$ uncorrected, random effect analysis) superimposed on a coronal section of a skull-stripped structural T1 image (Eickhoff et al., 2005). (B and C) Cerebral responses related to stimulus rotation over the right occipito-parietal cortex (OPC) and extrastriate body area (EBA), respectively. In these regions, the rotation-related effects were larger for right hands than for left hands. Other conventions as in Fig. 3. See also Table 3.

left hands but not for right hands (i.e. HAND (LEFT, RIGHT) × ORIENTATION (LATERAL, MEDIAL) interaction). We found significant activity in the right calcarine gyrus, mainly located in BA 17 (56.3% of the cluster was located in that region) and BA 18 (36.4% of the cluster was located in that region). The simple main effect of left hand stimuli in a lateral compared to a medial orientation revealed the same activity as found in the interaction (Table 4).

Last, we found no significant cerebral activity that was specifically related to mental rotation of left or right hands in a medial orientation.

3.6. Imaging data—posture-related effects

Here, we aimed to better characterize the respective roles of EBA and occipito-parietal cortex in mental rotation of the affected hand towards a lateral orientation. To do so, we post hoc investigated how these regions responded to the effect of biomechanical constraints when the affected right arm was either extended (i.e. in a neutral position between medial or lateral orientations) or flexed (i.e. in a medial position, thereby possibly further complicating simulated movements towards a lateral orientation). We found that the bilateral occipito-parietal cortex (i.e. V3A, V6, extending into the PPC) was specifically related to biomechanical constraints when the affected arm was flexed (Table 5; Fig. 6). Conversely, the right EBA responded to biomechanical constraints both when the right arm was flexed and when it was extended (Table 5; Fig. 6).

3.7. Imaging data—effective connectivity

From the contrasts mentioned above, it appeared that the right EBA and occipito-parietal cortex (including area V6) were specifically involved in mental rotation of right hands (as com-

Table 3
Cerebral activity—between-hands differences in rotation-related effects

Anatomical region	Functional region	Hemisphere	Cluster size	p-value	Local maximum			t-value
Right hand > left hand, rotation-related effect								
Middle occipital gyrus (BA's 17 and 18)	V1	L	868	<0.001	−14	−102	0	5.98
	V2				−18	−102	6	5.71
Middle temporal gyrus/	EBA	R	526	0.008	46	−78	6	4.63
Middle occipital gyrus					42	−64	14	4.37
Superior occipital gyrus		R	372	0.055*	28	−80	40	4.55
	V6				18	−84	40	3.45
	V3A				18	−86	18	3.09
Left hand > right hand, rotation-related effect								
Lingual gyrus (BA 18)/	V2	R	1166	<0.001	14	−86	−16	6.01
Calcarine gyrus (BA 17)	V1	L			−2	−82	−10	3.79

MNI stereotactic coordinates of the local maxima of regions showing activity that increased as a function of stimulus rotation, with stronger increases following presentation of right hands than left hands, and vice versa. 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 (i.e. the whole brain). The intensity threshold necessary to determine the cluster-level threshold was set at $p < 0.01$ uncorrected. EBA: extrastriate body area; V2: visual area 2; V6: visual area 6; *: borderline significance. See also Fig. 4.

Table 4
Cerebral activity—between-hands differences in responses related to biomechanical constraints

Anatomical region	Functional region	Hemisphere	Cluster size	*p*-value	Local maximum			*t*-value
Right hand, lateral > medial orientation								
Calcarine gyrus (BA 17/BA 18)	V1, V2	L	805	0.004	−10	−98	−6	6.92
Middle occipital gyrus/	EBA	R	1686	<0.001	50	−78	−2	5.05
Superior occipital gyrus	V6				24	−84	36	3.95
Dorsal intraparietal sulcus	PPC	R	293	0.003[&]	20	−64	56	3.80
Superior precentral sulcus	PMd	L	182	0.011[&]	−24	−0	60	3.79
Right hand > left hand, lateral > medial orientation								
Calcarine gyrus (BA 17/BA 18)	V1, V2	L	1304	<0.001	−12	−100	−2	8.53
Middle occipital gyrus	EBA	R	505	0.049	52	−76	−6	5.81
Superior occipital gyrus	V6	R	669	0.012	24	−84	36	3.77
Dorsal intraparietal sulcus	PPC	R	138	0.020[&]	22	−60	58	3.42
Left hand, lateral > medial orientation								
Calcarine gyrus (BA 17/BA 18)	V1, V2	R	646	0.014	14	−94	4	6.05
Left hand > right hand, lateral > medial orientation								
Calcarine gyrus (BA 17/BA 18)	V1, V2	R	941	0.001	14	−92	0	7.30

MNI stereotactic coordinates of the local maxima of regions showing activity that increased as a function of biomechanical constraints (stimuli in a lateral orientation evoked stronger responses than stimuli in a medial orientation), with stronger increases following presentation of right hands than left hands, or vice versa. There were no significant effects when stimuli in a medial orientation were compared to stimuli in a lateral orientation. Statistical inference ($p < 0.05$) was performed at the cluster-level, correcting for multiple comparisons (i.e. either the whole brain or specific volumes of interests—marked by '&'; see Section 2). The intensity threshold necessary to determine the cluster-level threshold was set at $p < 0.01$ uncorrected. EBA: extrastriate body area; V6: visual area 6. See also Fig. 5.

pared to left hands), and that these same regions were more strongly activated when the right hand needed to be mentally rotated towards a biomechanically difficult (e.g. lateral as compared to medial) orientation. If these regions contributed to motor imagery, then their activity should influence the parieto-premotor network supporting the motor imagery process (Fig. 3). We tested this hypothesis with PPI, a tool designed to assess changes in effective connectivity between cerebral regions (Friston et al., 1997). Using a SVC around the left and right PMd and PPC, we found significant activity in the left PMd that correlated with activity in area V6 ([−16 −12 58]; $t = 4.58$; $p = 0.038$, FWE corrected) and a trend towards activity in the left PMd that correlated with EBA ([−16 −4 58]; $t = 3.90$; $p = 0.065$, FWE corrected) as a function of stimulus orientation. The results indicate that right EBA and V6 increased their coupling to the left PMd when movements away from the body had to be simulated with the affected right hand. No activity was found in the right PMd or in the bilateral PPC. This finding suggests that visual information strongly influences the motor system during motor imagery of the affected hand.

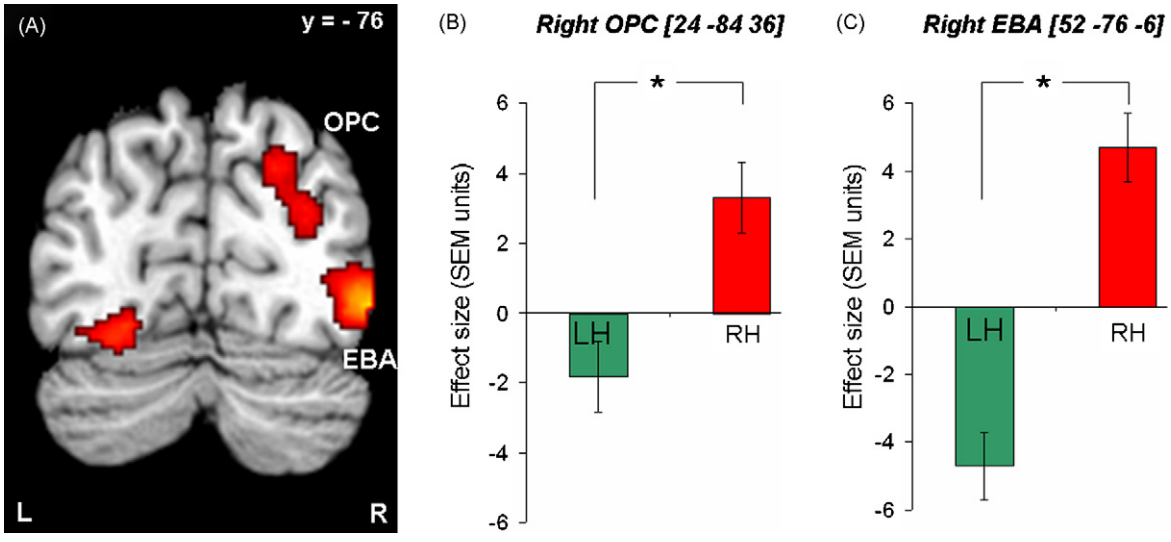

Fig. 5. Cerebral activity related to performance of the motor imagery task—between-hands differences in responses related to biomechanical constraints. (A) Spatial distribution of cerebral activity that increased as a function of biomechanical constraints (stimuli in a lateral orientation evoked stronger responses than stimuli in a medial orientation), with stronger increases following presentation of right hands than left hands. (B and C) Cerebral responses related to biomechanical constraints over the right occipito-parietal cortex (OPC) and extrastriate body area (EBA), respectively. In these regions, the effects of biomechanical constraints were larger for right hands than for left hands. Other conventions as in Fig. 4. See also Table 4.

Table 5
Cerebral activity—differences in activity related to biomechanical constraints as a function of patients' right hand posture

Anatomical region	Functional region	Hemisphere	Cluster size	*p*-value	Local maximum			*t*-value
Right hand, extended posture; lateral > medial orientation								
Calcarine gyrus (BA 17/BA 18)	V1, V2	L	249	0.005[a]	−10	−98	−6	4.69
Middle occipital gyrus	EBA	R	232	0.006[a]	50	−72	2	4.63
Right hand, flexed posture; lateral > medial orientation								
Calcarine gyrus (BA 17/BA 18)	V1, V2	L	267	0.004[a]	−12	−94	−8	5.48
Superior occipital gyrus	V6	L	690	0.01	−16	−70	48	3.83
		R	231	0.006[a]	26	−76	36	4.85
Middle occipital gyrus	EBA	R	80	0.049[a]	46	−80	−2	3.45
Right hand, extended posture; lateral > medial orientation ∩ Right hand, flexed posture; lateral > medial orientation								
Calcarine gyrus (BA 17/BA 18)	V1, V2	L	226	0.006[a]	−10	−98	−6	4.69
Middle occipital gyrus	EBA	R	80	0.049[a]	50	−78	−2	3.38
Right hand, flexed > extended posture; lateral > medial orientation								
Superior occipital gyrus	V6	L	1257	<0.001	−22	−72	34	3.84
		R	127	0.023[a]	26	−76	34	4.19

MNI stereotactic coordinates of the local maxima of regions showing activity that increased as a function of biomechanical constraints (right hand stimuli in a lateral orientation evoked stronger responses than right hand stimuli in a medial orientation), while the patients' right hand was either in an extended or in a flexed posture, and across the two postures (conjunction analysis, marked by ∩). These effects were searched within regions involved in motor imagery, i.e. showing rotation-related increases in activity following presentation of right hands (masking analysis; see Table 3 and Fig. 3), and within regions found to be modulated by biomechanical constraints of the right hand (SVC analysis, marked by 'a'; see Table 4). Statistical inference ($p < 0.05$) was performed at the cluster-level, correcting for multiple comparisons (i.e. either the whole brain or the VOI). The intensity threshold necessary to determine the cluster-level threshold was set at $p < 0.01$ uncorrected. EBA: extrastriate body area; V6: visual area 6. See also Fig. 6.

4. Discussion

In this study, we investigated whether motor imagery of the most and least affected hand relies on different functional networks in early, markedly asymmetrical PD patients. The experimental design allowed us to monitor imagery performance, showing that the patients performed the task proficiently. Furthermore, using motor imagery ensured that differences in cerebral responses between the most and least affected hand were not due to differences in motor output or sensory feedback. We found that for both hands, patients made an equal amount of errors and used the same strategy to solve the task. Motor imagery of the most affected hand was associated with increased activity in the right extrastriate body area (EBA) and occipito-parietal cortex (OPC). In the following sections, we will discuss these findings and their relevance for understanding compensatory mechanisms in PD.

4.1. Behavioural performance

Reaction times and error rates increased with increasing stimulus rotation for both hands, indicating that the patients used mental rotation to solve the task. This finding corresponds to previous studies in healthy controls (de Lange et al., 2006; Parsons, 1987, 1994) and PD patients (Dominey, Decety, Broussolle, Chazot, & Jeannerod, 1995). Crucially, in this study, we could verify that the orientation of the stimulus (lateral or medial with respect to the body axis) had an effect on the patients' behaviour, over and above mental rotation per se. This finding provides evidence that the patients imagined moving their *own* hand to the same position as the hand on the screen. Furthermore, we found that these lateralized PD patients, differently from a control group, had a specific difficulty with simulating movements away from the body and involving the affected hand. This impairment can be related to similar deficits observed during motor execution in PD patients. For instance, PD patients have greater deficits during isometric contractions and rapid single-joint elbow movements involving extensor muscles than flexor muscles (Robichaud, Pfann, Comella, Brandabur, & Corcos, 2004). These deficits have been related to a decreased tonic activation of extensor muscles (Corcos, Chen, Quinn, McAuley, & Rothwell, 1996). Our results suggest that this impairment is also present at a central level, confirming and extending previous findings on a specific deficit of PD patients in *planning* movements away from the body (Flash, Inzelberg, Schechtman, & Korczyn, 1992).

4.2. Cerebral activity

Patients performed the hand laterality judgement task by using the same cerebral structures previously shown to support imagery of hand movements in healthy controls, namely portions of the posterior parietal and dorsal premotor cortex (de Lange et al., 2006; Johnson et al., 2002; Parsons et al., 1995). These findings suggest that the patients used this parieto-premotor network during mental rotation of either hand. In addition to these common parieto-premotor responses, mental rotation of the affected (right) hand was associated with larger rotation-related activity in the right extrastriate body area (EBA), the right OPC and the left primary visual cortex (V1). Conversely, mental rotation of the unaffected (left) hand evoked larger rotation-related activity in the right V1. Given that V1 activity was systematically contralateral to the laterality of the hand on display, this cerebral activity was likely driven by marginal differences in

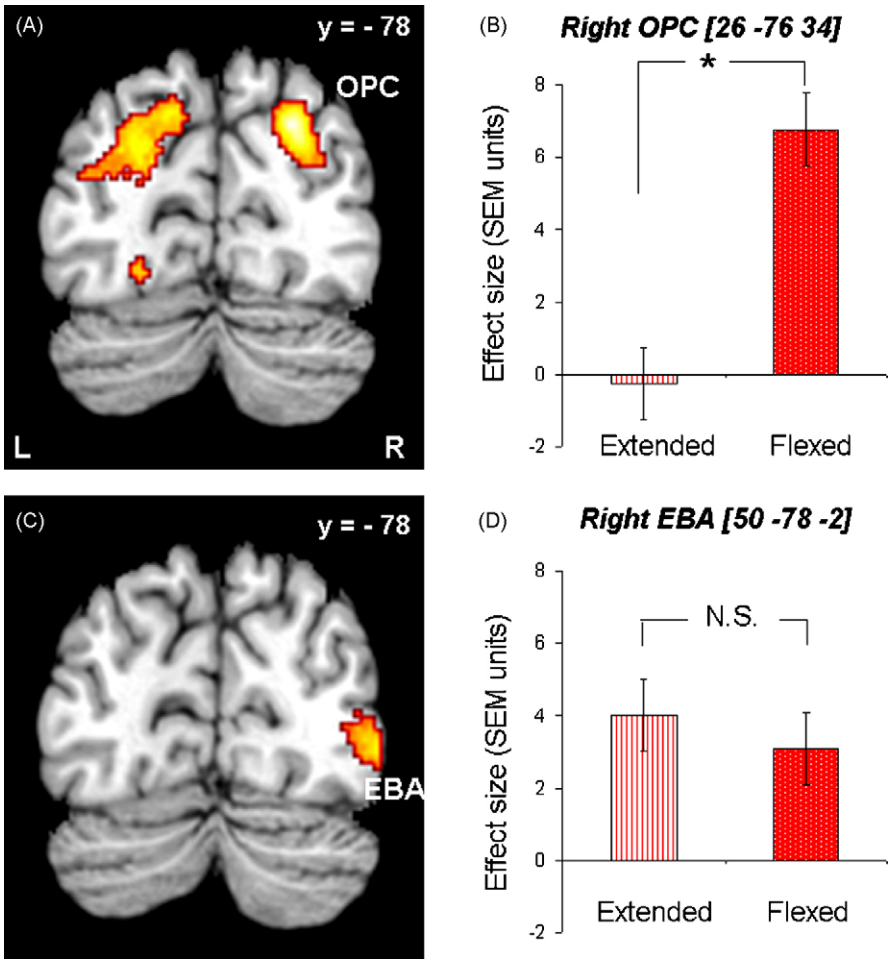

Fig. 6. Cerebral activity related to performance of the motor imagery task following presentation of right hands—differences in activity related to biomechanical constraints as a function of patients' right hand posture. (A and C) Spatial distribution of cerebral activity that increased as a function of biomechanical constraints, while the patients' right hand was either in an extended or flexed posture. Panels 'A' and 'C' show differential and common posture-related effects. (B and D) Cerebral responses related to biomechanical constraints over the right occipito-parietal cortex (OPC) and extrastriate body area (EBA), respectively. In OPC, the effect of biomechanical constraints was larger when the patients' right hand was flexed; in EBA, this effect was not influenced by the patients' own hand posture. Other conventions as in Fig. 4. See also Table 5.

visual features between the two sets of stimuli. In contrast, the differential rotation-related effect in the right EBA and OPC, being evoked only by stimuli involving the most affected hand and localized to areas involved in higher-order visual processing, is unlikely to be driven by stimulus-related differences. In addition, EBA and OPC were specifically involved in simulating movements of the affected hand towards biomechanically difficult (i.e. lateral) orientations. Moreover, the patients' own right hand posture influenced OPC, but not EBA activity. These findings further characterize the role of these two regions, as outlined below.

4.3. Extrastriate body area (EBA)

EBA has been linked to visual processing of human body parts (Downing et al., 2001), with a degree of right-hemisphere lateralization and imagery-related responses (Astafiev, Stanley, Shulman, & Corbetta, 2004; Downing et al., 2001; Saxe, Jamal, & Powell, 2006). It has been suggested that EBA may have a role in action planning and execution, even in the absence of vision of subjects' own hands (Astafiev et al., 2004). The increased EBA responses observed in this study might have been driven by an increased reliance on third-person motor imagery when dealing with biomechanically complex movements, supporting the suggestion that this region is mainly interested in processing body parts in an allocentric perspective (Saxe et al., 2006). However, this suggestion is controversial (Astafiev et al., 2004), and this interpretation implies that the patients performed an unlikely trial-by-trial switch from first- to third-person motor imagery. Rather, the enhanced EBA activity during biomechanically complex imagined movements of the affected hand may reflect the increased reliance of PD patients on a visually based body schema for the generation of the motor plan. More precisely, EBA activity could be driven by the difficulty of relating an egocentrically processed lateral hand stimulus to a body schema that is not updated by proprioceptive information, as indicated by the finding that the current hand position of the patient had no effect on EBA activity. This interpretation fits with the finding that, during pointing movements, PD patients profit more from visual information regarding their own hand

than healthy controls (Adamovich, Berkinblit, Hening, Sage, & Poizner, 2001; Keijsers, Admiraal, Cools, Bloem, & Gielen, 2005), possibly to compensate for proprioceptive impairments (Maschke, Gomez, Tuite, & Konczak, 2003).

4.4. Occipito-parietal cortex (OPC)

Besides EBA, right OPC (roughly corresponding to areas V3A and V6; Pitzalis et al., 2006) was involved in simulating movements with the most affected hand towards biomechanically difficult orientations (Fig. 5). In contrast to EBA, OPC activity was specifically enhanced when the patients had their right hand in a medial (flexed arm) position (Fig. 6). This suggests that OPC has a role in matching the hand stimulus with the *actual* hand position. The OPC activity can be related to areas V3A and V6 in the dorsal visual stream, which have a role in directing visual information to the parieto-premotor network during reaching or grasping movements (Galletti, Kutz, Gamberini, Breveglieri, & Fattori, 2003). This further supports the notion that enhanced visual processing during motor planning of the affected hand is an important phenomenon in Parkinson patients. Clinically, enhanced OPC activity might reflect the observation of improved motor functions when PD patients take advantage of visual cues (Bloem et al., 2004). It remains to be seen whether this reliance on visual information, mediated by EBA and portions of the OPC, is an early compensatory mechanism that decays as the disease progresses (Keijsers et al., 2005), and whether an increased reliance on EBA and occipito-parietal responses is a source of delayed movement initiation in PD patients.

4.5. Cerebral connectivity and compensation

When dealing with biomechanically complex imagined movements of the affected hand, the patients we tested were slower, but did not make more errors. It is possible that an increased reliance on EBA and occipito-parietal activity allowed these patients to solve the task without impairments, but ultimately a motor plan needs to be generated in premotor cortex during performance of the motor imagery task. Furthermore, it might also be argued that the EBA and occipito-parietal responses constitute collateral activities without relevance for task performance. Therefore, we tested for a compensatory role of these occipital regions by assessing whether there was (for the affected right hand) an orientation-specific relationship between their responses and the core parieto-premotor network known to be involved in the hand laterality judgement task (de Lange et al., 2005; Johnson et al., 2002). We found that, for the affected hand, EBA and OPC increased their coupling to the left PMd when movements directed away from the body had to be made. The inter-hemispheric coupling between right hemisphere visual areas and a left premotor region is likely a consequence of different hemispheric specializations in occipital and frontal areas. Namely, previous studies have reported a partial right-hemisphere functional lateralization of EBA (Astafiev et al., 2004; Downing et al., 2001; Saxe et al., 2006), and it is known that left PMd (in right-handed subjects) plays a dominant role in motor planning (and motor imagery) (de Lange et al., 2006; Haaland, Elsinger, Mayer, Durgerian, & Rao, 2004; Hlustik, Solodkin, Gullapalli, Noll, & Small, 2002). The increased functional couplings between right EBA/OPC and left PMd during the simulation of biomechanically complex movements of the affected hand point to a compensatory role of these regions in PD. The emphasis here is on compensatory activity arising from enhanced inter-regional interactions, and these findings complement previous reports on the relevance of PMd for compensating medial premotor dysfunction during motor execution in symptomatic PD patients (Haslinger et al., 2001; Samuel et al., 1997) and presymptomatic PD subjects (Buhmann et al., 2005).

4.6. Interpretational issues

In this study, we mainly performed within-patient comparisons. The lack of fMRI data from a control group limits our findings. However, there are reasons to believe that the cerebral findings are specific for PD patients. First, control subjects showed no between-hands asymmetry in imagined movements towards or away from the body (Fig. 2), supporting the specificity of the within-patients/between-hand fMRI analysis. Second, previous studies that investigated motor imagery in healthy controls have not reported differences between left and right hands in EBA or OPC, but found similar responses in the parieto-premotor network (de Lange et al., 2006; Kuhtz-Buschbeck et al., 2003).

Our findings suggest a compensatory role of EBA/OPC by means of increased couplings with the left PMd. However, the compensatory role of this circuit would need to be demonstrated by means of functional interferences, for instance with transcranial magnetic stimulation, showing that inhibition of these regions leads to visible impairments in performance.

4.7. Conclusion

We have compared the cerebral networks underlying motor imagery of the most and least affected hand in lateralized PD patients. Comparable behavioural performance of the most and least affected hand was supported by different cerebral networks. Simulating movements of the most affected hand revealed enhanced activity in the right EBA and occipito-parietal cortex, and enhanced coupling of each of these regions with the left PMd, in agreement with the notion that additional visual information processing is an important compensatory mechanism in PD.

A second relevant finding is that these patients had particular difficulties when the simulated movement involved the most affected hand and it was directed away from the body. Healthy controls did not show this between-hands asymmetry. This finding indicates that central factors contribute to the altered movements involving extensor muscles observed in PD patients.

It remains to be seen whether changes in cerebral activity and inter-regional couplings over the course of the disease can predict the appearance of overt behavioural impairments. This knowledge is crucial for developing therapeutical options aimed at exploiting these intrinsic compensatory mechanisms, in order

to postpone or even prevent symptoms in subjects in preclinical stages of PD.

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