Event-related functional magnetic resonance imaging in Parkinson’s disease before and after levodopa

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Summary
Event-related functional MRI (fMRI) was used to study blood oxygen level dependent cortical signal changes associated with volitional limb movements off and on levodopa in Parkinson’s disease. Eight patients with early stage akinetic Parkinson’s disease and eight healthy volunteers underwent three functional imaging runs (high speed echo planar imaging with 600 scans/run) while performing paced single joystick movements in a freely chosen direction every 7–15 s. The non-magnetic joystick was linked to a monitoring system for on-line registration of performance parameters along with timing of the pacing tones and fMRI-scan acquisition parameters. This allowed correlation of movement onset, i.e. event-onset, to scanning time. We repeated the scanning procedure in the Parkinson’s disease patients when akinesia improved 30 min after oral levodopa. Compared with the control group, patients both off and on levodopa showed movement-related impaired activation in the rostral supplementary motor area and increased activation in primary motor cortex (M1) and the lateral premotor cortex bilaterally. Levodopa led to a relative normalization of the impaired activation in the mesial premotor cortex and decreased signal levels in M1, lateral premotor and superior parietal cortex. We conclude that levodopa improves impaired motor initiation in the supplementary motor area and decreases hyperfunction of lateral premotor and M1 associated with Parkinson’s disease during simple volitional movements.

Keywords: FMRI; event-related; Parkinson’s disease; levodopa; blood oxygen level dependent

Abbreviations: AC = anterior commissure; BA = Brodmann area; BOLD = blood oxygen level dependent; EPI = echo planar imaging; fMRI = functional MRI; M1 = primary motor cortex; SMA = supplementary motor area

Introduction
Mesial premotor cortex activity is highly associated with basal ganglia function via the basal ganglia–thalamo-premotor loop (Schell and Strick, 1984; Alexander et al., 1990; DeLong, 1990). The dopaminergic deficit in Parkinson’s disease is thought to result in an excessive net-inhibition of thalamo-frontal/premotor projections. Additionally, direct dopaminergic projections from the mesolimbic system (ventrotegmental area) to the (pre)frontal cortex are thought to be affected in Parkinson’s disease. The supplementary motor area (SMA), in particular its rostral part by connections to the prefrontal cortex, has been shown to be active during internally generated, automated movements, movement preparation, movement sequencing or performance of complex movements (Roland et al., 1980; Goldberg, 1985; Passingham, 1987; Deiber et al., 1991; Mushiake et al., 1991; Halsband et al., 1993; Picard and Strick, 1996; Tanji and Shima, 1996; Boecker et al., 1998). Imaging studies using PET (Jenkins et al., 1992; Playford et al., 1992; Jahanshahi et al., 1995; Samuel et al., 1997a), SPECT (Rascol et al., 1992, 1994) and a recent fMRI study (Sabatini et al., 2000) showed underactivity in the mesial premotor and prefrontal areas in Parkinson’s disease patients off levodopa compared with healthy volunteers. Underactivity within mesial premotor structures due to the dopamine deficit has, therefore, been postulated to be a functional substrate underlying akinesia in Parkinson’s disease.
On the other hand, lateral premotor, parietal as well as cerebellar structures have been found to be overactive during sequential ongoing movements in more recent imaging studies (Rascol et al., 1997; Samuel et al., 1997a; Catalan et al., 1999; Hanakawa et al., 1999; Sabatini et al., 2000). This overactivity within cerebellar–parieto-lateral premotor loops has been suggested to compensate for the mesial premotor/prefrontal deficit. This finding has been linked to the clinical phenomenon of improved movement performance under guidance of external, especially visual, cues (Georgiou et al., 1994; Martin et al., 1994).

Parallel to the improvement in akinesia, the impaired motor activation in the mesial premotor cortex can be partially normalized after levodopa or apomorphine medication (Jenkins et al., 1992; Rascol et al., 1992, 1994), with high-frequency subthalamic nucleus stimulation (Limousin et al., 1997; Ceballos-Baumann et al., 1999), after pallidotomy (Ceballos-Baumann et al., 1994; Grafton et al., 1995; Samuel et al., 1997b) and mesencephalic grafting (Ceballos-Baumann et al., 1996). However, to date it is unclear what occurs with movement-associated increased activation in the lateral premotor (Samuel et al., 1997a; Catalan et al., 1999; Hanakawa et al., 1999; Sabatini et al., 2000) and primary motor cortex (M1) (Sabatini et al., 2000) when akinesia improves and how dopaminergic replacement therapy modulates cortical dysfunction in Parkinson’s disease.

Measurement of blood oxygen level dependent (BOLD) (Kwong et al., 1992; Ogawa et al., 1992) signal increases with functional MRI (fMRI) offers the opportunity to analyse the functional motor network in Parkinson’s disease and its pharmacological modulation with high spatial and temporal resolution. In contrast to PET or block-design fMRI, which both average movement-related cortical activation over long time periods of up to 1.5 min, event-related fMRI offers the advantage of enabling investigation of BOLD signal increases related to single movements (Buckner et al., 1996; Josephs et al., 1997; Buckner, 1998; Rosen et al., 1998; Josephs and Henson, 1999) and avoids the problem of long acquisition times which may confound PET and block-design fMRI data with processes not related to movement. Event-related fMRI may, therefore, reflect more precisely movement-related cerebral activity.

Here we report for the first time event-related fMRI of single volitional movements in early stage Parkinson’s disease patients. In addition, we investigated the modulatory effect of levodopa on the activation pattern. In order to be in a better position to compare our results with previous PET work, we chose the joystick activation paradigm used in several PET studies on Parkinson’s disease akinesia (Playford et al., 1992) and its modulation by treatment (Jenkins et al., 1992; Ceballos-Baumann et al., 1994, 1996; Brooks et al., 1997; Limousin et al., 1997; Samuel et al., 1997b; Ceballos-Baumann et al., 1999) and adapted it to event-related fMRI. Based on prior findings, we hypothesized underactivity of mesial premotor structures in patients off levodopa and a compensatory increase of lateral premotor and M1 activity. This effect should be partially reversed by dopaminergic stimulation.

Material and methods
Subjects
We investigated eight healthy volunteers (four male, four female, mean age 54.4 ± 5.0 years) and eight patients with the clinical diagnosis of Parkinson’s disease (seven male, one female, mean age 60.8 ± 7.6 years) according to the diagnostic criteria of the UK Parkinson’s Disease Society Brain Bank (Gibb and Lees, 1988). All subjects were strictly right-handed following the criteria of the Edinburgh inventory (Oldfield, 1971). Clinical and neurological examination in healthy volunteers was normal and none of them had any history of neurological disease. Akinesia was the leading symptom and Parkinson’s disease was dominant on the right side in every patient. None of the patients had a major resting tremor. Only patients showing significant clinical improvement following the oral application of levodopa were selected. Of the eight patients, four were constantly pretreated with levodopa or a dopamine agonist and four did not receive any drug treatment (clinical details of the patients are summarized in Table 1). Patients were examined while fasting, after at least 12 h withdrawal of any symptomatic treatment (cabergoline had to be stopped at least 4 days before). Thus, only patients with moderate Parkinson’s disease, mean Hoehn & Yahr 1.5 were selected (Hoehn and Yahr, 1967). Every patient was pretreated with domperidone (Motilium™ suspension; Byk Gulden, Konstanz, Germany) for 2 days prior to examination. In the middle of the imaging session, patients ingested 250 mg levodopa/benserazide (Madopar LT™; Roche, Grenzach-Wyhlen, Germany) in solution using a plastic tube. All patients were clinically examined before and after scanning, i.e. before (off) and after (on) administration of levodopa, according to the UPDRS [Unified Parkinson’s Disease Rating Scale (Fahn et al., 1987)] motor score and the Hoehn & Yahr ranking scale. Mean UPDRS motor score prior to levodopa application was 15.75 ± 6.26. The study protocol was approved by Ethikkommission der Medizinischen Fakultät der Technischen Universität München. Every subject gave written informed consent prior to examination.

Task
Movements were performed with the right hand using an in-house built non-magnetic joystick. A computer generated pacing tone with a randomized inter-tone interval of 7–15 s, asynchronous to fMRI scanning, was applied via earphones (EAR-Link 3a Cabot Safety, Indianapolis, Ind., USA). Subjects were instructed to keep their eyes closed and to answer each tone with a single joystick movement in one of four possible main directions, starting from and returning to the neutral position. Additionally they were told to avoid repetitions (one or two repetitions were allowed) or building fixed sequences of movement directions.
**Data acquisition**

fMRI measurements were performed on a 1.5 T Philips Gyroscan NT scanner (Hamburg, Germany) equipped with the PT 6000 upgrade and a circular polarized birdcage head coil. A forehead restraining strip and various foam pads served for head fixation. Based on our hypothesis, for the functional scans, six contiguous apical slices parallel to the intercommissural line were selected with a slice thickness of 0.6 cm. Thus a volume of $23 \times 23 \times 3.6$ cm was acquired, covering M1 and parietal as well as frontal motor association cortex. A high-speed echo planar imaging (EPI) sequence was applied for the functional scans. The acquisition parameters were: TR 500 ms, TE 50 ms, matrix = $64 \times 64$ pixels, flip angle = 50°. We performed three functional runs (600 scans/run, run-time = 300 s) for healthy volunteers and six functional runs for patients (three runs before and three runs after levodopa medication with 600 scans each). Additionally, a whole brain EPI image (slice thickness 0.6 cm) was recorded before and after each functional scan. For high resolution anatomical reference, a whole brain 3D T1-weighted data set was acquired for every subject after the first three functional runs.

The joystick was linked to a LabView™-based electrophysiological monitoring system which allowed the precise on-line registration of performance parameters of each single joystick movement along with the trigger tones and fMRI timing parameters. This allowed analysis of reaction and execution times as well as correlation of movement onset, i.e. event-onset, to scanning time.

Levodopa medication was applied orally via a small plastic tube with the patients resting positioned in the scanner. Thirty minutes after levodopa administration, functional imaging was continued. This break was used for recording the anatomical images.

**Data analysis**

SPM99 software (Wellcome Department of Cognitive Neurology, London, UK), based on the general linear model (Friston et al., 1995b, c), was applied for data analysis. Calculations were performed on dual-Pentium 400 PCs running LINUX. The first 10 scans of each session were omitted to allow equilibration of T1-saturation effects. Preprocessing of the data took several steps: in the first step, slice timing (Henson et al., 1999; Josephs and Henson, 1999) was performed to correct for differences in image acquisition time between slices so that the data of each slice represented the same point in time relative to response. In the second step, the exact position of the anterior commissure (AC) was determined for the anatomical images. Based on the geometrical MRI acquisition parameters, this value was transformed and applied to the coordinates for AC of the whole brain EPI images. The result of this transformation was verified via the SPM ‘Display’ option. As the functional six-slice EPI images were acquired with exactly the same acquisition parameters as the whole brain EPI images, the Z-coordinate for the AC within the functional scans was calculated without further coregistration. For each functional run, images were realigned to the first image of the session to account for head-motion in time. Those images were stereotactically normalized into a standard space approximating that of Talairach and Tournoux (Talairach and Tournoux, 1988). The two whole brain EPI images bracketing each functional scan were coregistered and the resulting mean image was used for determining the individual normalization parameters for each functional session. Finally images were smoothed with a Gaussian filter of $12 \times 12 \times 12$ mm to increase signal to noise ratio and to account for intersubject anatomical variability (Friston et al., 1995a; Hopfinger et al., 2000).

An event-related study design was applied for statistical analysis (Josephs et al., 1997; Friston et al., 1998b; Josephs and Henson, 1999): for each subject, the exact movement-onsets were entered into a design matrix including three functional scans (before and after medication separately). A high pass filter (Holmes et al., 1997) was applied for filtering low frequency noise (range of cut offs: 33–81 s). Data were convolved with a canonical haemodynamic response function

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Duration</th>
<th>Medication</th>
<th>Hoehn &amp; Yahr</th>
<th>UPDRS off</th>
<th>UPDRS on</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (M)</td>
<td>60</td>
<td>2</td>
<td>D/DA</td>
<td>2</td>
<td>18.5</td>
<td>11.5</td>
</tr>
<tr>
<td>2 (M)</td>
<td>69</td>
<td>1.25</td>
<td>no</td>
<td>1</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>3 (M)</td>
<td>69</td>
<td>1.5</td>
<td>no</td>
<td>2</td>
<td>24.5</td>
<td>18</td>
</tr>
<tr>
<td>4 (M)</td>
<td>65</td>
<td>1.5</td>
<td>D/DA</td>
<td>2</td>
<td>20.5</td>
<td>15</td>
</tr>
<tr>
<td>5 (M)</td>
<td>59</td>
<td>0.5</td>
<td>no</td>
<td>1</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td>6 (M)</td>
<td>60</td>
<td>0.5</td>
<td>no</td>
<td>1</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>7 (M)</td>
<td>59</td>
<td>4</td>
<td>D/DA</td>
<td>2</td>
<td>20.5</td>
<td>16</td>
</tr>
<tr>
<td>8 (F)</td>
<td>45</td>
<td>3.5</td>
<td>D/DA</td>
<td>1</td>
<td>9</td>
<td>5.5</td>
</tr>
</tbody>
</table>

Mean (SD) 60.75 (7.65) 1.84 (1.29) 1.5 (0.73) 15.75 (6.26) 11.75 (4.42)

D = levodopa; DA = dopamine agonist; UPDRS = Unified Parkinson’s Disease Rating Scale motor score; off = before levodopa medication; on = after levodopa medication; M = male; F = female.
for modelling the event-related responses (Josephs et al., 1997; Friston et al., 1998a). Proportional scaling was applied to take into account global blood flow changes. Thus, in a first level (fixed effects) analysis, we obtained one statistical parametric map (SPM) and a corresponding contrast image/run for each healthy control subject and two for each patient, one before and one after levodopa administration, reflecting the effect of motor activation against rest. Those contrast images were entered into a second level (random effects) analysis for group comparison. The latter takes into account between-subject variability and allows more generalized inferences from the data than a fixed-effects model (Searle et al., 1992; Holmes and Friston, 1998; Josephs and Henson, 1999; Strange et al., 1999; McGonigle et al., 2000). A one sample \( t \)-test was used for calculation of the main motor-effect within the group of normals and patients off and on levodopa. A paired \( t \)-test comparing the contrast images of the corresponding runs/subject before/after levodopa was applied for consideration of medication effects within the group of patients with Parkinson’s disease (assuming that inter-subject variance greatly exceeded within-subject between-session variance); between-group comparison was performed with a two sample \( t \)-test. Based on the results of previous PET studies and our \textit{a priori} hypotheses, a statistical threshold of \( P < 0.001 \) uncorrected was considered to show significant activation. Voxels surviving a threshold of \( P < 0.01 \) uncorrected were described as showing a trend towards activation.

### Results

#### Clinical measurements and performance parameters

All patients showed significant improvement in the UPDRS motor score: mean UPDRS III was 15.75 ± 6.26 before and 11.75 ± 4.42 after levodopa (\( P < 0.001 \)) (see Table 1). One patient developed slight nausea following levodopa administration. All the other patients tolerated medication without any further side-effects. Measurement of performance parameters revealed no significant differences concerning reaction times between healthy volunteers and patients. Execution times were significantly longer in patients both before and after levodopa application. No significant shortening of the execution times in patients following medication was detectable (Table 2).

#### fMRI measurements

**Motor activation in healthy volunteers**

At a statistical threshold of \( P < 0.001 \) uncorrected, the second-level group analysis for healthy volunteers showed BOLD contrast increases related to the joystick-movements in primary sensorimotor cortex, Brodmann area (BA) 4/3, adjoining lateral premotor (BA 6) and superior parietal (BA 7).

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**Table 2 Performance parameters in the motor task**

<table>
<thead>
<tr>
<th>Patients</th>
<th>RT (ms) off</th>
<th>RT (ms) on</th>
<th>ET (ms) off</th>
<th>ET (ms) on</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>271.50</td>
<td>296.93</td>
<td>865.75</td>
<td>811.72</td>
</tr>
<tr>
<td>2</td>
<td>224.45</td>
<td>228.63</td>
<td>979.54</td>
<td>1128.16</td>
</tr>
<tr>
<td>3</td>
<td>367.55</td>
<td>444.62</td>
<td>1076.71</td>
<td>1110.98</td>
</tr>
<tr>
<td>4</td>
<td>298.08</td>
<td>327.55</td>
<td>916.27</td>
<td>1004.70</td>
</tr>
<tr>
<td>5</td>
<td>386.75</td>
<td>316.58</td>
<td>1066.50</td>
<td>811.11</td>
</tr>
<tr>
<td>6</td>
<td>477.16</td>
<td>586.94</td>
<td>1027.93</td>
<td>894.75</td>
</tr>
<tr>
<td>7</td>
<td>508.83</td>
<td>456.65</td>
<td>1609.45</td>
<td>1931.63</td>
</tr>
<tr>
<td>8</td>
<td>354.61</td>
<td>310.51</td>
<td>1304.27</td>
<td>1058.36</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>360.84 (115.94)</td>
<td>371.05 (246.31)</td>
<td>1107.0 (359.07)</td>
<td>1093.93 (359.07)</td>
</tr>
</tbody>
</table>

RT = reaction time; ET = execution time; off = before levodopa medication; on = after levodopa application.

**Table 3 Within group comparison: sites of cortical activation**

<table>
<thead>
<tr>
<th>Cluster</th>
<th>BA</th>
<th>( x )</th>
<th>( y )</th>
<th>( z )</th>
<th>( t )-level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>1 L primary sensorimotor</td>
<td>4/3</td>
<td>–40</td>
<td>–32</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td>L lateral premotor</td>
<td>6</td>
<td>–34</td>
<td>–10</td>
<td>68</td>
</tr>
<tr>
<td></td>
<td>L superior parietal</td>
<td>7</td>
<td>–26</td>
<td>–64</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td>2 R superior parietal</td>
<td>5/7</td>
<td>48</td>
<td>–44</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>R lateral premotor/primary sensorimotor</td>
<td>6/4</td>
<td>40</td>
<td>–2</td>
<td>66</td>
</tr>
<tr>
<td></td>
<td>3 L mesial premotor/pre-SMA</td>
<td>6</td>
<td>–6</td>
<td>6</td>
<td>46</td>
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</tbody>
</table>

Patients off levodopa

<table>
<thead>
<tr>
<th>Cluster</th>
<th>BA</th>
<th>( x )</th>
<th>( y )</th>
<th>( z )</th>
<th>( t )-level</th>
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<tbody>
<tr>
<td></td>
<td>1 L primary motor</td>
<td>4</td>
<td>–42</td>
<td>–22</td>
<td>60</td>
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<tr>
<td></td>
<td>L lateral premotor</td>
<td>6</td>
<td>–18</td>
<td>–16</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td>L superior parietal</td>
<td>7</td>
<td>–34</td>
<td>–54</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td>2 R lateral premotor</td>
<td>6</td>
<td>34</td>
<td>–20</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td>R primary sensorimotor</td>
<td>4</td>
<td>54</td>
<td>–2</td>
<td>52</td>
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</tbody>
</table>

Patients on-levodopa

<table>
<thead>
<tr>
<th>Cluster</th>
<th>BA</th>
<th>( x )</th>
<th>( y )</th>
<th>( z )</th>
<th>( t )-level</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 L primary sensorimotor</td>
<td>3/4</td>
<td>–36</td>
<td>–32</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td>L lateral premotor</td>
<td>6</td>
<td>–26</td>
<td>–20</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td>L superior parietal</td>
<td>7</td>
<td>–12</td>
<td>–40</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td>R lateral premotor/primary motor</td>
<td>4/6</td>
<td>26</td>
<td>–16</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td>Mesial premotor cortex/SMA</td>
<td>6</td>
<td>–12</td>
<td>58</td>
<td>7.03</td>
</tr>
</tbody>
</table>

L = left; \( R = \) right. \( x \), \( y \) and \( z \) express the position of the voxel with peak activation level (\( P < 0.001 \), uncorrected, extent threshold 10 voxels) within the cluster in millimetres relative to the AC in the stereotactic space (Talairach and Tournoux, 1988): \( x \) = lateral distance from the midline (+ right, – left); \( y \) = anteroposterior distance from the AC (+ anterior, – posterior); \( z \) = height relative to the AC line (+ above, – below).
motor activation in patients off/on levodopa

The group analysis at $P < 0.001$ for all Parkinson’s disease patients off levodopa revealed signal increases bilaterally in the primary sensorimotor (BA 4) and lateral premotor (BA 6) cortex. Additionally, activation was shown in the left superior parietal (BA 7) cortex (Fig. 1B and Table 3). After application of levodopa, patients showed a comparable pattern of motor activation as off levodopa (primary sensorimotor, adjoining lateral premotor cortex bilaterally and left superior parietal cortex). Additionally, significant ($P < 0.001$) BOLD
overactivity bilaterally in the lateral premotor cortex (BA 6) primary sensorimotor cortex (BA 4/3) and trend towards

4A). Furthermore, we found overactivity bilaterally in the observed in the right superior parietal cortex (BA 7) (Fig. 3).

premotor cortex (BA 6). A trend (P < 0.01 uncorrected, extent threshold 10 voxels) within the cluster in mm relative to the AC in the stereotactic space (Talairach and Tournoux, 1988):

contrast increases were detected bilaterally in the mesial premotor cortex/SMA (BA 6) (Fig. 1C and Table 3).

Within group comparison patients off on levodopa

Investigating the effect of levodopa on motor activation in Parkinson’s disease patients, a paired t-test was applied on the second level analysis (P < 0.001 uncorrected, t(22) = 3.50; Table 4). This revealed significant increases in motor activation after levodopa application in both the bilateral rostral and caudal mesial premotor cortex (pre-SMA/SMA proper, BA 6) and also bilaterally in the adjoining lateral premotor cortex (BA 6) (Fig. 2). In contrast, activation was significantly higher off levodopa in the bilateral primary sensorimotor cortex (BA 4/3) and the right lateral premotor (BA 6) cortex. A trend towards increased activation (P < 0.01, t = 2.51) before levodopa was detected in the left lateral premotor cortex and bilaterally in the superior parietal cortex (BA 7) (Fig. 3).

Between group comparison

A two-sample t-test was applied for comparison of healthy volunteers to Parkinson’s disease patients on/off levodopa (Table 5): patients off levodopa showed significant [t(P < 0.001, t(46) = 3.28] underactivity in the rostral mesial premotor (pre-SMA) and bilaterally in the adjoining lateral premotor cortex (BA 6). A trend (P < 0.01, t = 2.41) was observed in the right superior parietal cortex (BA 7) (Fig. 4A). Furthermore, we found overactivity bilaterally in the primary sensorimotor cortex (BA 4/3) and trend towards overactivity bilaterally in the lateral premotor cortex (BA 6) compared with healthy volunteers (Fig. 5A). On levodopa, underactivity within the rostral mesial premotor cortex, right superior parietal and sensory (BA 2) cortex in Parkinson’s disease patients compared with healthy volunteers remained (Fig. 4B), as well as overactivity in bilateral primary motor and lateral premotor areas (Fig. 5B).

Discussion

To our knowledge, this study represents the first fMRI investigation on modulation of cortical motor activation by levodopa in Parkinson’s disease. Furthermore, it exploits the unique advantage of fMRI to study event-related cortical signal changes and shows that cortical dysfunction in Parkinson’s disease is more complex than has been shown in previous PET studies. There are three main findings: (i) mesial premotor hypofunction in Parkinson’s disease is shown to be directly associated with freely selected motor activity; (ii) lateral premotor and primary motor overactivity is demonstrated; and (iii) relative normalization of dysfunctional activation occurs not only in the mesial frontal cortex but also in the lateral premotor, primary motor and parietal cortices after levodopa.

At this point, we would like to draw attention to a methodological issue in the discussion of our results. The event-related set-up specifically reflects task-associated changes because data acquisition is closely linked to the motor event. In contrast, in PET and fMRI bloc-design studies comparing activation effects between patients and healthy controls, data acquisition goes over 30–90 s with movements performed typically every 3 s (Jenkins et al., 1992; Playford et al., 1992; Samuel et al., 1997a) and up to

<table>
<thead>
<tr>
<th>Cluster</th>
<th>BA</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>t-level</th>
</tr>
</thead>
<tbody>
<tr>
<td>On &gt; off</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 mesial premotor (SMA proper)</td>
<td>6</td>
<td>8</td>
<td>-4</td>
<td>48</td>
<td>5.74*</td>
</tr>
<tr>
<td>L lateral premotor</td>
<td>6</td>
<td>-16</td>
<td>16</td>
<td>58</td>
<td>5.54*</td>
</tr>
<tr>
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<td>6</td>
<td>32</td>
<td>0</td>
<td>50</td>
<td>4.33*</td>
</tr>
<tr>
<td>mesial premotor (pre-SMA)</td>
<td>6</td>
<td>10</td>
<td>4</td>
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<td>3.96*</td>
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<tr>
<td>Off &gt; on</td>
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</tr>
<tr>
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<td>-22</td>
<td>60</td>
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</tr>
<tr>
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<td>54</td>
<td>3.50*</td>
</tr>
<tr>
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<td>-46</td>
<td>-18</td>
<td>56</td>
<td>3.91*</td>
</tr>
<tr>
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<td>-20</td>
<td>-56</td>
<td>62</td>
<td>3.45</td>
</tr>
<tr>
<td>4 R superior parietal</td>
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<td>-50</td>
<td>62</td>
<td>3.02</td>
</tr>
<tr>
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<td>6</td>
<td>-50</td>
<td>8</td>
<td>42</td>
<td>2.81</td>
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</tbody>
</table>

L = left; R = right, x, y and z express the position of the voxel with peak activation level (*P < 0.001 or P < 0.01, uncorrected, extent threshold 10 voxels) within the cluster in mm relative to the AC.
Fig. 3 Cortical areas with significant signal increases off versus on levodopa in Parkinson’s disease \((P < 0.01\) uncorrected, extent threshold 10 voxels). BOLD signal increases are overlaid onto three consecutive axial slices of a normalized T1-weighted anatomical magnetic resonance image. R = right; L = left.

### Table 5 Inter-group comparison: differences in activation between controls and patients

<table>
<thead>
<tr>
<th>Cluster</th>
<th>BA</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>t-level</th>
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<tr>
<td>Patients &lt; controls off levodopa</td>
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</tr>
<tr>
<td>1 L mesial/adj. lateral premotor</td>
<td>6</td>
<td>-18</td>
<td>18</td>
<td>48</td>
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<td>14</td>
<td>-50</td>
<td>68</td>
<td>2.68</td>
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<tr>
<td>Patients &gt; controls off levodopa</td>
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<td></td>
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<tr>
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<td>-20</td>
<td>64</td>
<td>4.35*</td>
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<tr>
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<td>-18</td>
<td>48</td>
<td>3.56*</td>
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<tr>
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<td></td>
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</tr>
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<td>-4</td>
<td>48</td>
<td>2.66</td>
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</tbody>
</table>

L = left; R = right. \(x, y, \) and \(z\) express the position of the voxel with peak activation level \((P < 0.001\) or \(P < 0.01,\) uncorrected, extent threshold 10 voxels) within the cluster in mm relative to the AC in the stereotactic space (Talairach and Tournoux, 1988): \(x = \) lateral distance from the midline \((\pm \text{right}, - \text{left})\); \(y = \) anteroposterior distance from the AC \((\pm \text{anterior}, - \text{posterior})\); \(z = \) height relative to the AC line \((\pm \text{above}, - \text{below})\); \(> = \) higher BOLD signal levels than; \(< = \) lower BOLD signal levels than; adj = adjoining.

The brain states associated with the task are still comparable in both groups.

In our study we revisited the well-established joystick paradigm (Deiber et al., 1991) and implemented it for event-related fMRI. This allowed us to compare the present event-related fMRI results to those of previous PET studies on joystick movements in Parkinson’s disease which have emphasized the concept of frontal mesial hypofunction associated with akinesia and its relative normalization after clinical improvement irrespective of which therapeutic interventions were used (apomorphine, pallidotomy, subthalamic nucleus stimulation, embryonic grafting) (Jenkins et al., 1992; Playford et al., 1992; Ceballos-Baumann et al., 1994, 1996, 1999; Brooks et al., 1997; Limousin et al., 1997; Samuel et al., 1997b).

### Mesial premotor cortex

Our finding of a relative hypofunction within SMA is well in line with previous PET and SPECT activation studies: significant underactivity within SMA has been shown in Parkinson’s disease patients compared with healthy controls when investigating self-selected, externally triggered single joystick movements (Playford et al., 1992). Decreased movement-associated SMA activation was also described in other PET/SPECT activation studies with self-initiated/externally triggered finger movements (Rascol et al., 1992, 1994; Jahanshahi et al., 1995; Samuel et al., 1997a) or complex sequential movements (Sabatini et al., 2000). A relative normalization of this activation pattern was shown after improvement of akinesia (Jenkins et al., 1992; Rascol et al., 1992; Ceballos-Baumann et al., 1994, 1996, 1999; Rascol et al., 1994; Grafton et al., 1995; Limousin et al., 1997; Samuel et al., 1997b). Only one PET study, carried out by Catalan and colleagues, reported anterior SMA/cingulate overactivation in Parkinson’s disease associated with finger movements (Rascol et al., 1994). However, it may be questioned whether...
Event-related fMRI in Parkinson’s disease

Fig. 4 Between-group analysis showing cortical areas with significant underactivity in Parkinson’s disease patients off (A) and on (B) levodopa compared with healthy volunteers (P < 0.01 uncorrected, extent threshold 10 voxels). Activation is displayed onto three orthogonal sections of a normalized T1-weighted anatomical magnetic resonance image. R = right; L = left.

Motor cortex

In our study we demonstrated that the dysfunctional activation of M1 can be partially normalized with dopaminergic replacement. Indirect functional imaging evidence for pathophysiological involvement of M1 in Parkinson’s disease can be drawn from PET work during subthalamic nucleus stimulation. Two independent studies have shown profound decreases in rCBF in M1 associated with effective subthalamic nucleus stimulation and akinesia improvement (Limousin et al., 1997; Ceballos-Baumann et al., 1999). One explanation for the BOLD signal decreases would be that there is less afferent noise in the motor cortex from dysfunctional premotor areas after basal ganglia frontal cortex reafferentation with levodopa. Unfortunately, BOLD signal changes do not allow differentiation between afferent or local, excitatory or inhibitory synaptic activity. Uncontrolled afferent noise in the motor cortex would be consistent with the postulated defective cortico-cortical inhibition in motor cortex excitability which has been described in transcranial magnetic stimulation studies and is alleviated with levodopa (Ridding et al., 1995) and dopamine agonists (Ziemann et al., 1996, 1997; Strafella et al., 2000). Possibly, increased BOLD signal in both the primary motor and premotor cortices reflects basal ganglia dysfunction in Parkinson’s disease to approximately focus motor and premotor cortex excitability for willed motor action. Increased M1 activity could contribute to the difficulties in motor execution and possibly represent the neural substrate of rigidity.

Up to now, only two fMRI studies, the first as abstract, also described higher movement-associated increases in BOLD signal in M1 in Parkinson’s disease (Humberstone et al., 1998; Sabatini et al., 2000). However, previous PET/SPECT studies, both with the joystick and with sequential finger movements, failed to detect motor cortex hyperfunction, though movement-associated hyperactivity in the premotor and parietal cortices was observed in functional imaging with the performance of long sequences of finger movements (Catalan et al., 1999). These authors reasoned that, as the SMA is crucially involved in generating sequential movements, Parkinson’s disease patients recruit mesial premotor areas ‘more vigorously’ to perform sequential movements successfully. This is in contrast to the findings of Sabatini and colleagues who found significant underactivation in rostral SMA when Parkinson’s disease patients were performing a long and complex sequence of finger/hand-movements (Sabatini et al., 2000).

Former PET studies with the freely selected joystick paradigm did not differentiate between rostral and caudal parts of the mesial premotor cortex (Jenkins et al., 1992; Playford et al., 1992). Our results and recent studies using 3D acquisition with PET (Samuel et al., 1997a) and fMRI (Sabatini et al., 2000) were able to demonstrate in Parkinson’s disease that the rostral parts (pre-SMA) especially are underactive and that activation of this area can be restored by treatment (Limousin et al., 1997; Samuel et al., 1997b; Ceballos-Baumann et al., 1999). While former imaging studies integrated various aspects of movement preparation and ‘readiness to move’ due to the longer acquisition times, our study demonstrates that the functional deficit in pre-SMA in Parkinson’s disease patients is related to the event of performing a small ballistic, externally triggered hand movement.
Fig. 5 Inter-group comparison showing cortical areas with significant overactivity in Parkinson’s disease patients off (A) and on (B) levodopa compared with healthy controls ($P < 0.01$ uncorrected, extent threshold 10 voxels). BOLD signal increases are overlaid onto three consecutive axial slices of a normalized T1-weighted anatomical magnetic resonance image. R = right; L = left.

studies in the latter paradigm (Samuel et al., 1997a; Catalan et al., 1999). In our study, relative signal increases within the primary motor as well as the lateral premotor cortex occurred bilaterally. Previous imaging studies with PET (Shibasaki et al., 1993; Sadato et al., 1996; Catalan et al., 1998; Kawashima et al., 1998) and fMRI (Kim et al., 1993; Rao et al., 1993), electrophysiological studies using repeated transcranial magnetic stimulation (Chen et al., 1997; Gerloff et al., 1998), or measurements of movement-related potentials (Kitamura et al., 1993) also showed ipsilateral M1 involvement in the normal brain during performance of (complex) movements. Investigations of patients with functional recovery after stroke revealed a recruitment of the ipsilateral motor cortex compensating for the contralateral deficit (Chollet et al., 1991; Weiller et al., 1992). We assume that our finding of bilateral primary motor/lateral premotor hyperactivity in Parkinson’s disease even in simple/single hand movements reflects compensatory cortical reorganization. This is analogous to imaging findings in patients with acquired dystonia which show M1 overactivity (Ceballos-Baumann et al., 1995).

**Lateral premotor and parietal cortex**

Increased bilateral activation within the lateral premotor cortex in Parkinson’s disease patients, both off and on levodopa, is demonstrated here during simple ballistic movements, while previously it was only shown for sequential movements (Samuel et al., 1997a; Catalan et al., 1999; Sabatini et al., 2000). This proves that Parkinson’s disease patients already use the lateral premotor cortex to compensate for the hypofunction in the striatofrontal projections, even in simple movements. It also suggests that, in Parkinson’s
disease, there is a switch from the use of defective striato-
mesial frontal to relatively intact circuitry involving the
premotor cortex in order to facilitate movement initiation.
Former 2D PET studies, investigating single joystick or finger
movements in Parkinson’s disease, failed to show abnormal
lateral premotor activation (Jenkins et al., 1992; Playford
et al., 1992; Jahanshahi et al., 1995). The lateral premotor
cortex is reported to be predominantly involved in the
execution of externally triggered, sensory-cued movements
(Deiber et al., 1991; Mushiake et al., 1991). As part of a
working memory system that is responsible for movements
under sensory guidance and for the ‘retieval of abstract
action plans that are stored in the parietal lobe’ (Harrington
et al., 2000), it could provide the basis of sensory guided
movement generation in Parkinson’s disease without the
need for an intact basal ganglia mesial frontal circuit. A
compensatory hyperactivity in premotor connections may
explain why the initiation of movements can be facilitated
in Parkinson’s disease patients with external cues. A recent
study by Hanakawa and colleagues using 99mTc-HMPAO-
SPECT showed enhanced recruitment of the right premotor
cortex along with parietal and cerebellar signal increases
during the phenomenon of ‘paradoxical gait’ in Parkinson’s
disease, i.e. improvement of gait through visual landmarks
such as tranversal lines on the floor (Hanakawa et al., 1999).
Analogous to this, overactivity of the ipsilateral cerebellar
hemisphere has been demonstrated in patients with
Parkinson’s disease (Rascol et al., 1997).

Direct anatomical connections exist between the premotor
cortex (PMC and SMA), and superior parietal cortex/area 7
(Godschalk et al., 1984; Petrides and Pandya, 1984; Cavada
and Goldman-Rakic, 1989). Bilateral BOLD signal increases
in the superior parietal cortex were significantly higher in
patients off levodopa, implying that levodopa modulates
dysfunctional parietal cortex activation. We did not observe
overactivity in the parietal cortex in Parkinson’s disease
patients off and on levodopa compared with healthy controls,
as our paradigm posed minor working memory demands in
contrast to those studies which scanned Parkinson’s disease
patients during complex sequential ongoing movements
(Samuel et al., 1997a; Catalan et al., 1999; Sabatini et al.,
2000).

fMRI and Parkinson’s disease
The results of our comparison between the Parkinson’s
disease patients off levodopa and the control group show
reasonable accordance with the block design fMRI study by
Sabatini and colleagues, who did not study the effects of
dopaminergic replacement (Sabatini et al., 2000). These
investigators compared the activation effects of a complex
sequential task in more advanced Parkinson’s disease (Hoehn
& Yahr 2.79) than our patients (Hoehn & Yahr 1.5). Their
patients performed unidirectional finger to thumb oppositions,
opened and clenched their fist twice, completed the finger to
thumb oppositions in the opposite direction and again opened
and clenched their fist twice at a self-paced frequency of
~1 Hz. This was repeated continuously over a 30 s data
acquisition period. Movement performance apart from
observation and video taping was not monitored in this task,
which may have differed significantly in the amount of
attention and effort involved in the group of advanced akinetic
Parkinson’s disease patients compared with the controls.
When comparing the data, the problem of motion artefacts
has to be considered, especially in block-design fMRI which
is substantially more susceptible to motion artefacts than
event-related fMRI (in event-related fMRI, the measured
haemodynamic response associated with brief single
movements actually appears after the movement itself).
Sabatini and colleagues reported bilateral overactivity within
M1 in Parkinson’s disease patients off levodopa (Sabatini
et al., 2000). Motor cortex hyperfunction has never been
described in PET studies. We believe that this divergence
between fMRI and PET in M1 might be due to the higher
sensitivity of fMRI in detecting differences in movement-
associated signal changes between Parkinson’s disease
patients and healthy controls.

The effect of levodopa
For the first time, the impact of levodopa on movement-
related fMRI BOLD signal changes in cortical areas known
to be dysfunctional in Parkinson’s disease is described here.
Comparing patients off and on medication, significant signal
increases off levodopa were detected bilaterally in the primary
motor/lateral premotor cortex and the superior parietal cortex.
As a novel finding, this study shows that efficient
dopaminergic therapy leads to a partial reversal of lateral
premotor/primary motor/parietal cortical hyperfunction in
Parkinson’s disease. Additionally, we found a significant
signal increase in rostral/caudal SMA following levodopa
medication correlated with the clinical improvement of
akinnesia. This corresponds to the results of prior imaging
studies in Parkinson’s disease patients investigating the effect
of apomorphine, levodopa, pallidotomy, high-frequency
stimulation or foetal grafting. Similarly, electrophysiological
measurements have demonstrated that the early amplitude of
the ‘Bereitschaftspotential’ which has been shown to be
reduced in Parkinson’s disease (Deecke et al., 1977; Shibasaki
et al., 1978; Dick et al., 1989; Cunnington et al., 1995;
Jahanshahi et al., 1995) and in patients with SMA (Deecke
et al., 1987) and basal ganglionic lesions (Feve et al., 1994),
can be partially recovered following treatment of the akinesia
(Dick et al., 1987; Feve et al., 1992; Gerschlager et al.,
1999). Thus, our findings demonstrate a partial normalization
of functional mesial frontal circuitry by dopaminergic
medication correlated with the clinical improvement of
akinnesia. The compensatory hyperactivity within the lateral
premotor/parietal/primary motor circuitry is reversed in
parallel to the restoration of mesial premotor function.
Nevertheless, deficits in cortical motor function are only
partially reversed. Despite a significant improvement of
akinnesia, patients on levodopa still show abnormal motor
activation compared with healthy controls. The interpretation
of these BOLD contrast results might be affected by the limited knowledge about the effect of levodopa on neurovascular coupling mechanisms. Krimer and colleagues reported direct in-vitro dopaminergic vasocostructive effects on frontal cortical vasculature (Krimer et al., 1998). Pharmacological MRI studies in future will need to clarify to what extent levodopa induces BOLD signal changes which represent direct drug effects on cerebral vasculature and not changes in neuronal firing.

Conclusion
This first event-related fMRI study in early Parkinson’s disease in patients off and on levodopa, investigating ballistic freely selected joystick movements, underlines the concept of a switch from the use of defective striato-mesial frontal circuitry to relatively intact parietal–lateral premotor circuits in akinetic Parkinson’s disease patients in order to facilitate motor acts. The finding of a diffuse disinhibition of M1 possibly represents the neural substrate of rigidity. We have shown that, parallel to the clinical improvement of akinesia, orally applied levodopa leads not only to a partial recovery of defective mesial premotor activation, but also to a reduction of primary motor/lateral premotor hyperactivity in akinesia.

Acknowledgements
This study was supported by the SFB 462 ‘Sensomotorik’, Deutsche Forschungsgemeinschaft Bonn, the ‘Kommission Klinische Forschung’ and the ‘Gerhard und Irmgard Schulz Fond’, Neurologische Klinik, Klinikum Rechts der Isar and the Deutsche Parkinson Vereinung e.V., Neuss, Germany.

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Received August 30, 2000. Revised October 25, 2000
Accepted November 21, 2000