Motor reorganization in asymptomatic carriers of a single mutant Parkin allele: a human model for presymptomatic parkinsonism

C. Buhmann,1,2 F. Binkofski,1,3 C. Klein,3 C. Büchel,1,2 T. van Eimeren,1,2 C. Erdmann,3 K. Hedrich,3 M. Kasten,3 J. Hagenah,3 G. Deuschl,4 P. P. Pramstaller5 and H. R. Siebner 1,4

1NeuroImage-Nord, Hamburg-Kiel-Lübeck, Germany, 2Department of Neurology, University Hospital Hamburg-Eppendorf, Hamburg, Germany, 3Department of Neurology, University of Lübeck, Lübeck, Germany, 4Department of Neurology, Christian-Albrechts-University, Kiel, Germany and 5Department of Neurology, Central Hospital and Department of Medical Genetics, Eurac Research, Bolzano/Bozen, Italy

Correspondence to: Hartwig Siebner, MD, Department of Neurology, Christian-Albrechts University, Schittenhelmstrasse 10, 24105 Kiel, Germany
E-mail: h.siebner@neurologie.uni-kiel.de

Mutations in the Parkin gene are the most common known single cause of early-onset parkinsonism. It has been shown that asymptomatic carriers with a single mutant allele have latent presynaptic dopaminergic dysfunction in the striatum. Here we used functional MRI to map movement-related neuronal activity during internally selected or externally determined finger movements in 12 asymptomatic carriers of a Parkin mutation and 12 healthy non-carriers. Mean response times were 63 ms shorter during internally selected movements than during externally guided movements (P = 0.003). There were no differences in mean response times between groups (P > 0.2). Compared with externally determined movements, the internal selection of movements led to a stronger activation of rostral motor areas, including the rostral cingulate motor area (rCMA), rostral supplementary motor area, medial and dorsolateral prefrontal cortices. The genotype had a significant impact on movement-related activation patterns. Asymptomatic carriers showed a stronger increase in movement-related activity in the right rCMA and left dorsal premotor cortex, but only if movements relied on internal cues. In addition, synaptic activity in the rCMA had a stronger influence on activity in the basal ganglia in the context of internally selected movements in asymptomatic carriers relative to non-carriers. We infer that this reorganization of striatocortical motor loops reflects a compensatory effort to overcome latent nigrostriatal dysfunction.

Keywords: functional magnetic resonance imaging; motor reorganization; Parkin gene; Parkinson’s disease; presymptomatic parkinsonism

Abbreviations: ANOVA = analysis of variance; BOLD = blood oxygen level-dependent; 18F-DOPA = 18F-fluorodopa; MPTP = N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; PET = positron emission tomography; PMd = dorsal premotor cortex; PPI = psycho-physiological interaction; rCMA = rostral cingulate motor area; SMA = supplementary motor area; SPMt = statistical parametric t-map; SVC = small volume correction

Received March 19, 2005. Revised May 17, 2005. Accepted May 19, 2005. Advance Access publication June 9, 2005

Introduction

Parkinson’s disease is a common neurodegenerative disorder which predominantly affects the dopaminergic system (Braak and Braak, 2000). Motor symptoms (referred to as parkinsonism) result from progressive loss of dopaminergic nigrostriatal neurons in the substantia nigra pars compacta. The characteristic motor symptoms of Parkinson’s disease become apparent when >70–80% of nigrostriatal nerve terminals have undergone degeneration (Bernheimer et al., 1973; Fearnley and Lees, 1991). It has been estimated that the presymptomatic stage of Parkinson’s disease lasts ~5 years after...
the pathological process begins (Fearnley and Lees, 1991). This long presymptomatic period indicates a substantial capacity of the motor system to compensate for the slowly progressive nigrostriatal dopamine depletion.

The presymptomatic stage of parkinsonism has been studied in primates using the neurotoxin 2,3,6-tetrahydropyridine (MPTP). In this model, low doses of MPTP were repeatedly administered over a time course of ~1 month to cause progressive striatal dopaminergic denervation (Bezard et al., 2001). The 'subacute' MPTP model revealed that progressive striatal dopamine depletion triggers several compensatory mechanisms within and outside the basal ganglia (Bezard et al., 2003a). In humans, it is virtually unknown how the motor system adapts to the slowly progressive nigrostriatal dopaminergic denervation, mainly because we have no feasible diagnostic test at hand that can be applied to the general population to identify individuals during the presymptomatic stage of Parkinson’s disease. A possible approach to tackle this issue is to study a population at risk for parkinsonism, such as family members of patients with Parkinson’s disease (Piccini et al., 1999) or carriers of a mutation that has been shown to be associated with non-carriers of a single heterozygous Parkin mutation (Hilker et al., 2001; Scherfler et al., 2004; Khan et al., 2005).

In recent years, mutations in several genes have been identified that cause familial parkinsonism in humans. Mutations in the Parkin gene (PARK2) are a frequent cause of early onset parkinsonism (Hedrich et al., 2004). Although patients may present with additional clinical features (Lohmann et al., 2003), there is a substantial phenotypic overlap between Parkin-associated parkinsonism and idiopathic Parkinson’s disease without Parkin mutations (Klein et al., 2000; Khan et al., 2003). Using positron emission tomography (PET), we have demonstrated a reduction of presynaptic 18F-fluorodopa (18F-DOPA) uptake in the dorsal putamen in asymptomatic carriers of heterozygous Parkin mutations (Hilker et al., 2001). This finding has recently been confirmed in another population (Khan et al., 2002, 2005; Scherfler et al., 2004) indicating a moderate chronic dysfunction of the nigrostriatal dopaminergic pathway in this condition that is fully compensated for by the motor system. Therefore, asymptomatic carriers of heterozygous Parkin mutations represent an ideal study population to investigate the functional consequences of chronic dopaminergic dysfunction in vivo.

In the present study, we used blood oxygen level-dependent (BOLD) functional MRI to map motor reorganization in response to a subclinical dysfunction of striatal dopaminergic innervation in asymptomatic carriers of a single heterozygous mutation in the Parkin gene and healthy controls without Parkin mutation. We chose a sequential motor task because this type of motor task has been shown to activate motor areas involved in motor execution and programming (Samuel et al., 1997; Catalan et al., 1999; Sabatini et al., 2000). More importantly, sequential motor tasks have been shown to be particularly well suited for studying compensatory mechanisms in the presence of nigrostriatal dopaminergic dysfunction. When patients with Parkinson’s disease perform sequential manual movements, they show a relative increase in activity in lateral premotor and parietal areas (Samuel et al., 1997; Catalan et al., 1999; Sabatini et al., 2000) as well as in the anterior cingulate cortex (Catalan et al., 1999; Sabatini et al., 2000) compared with healthy controls. These relative increases have been interpreted as a compensatory mechanism to counterbalance defective striatofrontal motor circuits (Samuel et al., 1997; Sabatini et al., 2000). In analogy to symptomatic Parkinson’s disease, we reasoned that a similar set of motor areas would exhibit compensatory overactivity in asymptomatic carriers of a single heterozygous Parkin mutation to cope with chronic nigrostriatal dysfunction.

We contrasted internally selected with externally guided movements because patients affected with Parkinson’s disease exhibit the greatest motor deficits when external cues are absent (i.e. when movement must be internally selected) (Georgiou et al., 1994). Accordingly, external cues can markedly improve movement performance (Georgiou et al., 1994). Moreover, patients with symptomatic Parkinson’s disease show attenuated neuronal activity in the rostral supplementary motor area (SMA) and right dorsolateral prefrontal cortex when the patients choose the onset or type of movement (Playford et al., 1992; Jahanshahi et al., 1995). Given this reliance of patients with Parkinson’s disease on external cues, we predicted that in asymptomatic mutation carriers, adaptive changes in the motor system would be evident during internally selected movements.

In terms of effective motor connectivity, we hypothesized that rostral premotor areas change their influence on neuronal activity in executive motor areas (e.g. the caudal premotor and primary motor areas) as well as the motor basal ganglia (i.e. posterior putamen) when movements are internally selected. This context-dependent modulation in coupling was expected to be altered in asymptomatic carriers relative to non-carriers of a single Parkin mutation.

Methods

Participants and methods

Twelve asymptomatic individuals (mean age 36 ± 7 years, 7 males) with a single mutation in one allele of the Parkin gene participated in the study. All asymptomatic carriers were recruited from a large kindred (Family LA) from northern Italy with familial, adult-onset parkinsonism caused by two mutations in the Parkin gene. Seven individuals had a large deletion of exon 7 and adjacent intronic regions (designated MUT1), whereas the remaining individuals carried a 1 bp deletion in exon 9 (designated MUT2). Details of the genetic analysis of the core branch of Family LA are presented elsewhere (Klein et al., 2000; Hedrich et al., 2001). Eight of the twelve asymptomatic carriers of a single mutant Parkin allele had previously been examined with PET showing a small, but statistically significant decrease of 18F-DOPA uptake in the putamen (Hilker et al., 2002).

A group of 12 healthy age-matched volunteers (mean age 36 ± 6 years, 9 males) without a mutation in the Parkin gene were studied as controls and were recruited from a departmental register of
Activity of Daily Living Score. Only individuals with normal Mini-Mental State Examination Score and the Schwab-England evaluation included the Unified Parkinson Disease Rating Scale, the Parkin mutation versus individuals without a mutation in the Parkin gene) and within-subject factors task (two levels, internally cued versus externally cued movements) and order of measurements (two levels, first, second, third, fourth and fifth blocks during the functional MRI run). The Greenhouse–Geisser method was used to correct for non-sphericity. P-values of <0.05 were considered significant.

MRI data acquisition and analyses
Subjects lay supine in the MR scanner. Visual cues (i.e. depictions of the palm of the right hand with and without red dots) were projected onto a screen in front of the MR scanner and participants could see the instructions through a mirror mounted on the head coil. The head was fixated by firm foam pads. The right forearm was slightly supinated. Both arms were supported by foam pads and cushions to favour muscle relaxation of proximal limb muscles.

Scanning was performed on a 1.5 T MR scanner (Symphony; Siemens, Erlangen, Germany) equipped with a standard quadrature head coil. For functional MRI, 30 contiguous axial slices were acquired every 3 s covering the rostral two-thirds of the brain including the basal ganglia, thalamus and the upper cerebellum (4 mm thickness, 1 mm gap), using a gradient-echo echo-planar sequence (TR = 3000 ms, TE = 40 ms, flip angle = 90°, matrix = 64 × 64 voxels, field of view = 256 × 256 mm2). One hundred and sixty volumes of the whole brain were acquired per session. A whole-brain structural MRI dataset was acquired for anatomical reference. We used a three-dimensional T1-weighted FLASH sequence (TR = 15 ms, TE = 5 ms, 192 axial slices, voxel size = 1 × 1 × 1 mm3, axial field of view = 256 × 256 mm2).

Images were processed and analysed using SPM2 software (Wellcome Department of Imaging Neuroscience, Institute of Neurology, University of London, London, UK; http://www.fil.ion.ucl.ac.uk/spm). The first two scans of each session were discarded to allow for steady-state magnetization. The remaining images were realigned to the first image and spatially normalized to a standard EPI template. The normalized images were spatially smoothed with a Gaussian kernel of 12 mm at full-width half-maximum (FWHM) to reduce intersubject differences in anatomy and enable the application of the Gaussian random field theory.

In a first analysis, we evaluated relative differences in movement-related activity between motor tasks and groups. The second set of analyses focused on changes in effective connectivity depending on the genotype of the participants.

Categorical analysis
For individual subject analysis (first level), a general linear model was specified using separate regressors for each sequential motor task. Each regressor was convolved by a haemodynamic response function. Regression coefficients (parameter estimates) for all
regressors were estimated in a subject-specific fixed effect model (Friston et al., 1995). Low frequency drifts in BOLD signal were removed by a high pass filter with a cut-off of 120 s. Using appropriate linear contrasts, contrast images of interest were selected for each participant, including BOLD signal increases associated with each motor task as well as relative differences in BOLD signal between motor tasks.

At a second level, random effects models were used for between-group differences in movement-related brain activations. For each contrast, the contrast images from the first level were entered into a second level t-test, to create statistical parametric t-maps (SPMt). We used a one-sample t-test for within-group analysis (df = 11) and a two-sample t-test for between-groups comparisons (df = 22). A statistical threshold of \( P < 0.05 \) was applied for all analyses. P-values were corrected for multiple non-independent comparisons across the entire brain volume. Correction for multiple testing was performed at a cluster level using an extent threshold of \( P < 0.01 \) (uncorrected). For each cluster, stereotactic coordinates \((x, y, z)\) in mm refer to local maxima and \( t_{\text{max}} \) to the corresponding t-value.

Effective connectivity analysis

For connectivity analysis, we employed the psychophysiological interaction (PPI) method described by Friston et al. (1997). 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. Although the psychological factor (e.g. genotype) entered explicitly in the model, the effect of movement entered vicariously as the principal cause of variance in the index region. 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 depending on the mode of movement selection or genotype.

Connectivity analyses used the left dorsal premotor cortex (PMd) and the rostral cingulate motor area (rCMA) as index areas because these areas showed increased activity during internally selected movements in asymptomatic carriers. The index area was defined by the first eigentime series of all voxels within a 6 mm radius sphere centred on the maximal activation in the left PMd and rCMA that showed a relative increase in movement-related BOLD signal during internally selected movements in asymptomatic carriers. It is worthwhile to recall that the PPI analysis provided complementary insights into the impact of genotype on the movement-related activity patterns. Although a categorical analysis was used to pinpoint brain areas showing increased movement-related activity depending on the genotype, the PPI analysis allowed us to characterize how the carrier status and the motor task modified the coupling strength between these overactive motor areas and other components of the motor network (Friston et al., 1997).

Between-group comparisons of PPIs were performed at the second level. For each index area, individual PPI contrast images were entered into a two-sample t-test to test for commonalities and differences in effective connectivity between groups.

Based on our a priori hypothesis, we considered only those voxels in the frontal motor cortex and the basal ganglia that showed a consistent activation during the INT and EXT task at a corrected \( P \)-value of \( < 0.05 \). For these voxels, the statistical threshold was set to \( P < 0.05 \) after small volume correction (SVC) for multiple non-independent comparisons. The SVC procedure included all voxels within a 15 mm radius sphere centred on the maxima of the main effect of movement (Genovese et al., 2002).

Results

Behaviour

All participants reported that they could perform both thumb-to-finger opposition tasks without any problem. During the INT task, participants made no errors (i.e. no omissions). During the EXT task, the mean number of false responses was \( 1.0 \pm 1.2 \) in asymptomatic non-carriers and \( 0.9 \pm 1.5 \) in healthy non-carriers, and the error rate did not differ between groups \((t = -0.11, df = 22, \text{n.s.})\). Mean response times of asymptomatic carriers of a single mutant Parkin allele and healthy controls without Parkin mutation are illustrated in Fig. 1A. Repeated measures ANOVA revealed no between-group difference in mean response times and no group-by-task interaction. There were also no differences in mean response times among blocks of measurements, indicating a stable level of motor performance throughout the experiment. In both groups, mean response times were 63 ms shorter for the INT task compared with the EXT task \((F = 12.39, P = 0.003)\).

Functional MRI

Both thumb-to-finger opposition tasks caused an increase in BOLD signal (as an index of regional synaptic activity) in a widespread motor network implicated in the generation of right-hand movements (Table 1). The type of cue had a significant effect on task-related BOLD signal changes (Table 2). Selecting one of four possible movements (i.e. the INT task) led to a stronger increase in BOLD signal in the rostral part of the rCMA and adjacent rostral SMA compared with the externally guided motor task (Fig. 1C). Also, the medial and dorsolateral prefrontal areas showed increased activity during free selection of movements relative to externally determined movements in both groups (Fig. 1B). Conversely, there were stronger activations in posterior visual areas when finger movements were specified by visual cues (Fig. 1B).

We found no movement-related overactivity of motor areas in asymptomatic carriers when both motor tasks were considered together. However, movement-related activity in two frontal motor areas showed a significant interaction between motor task and genotype. Compared with healthy non-carriers, asymptomatic carriers showed a greater relative increase in BOLD signal in the left PMd and right rCMA when movements were internally selected (Fig. 2). The cluster in the rCMA had its local maximum at MNI coordinates \( x, y, z = 12, 15, 45 \) \((t_{\text{max}} = 4.4, df = 22)\) and extended into the adjacent right PMd and rostral SMA (Fig. 2). In the left PMd, there were two distinct maxima showing a relative increase in activity during the INT task in asymptomatic carriers. The first maximum was located in the rostroventral part of the PMd \((x, y, z = -39, 6, 42, t_{\text{max}} = 4.8, df = 22)\) whereas the second maximum was found in the caudodorsal part of the PMd \((x, y, z = -24, -12, 51, t_{\text{max}} = 3.5, df = 22)\).

None of the cortical and subcortical motor areas showed a relative underactivation in asymptomatic carriers, even when both motor tasks were considered separately. The only region
that showed a relative reduction in movement-related activity in asymptomatic carriers of a single mutant Parkin allele was the posterior cingulate cortex \((x, y, z = 9, 39, 36, t_{\text{max}} = 6.1, df = 22)\). The decrease in activity in the posterior cingulate cortex was not influenced by the mode of movement selection.

**Effective connectivity**

To further characterize motor reorganization, we used the overactive areas in the left PMd and right rCMA as seed areas and performed an analysis of effective connectivity to assess task-dependent changes in coupling between the seed areas and other motor areas. In the context of internal movement selection, activity in the left PMd increased its influence on the contralateral right PMd relative to externally guided movements (Fig. 3A). Internal selection was also associated with an increased contribution of the rCMA to activity in the left primary sensorimotor area as well as left and right PMd (Fig. 3B). These context-dependent changes in coupling with lateral premotor and primary sensorimotor areas were comparable in carriers and non-carriers of a single mutant Parkin allele.

However, task-dependent changes in coupling also depended on the Parkin genotype (Fig. 3). In the context of internally selected movements, asymptomatic carriers of a single mutant Parkin allele showed a decrease in connection strength between the left PMd and right caudal SMA compared with healthy non-carriers \((x, y, z = 9, -18, 75, t_{\text{max}} = 4.5, df = 22, \text{Fig. 3A})\). In contrast, the rCMA had a stronger influence on activity in the left posterior putamen in the context of internally selected movements relative to healthy non-carriers \((x, y, z = -31, -12, -5, t_{\text{max}} = 3.7, df = 22, \text{Fig. 3B})\). Asymptomatic carriers also showed a non-significant trend towards an increased coupling between the rCMA and the left anterior putamen \((x, y, z = -27, 12, 12, t_{\text{max}} = 3.3, df = 22)\), and the right anterior putamen \((x, y, z = 24, 12, 6, t_{\text{max}} = 3.3, df = 22)\) in the INT task.

**Discussion**

To our best knowledge, this is the first study to demonstrate functional reorganization of the motor system in asymptomatic individuals with a latent nigrostriatal dysfunction. Only when movements were internally selected, we found an over-activation of the left PMd and rCMA in asymptomatic carriers...
of a single mutant Parkin allele relative to healthy non-carriers. In addition, there were genotype-dependent changes in functional coupling between these overactive areas and other motor areas. In asymptomatic carriers, activity in the rCMA had a stronger influence on activity in the basal ganglia during internally selected movements. We attribute these changes in movement-related activity and coupling to a large-scale motor reorganization which compensates for the latent nigrostriatal dysfunction in these asymptomatic carriers. It is noteworthy, that nigrostriatal dysfunction had been previously demonstrated using 18F-DOPA PET in 8 of the 12 asymptomatic mutation carriers who participated in our study (Hilker et al., 2001, 2002).

### Changes in movement-related activity

In asymptomatic carriers of a single mutant Parkin allele, the left PMd and rCMA were overactive during internally selected movements.
but not externally cued finger movements. This pattern of movement-related overactivity is in good agreement with previous functional imaging studies on symptomatic patients affected by Parkinson’s disease. A relative overactivity of the left PMd and rCMA has previously been observed when unmedicated patients with Parkinson’s disease performed a sequential motor task (Catalan et al., 1999; Sabatini et al., 2000). Since the rostral PMd and the cingulate motor area have been shown to be implicated in the voluntary guidance of actions in healthy individuals (Picard and Strick, 2001; Rowe et al., 2002), overactivity in these areas has been interpreted as an attempt to compensate for the underlying dysfunction in the basal ganglia. The present findings support this interpretation by showing that these areas ‘work harder’ in individuals with a subclinical dysfunction of the basal ganglia.

It is noteworthy, that the influence of the genotype on movement-related activity critically depended on the mode of movement selection. Overactivity was evident only during the performance of internally selected but not externally determined finger movements. Behavioural and functional imaging studies on symptomatic Parkinson’s disease have shown that internaly selected movements are particularly affected by a dysfunction of the basal ganglia (Playford et al., 1992; Georgiou et al., 1994; Jahanshahi et al., 1995).

### Table 2 Main effect of motor task (both groups)

<table>
<thead>
<tr>
<th>Region</th>
<th>Side</th>
<th>Extent: no. of voxels</th>
<th>Peak change</th>
<th>T-value</th>
<th>Coordinates (mm)</th>
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<td>INT-task minus EXT-task</td>
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<tr>
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<td>18 36</td>
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<tr>
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<td>15 54</td>
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<tr>
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<tr>
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<td>5.0</td>
<td>39</td>
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<tr>
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<td>4.0</td>
<td>−63</td>
<td>−12 18</td>
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<td>EXT-task minus INT-task</td>
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<td>Fusiform gyrus</td>
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<td>−21</td>
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<tr>
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<td>6.4</td>
<td>−39</td>
<td>−66 −3</td>
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<tr>
<td>Middle temporal gyrus</td>
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<td>70</td>
<td>3.7</td>
<td>54</td>
<td>−3 −15</td>
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*P < 0.05, corrected at the cluster level. Brain regions showing significant differences in regional BOLD signal between the two motor tasks: (INT task > EXT task) and (EXT task > INT task); R = right; L = left; M = mesial.

**Fig. 2** The Z-score maps delineate voxels with relative overactivity during internally selected movements in asymptomatic carriers of a single mutant Parkin allele relative to healthy non-carriers (*P* < 0.05, corrected at the cluster level). Asymptomatic carriers showed increased activity in the rCMA and adjacent rostral SMA as well as the left PMd. The sagittal, coronal and axial Z-score maps are superimposed on the T1-weighted MRI template implemented in SPM2 and the corresponding stereotactic coordinate (in mm) is given for each map.
In previous neuroimaging studies, healthy volunteers showed an increase in activity in the rCMA and adjacent rostral SMA during self-initiated finger movements relative to externally triggered movements (Jahanshahi et al., 1995; Jenkins et al., 2000). In the present study, the motor tasks differed in terms of internal selection of the type of movement rather than internal pacing of movement onset as movements were always paced by a visuospatial cue. We found increased activity in the rCMA during internal movement selection (i.e. the INT task) compared with externally determined movements. Since each trial required a fresh deliberate choice between four possible actions, the INT task was more demanding in terms of action selection and conflict monitoring. The increased activity of the rCMA during internally paced movements (Jahanshahi et al., 1995; Jenkins et al., 2000) and internally selected movements (present study) is in good concordance with previous neuroimaging studies on healthy volunteers showing a consistent activation of the rCMA in motor tasks with a high level of cognitive control (Botvinick et al., 1999; MacDonald et al., 2000; Kerns et al., 2004). Since asymptomatic mutation carriers showed increased activation of the rCMA during the internal selection of movements, it is tempting to speculate that asymptomatic mutation carriers employed a higher level of cognitive control during internally guided actions.

Previous neuroimaging studies on Parkinson’s disease have consistently shown impaired movement-related activation in distinct frontal motor areas in patients being off dopaminergic medication (Playford et al., 1992; Jahanshahi et al., 1995; Samuel et al., 1997; Buhmann et al., 2003). For instance, the rostral SMA or right dorsolateral prefrontal cortex showed deficient activation during internal selection of movement onset (Jahanshahi et al., 1995) or the type of movement (Playford et al., 1992) in unmedicated patients with Parkinson’s disease. This relative hypoactivity in frontal motor areas could be at least partially reversed by dopaminergic therapy (Jenkins et al., 1992; Haslinger et al., 2001; Buhmann et al., 2003). In contrast to symptomatic patients with Parkinson’s disease, asymptomatic carriers of a single mutant Parkin allele showed no relative decreases in frontal motor areas. In fact, the only area in which movement-related activity was reduced was located in the posterior cingulate cortex. It is possible that in the present study, nigrostriatal dopamine depletion was below the threshold causing impaired movement-related activation of frontal motor areas in asymptomatic mutation carriers. Alternatively, a normal level of activation may be maintained by adaptive mechanisms which facilitate movement-related activity in frontal motor areas and effectively compensate for deficient cortical activation via the corticobasal ganglia–thalamocortical motor loop. Whatever the cause, our findings lend further support to the notion that the clinical manifestation of parkinsonism ultimately results from a failure of compensatory mechanisms to maintain a sufficient level of movement-related activity in frontal motor areas (Bezard et al., 2003b).

We argue that subclinical nigrostriatal dysfunction hampered motor control when movements relied on internal representations, calling compensatory mechanisms into action. In contrast, sequential movements guided by visuospatial cues did not rely on intact function of the basal ganglia and, therefore, induced no compensatory activity in the motor network.

We deliberately chose a relatively simple motor task which all participants could easily perform. In fact, error rates were very low and response times were matched between groups and were stable throughout the functional MRI session. Given the normal behaviour, differences in movement-related activity between groups cannot be attributed to altered task performance in asymptomatic carriers. It is worthwhile to recall that the left PMd and rCMA were consistently activated during internally selected movements in both groups. Therefore, we infer that relative overactivity of the left PMd and rCMA reflects true neuronal reorganization within the pre-existing motor network (Price and Friston, 1999).
Changes in functional coupling

Analysis of effective connectivity revealed that during internally selected finger movements, the rCMA increased its influence on activity in the left PMd as well as in the left premotor sensorimotor cortex compared with externally guided movements. The left PMd as well as the rCMA also showed stronger coupling with the right PMd when movements were internally selected. The stronger influence of activities in PMd and rCMA on activity in other premotor and primary sensorimotor areas indicates that the two areas showing ‘overactivity’ in asymptomatic mutation carriers were relevant to the internal selection of right-hand movements. These increases in coupling were comparable in magnitude for both asymptomatic carriers and healthy non-carriers, indicating that this pattern of cortico-cortical effective connectivity was not altered in asymptomatic carriers relative to healthy non-carriers. This implies that compensatory overactivity in the left PMd and rCMA could draw on a normal pattern of effective connectivity between these areas and lateral frontal motor areas.

This is not to say that the carrier status did not shape the connectivity pattern. On the contrary, task-dependent changes in connection strength were influenced to some extent by the genotype both in the left PMd and rCMA. For instance, the left PMd had less influence on activity in right caudal SMA in asymptomatic carriers when movements were internally selected. Attentional modulation of effective connectivity between the prefrontal, premotor cortex, and the SMA has been shown to be deficient in unmedicated patients with Parkinson’s disease (Rowe et al., 2002). The relative reduction in the connection strength between the left PMd and the right caudal SMA during internally selected movements indicates that asymptomatic carriers of a single mutant Parkin allele already show some degree a context-specific functional disconnection between lateral and mesial premotor frontal areas.

Although the coupling between the left PMd and caudal SMA was weaker, the rCMA showed stronger coupling with the sensorimotor compartment of the basal ganglia (i.e. the posterior part of the putamen) when asymptomatic carriers produced internally cued movements. This increase in the connection strength suggests that, in asymptomatic mutation carriers, the rCMA counteracted nigrostriatal dysfunction by increasing the corticostriatal excitatory input to the sensorimotor compartment of the basal ganglia. Since the majority of corticostriatal projections onto the posterior part of the putamen originate in the primary sensorimotor cortex, adjacent premotor cortex and the caudal SMA (Yeterian and Van Hoesen, 1978; Sehlev and Goldman-Rakic, 1985; Lehericy et al., 2004), we infer that the increased influence of the rCMA in terms of effective connectivity was mediated through caudal frontal motor areas using the primary sensorimotor cortex or PMd as a relay station.

We conclude that in asymptomatic carriers of a single mutant Parkin allele, the preexisting nigrostriatal dysfunction triggers a large-scale reorganization within the human motor system. Our findings extend recent studies in monkeys that have disclosed several compensatory mechanisms within the corticobasal ganglia–thalamocortical circuitry during the presymptomatic period of MPTP-induced parkinsonism (Bezard et al., 2003b; Escola et al., 2003; Fessigolone et al., 2003). The need for a better understanding of early presymptomatic parkinsonism is driven by the evolution of putative neuroprotective agents (Stocchi and Olanow, 2003). Functional neuroimaging of asymptomatic individuals carrying mutations that are associated with familial parkinsonism provides a unique opportunity to advance our understanding of the presymptomatic phase of parkinsonism in humans. This may have implications for a presymptomatic diagnosis of Parkinson’s disease and for developing novel therapeutic strategies.

Acknowledgements

This study was supported by grants from the Deutsche Forschungsgemeinschaft (KL 1134/2-2 and 3-1). NeuroImage Nord is supported by structural grants from the DFG and BMBF. Ch.B., F.B., C.K. and H.R.S. are supported by the VolkswagenStiftung. C.A.B. was supported by the BMBF-Kompetenzzentrum Parkinson (grant No 0191 0401).

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