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Compensatory premotor activity during affective face processing in subclinical carriers of a single mutant *Parkin* allele

Silke Anders,[1] Benjamin Sack,[1] Anna Pohl,[2,3] Thomas Münte,[1] Peter Pramstaller,[4] Christine Klein[1] and Ferdinand Binkofski[1,5]

1 Department of Neurology, University of Lübeck, 23538 Lübeck, Germany
2 Department of Psychiatry and Psychotherapy, RWTH Aachen University, 52056 Aachen, Germany
3 JARA - Translational Brain Medicine, Germany
4 Centre for Biomedicine, European Academy, 39100 Bolzano, Italy
5 Section for Cognitive Neurology, RWTH Aachen University, 52056 Aachen, Germany

Correspondence to: Silke Anders,
Department of Neurology,
University of Lübeck,
Ratzeburger Alle 160,
23538 Lübeck,
Germany
E-mail: silke.anders@neuro.uni-luebeck.de

Patients with Parkinson's disease suffer from significant motor impairments and accompanying cognitive and affective dysfunction due to progressive disturbances of basal ganglia–cortical gating loops. Parkinson's disease has a long presymptomatic stage, which indicates a substantial capacity of the human brain to compensate for dopaminergic nerve degeneration before clinical manifestation of the disease. Neuroimaging studies provide evidence that increased motor-related cortical activity can compensate for progressive dopaminergic nerve degeneration in carriers of a single mutant *Parkin* or *PINK1* gene, who show a mild but significant reduction of dopamine metabolism in the basal ganglia in the complete absence of clinical motor signs. However, it is currently unknown whether similar compensatory mechanisms are effective in non-motor basal ganglia–cortical gating loops. Here, we ask whether asymptomatic *Parkin* mutation carriers show altered patterns of brain activity during processing of facial gestures, and whether this might compensate for latent facial emotion recognition deficits. Current theories in social neuroscience assume that execution and perception of facial gestures are linked by a special class of visuomotor neurons ('mirror neurons') in the ventrolateral premotor cortex/pars opercularis of the inferior frontal gyrus (Brodmann area 44/6). We hypothesized that asymptomatic *Parkin* mutation carriers would show increased activity in this area during processing of affective facial gestures, replicating the compensatory motor effects that have previously been observed in these individuals. Additionally, *Parkin* mutation carriers might show altered activity in other basal ganglia–cortical gating loops. Eight asymptomatic heterozygous *Parkin* mutation carriers and eight matched controls underwent functional magnetic resonance imaging and a subsequent facial emotion recognition task. As predicted, *Parkin* mutation carriers showed significantly stronger activity in the right ventrolateral premotor cortex during execution and perception of affective facial gestures than healthy controls. Furthermore, *Parkin* mutation carriers showed a slightly reduced ability to recognize facial emotions that was least severe in individuals who showed the strongest increase of ventrolateral premotor activity. In addition, *Parkin* mutation carriers showed a significantly weaker than normal increase of activity in the left lateral orbitofrontal cortex (inferior frontal gyrus pars orbitalis, Brodmann area 47), which was unrelated to facial emotion recognition ability. These findings are consistent with the hypothesis

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that compensatory activity in the ventrolateral premotor cortex during processing of affective facial gestures can reduce impairments in facial emotion recognition in subclinical *Parkin* mutation carriers. A breakdown of this compensatory mechanism might lead to the impairment of facial expressivity and facial emotion recognition observed in manifest Parkinson's disease.

Keywords: Parkinson's disease; functional MRI; emotional facial expression; mirror neurons; functional reorganization

Abbreviation: OFC = orbitofrontal cortex

Introduction

Progressive loss of dopaminergic nerve cells in the substantia nigra leads to Parkinson's disease, a common neurodegenerative disorder. In addition to a characteristic triad of motor symptoms, patients with Parkinson's disease often show cognitive and affective impairments. In particular, a reduced ability to decode facial expressions of emotion has been reported in a number of studies (Gray and Tickle-Degnen, 2010).

The characteristic motor signs of Parkinson's disease (tremor, rigor, bradykinesia) are a result of imbalance of neural activity in basal ganglia–thalamocortical motor gating loops, caused by loss of dopaminergic nerve cells in the pars compacta of the substantia nigra and subsequent nerve degeneration in the putamen. However, in addition to the well-described motor loops, the basal ganglia have numerous interconnections with other cortical areas (Alexander *et al*., 1986, 1990; Lehericy *et al*., 2004; DeLong and Wichmann, 2007, 2010). Cognitive and affective impairments observed in patients with Parkinson's disease have often been ascribed to disturbances in 'cognitive' or 'limbic' basal ganglia–cortical gating loops (Holthoff-Detto *et al*., 1997; Sprengelmeyer *et al*., 2003; Clark *et al*., 2008; van Beilen *et al*., 2008; Gray and Tickle-Degnen, 2010), but the pathophysiology underlying cognitive and affective dysfunction in Parkinson's disease is still not well understood.

Parkinson's disease has a long and not well-defined presymptomatic course of disease. Based on PET with ^{18}F-fluoro-L-DOPA, it has been estimated that first characteristic motor signs become apparent ~5 years after onset of the pathophysiological process, when dopamine metabolism in the basal ganglia is reduced by 30–50% (Morrish *et al*., 1996; Hilker *et al*., 2005). This long presymptomatic period in Parkinson's disease suggests that the human motor system has a substantial capacity to compensate for loss of nigrostriatal dopaminergic nerve cells. Empirical support for this assumption comes from functional MRI studies in individuals who carry a single mutation in the *Parkin* (*PARK2*) or in the *PINK1* (*PARK6*) gene. Mutations in these genes are a common cause of early-onset Parkinson's disease (Klein *et al*., 2007). While heterozygous carriers of a single *Parkin* or *PINK1* mutation are usually free of clinical motor symptoms, it is now well established that these asymptomatic mutation carriers show a significant reduction of ^{18}F-fluoro- L-DOPA metabolism in the putamen (Hilker *et al*., 2001, 2002; Khan *et al*., 2002, 2005; Scherfler *et al*., 2004; Pavese *et al*., 2009; Guo *et al*., 2011). Two recent functional MRI studies have indicated that asymptomatic *Parkin* and *PINK1* mutation carriers show a stronger increase of cortical motor-related activity during execution of self-initiated movements than non-mutation carriers (Buhmann *et al*., 2005; van Nuenen *et al*., 2009*a*). This stronger than normal increase in cortical activity and concomitant changes in functional connectivity in the motor system have been interpreted as evidence for a large-scale reorganization of the motor system in the presymptomatic stage of Parkinson's disease (Buhmann *et al*., 2005; Schneider *et al*., 2008; van Nuenen *et al*., 2009*a*, *b*). Whether similar compensatory mechanisms are effective in non-motor basal ganglia–cortical gating loops is currently unknown.

Here, we examine whether asymptomatic *Parkin* mutation carriers show altered patterns of brain activity during processing of facial gestures, and whether such altered patterns of brain activity can compensate for latent deficits in facial emotion recognition. Current theories in cognitive neuroscience suggest that motor execution and action perception are strongly linked by a special class of visuomotor neurons, so-called 'mirror neurons'. Mirror neurons, defined by their property to fire not only during motor execution, but also during action perception, were first described in the premotor cortex F5 of the macaque *Macaca nemestrina* (di Pelligrino *et al*., 1992). Overlapping activity during action execution and action observation in functional MRI studies has subsequently been taken as evidence that homologue mirror neuron areas exist in the human brain (Iacoboni *et al*., 1999; Shmuelof and Zohary, 2006; Gazzola and Keysers, 2009; Schippers *et al*., 2009). In particular, it has been suggested that mirror neurons in the ventrolateral premotor cortex in the pars opercularis of the inferior frontal gyrus link execution and perception of facial gestures and thereby help a receiver to decode another person's facial expression (Carr *et al*., 2003; Leslie *et al*., 2004; Hennenlotter *et al*., 2005; van der Gaag *et al*., 2007). In Parkinson's disease, a reduced ability to decode facial expressions is almost always associated with reduced facial expressivity, and there are observations that indicate a positive relation between reduced expressivity and facial emotion recognition deficits (Jacobs *et al*., 1995). In sum, these findings could point to a common cause behind reduced facial expressivity and facial emotion recognition deficits in Parkinson's disease.

In the current study, we asked whether asymptomatic carriers of a single mutant *Parkin* gene would show a stronger than normal increase of activity in ventrolateral premotor cortex during execution and observation of facial gestures, mirroring the stronger than normal increase of motor-related activity observed in *Parkin* and *PINK1* mutation carriers during execution of self-initiated finger movements. Furthermore, we examined whether the strength of activity in ventrolateral prefrontal cortex would be positively correlated with the participants' ability to decode facial emotional expressions. In other words, we tested whether those *Parkin* mutation carriers who show a strong increase of ventrolateral premotor

activity during processing of facial gestures would show less impairment in facial emotion recognition than those *Parkin* mutation carriers who show weaker ventrolateral premotor activity. This would speak for a beneficial effect of stronger than normal ventrolateral premotor activity on facial emotion recognition in *Parkin* mutation carriers. Finally, we explored whether *Parkin* mutation carriers would show altered brain activity in limbic and/or higher cognitive areas associated with affective processing. Such a finding could point towards compensatory processes in 'limbic' and/or 'cognitive' basal ganglia–thalamocortical gating loops.

Materials and methods

Participants

Eight asymptomatic individuals with a single mutation in one allele of the *Parkin* gene participated in the study (four males, four females; age range 35–50 years; mean age of males 43 years, mean age of females 46 years). Mutation carriers were recruited from a large family (Family LA) from the German-spoken part of northern Italy (Tyrol) with familial adult-onset parkinsonism caused by mutations in the *Parkin* gene. Four individuals had a deletion of exon 7 and four individuals carried a 1-bp deletion in exon 9. Details of the genetic analysis of the core branch of Family LA have been described elsewhere (Klein *et al.*, 2000). Six of the mutation carriers had previously undergone PET, showing a small but statistically significant decrease of ^{18}F-fluoro-L-DOPA uptake in the putamen as reported above (Hilker *et al.*, 2001, 2002). All *Parkin* mutation carriers scored within the normal range on all subscales of the Unified Parkinson Disease Rating Scale [UPDRS I/II (cognitive function/daily activities) range 0–1, mean 0.5; UPDRS III (motor abilities) range 0–5, mean 2.25] and the Beck Depression Inventory (Beck, 1961) (range 0–8, mean 1.875). An overview of clinical data of all *Parkin* mutation carriers is given in Table 1.

A group of eight age- and sex-matched healthy individuals (four males, four females; age range 35–55 years; mean age of males 44.25 years, mean age of females 46.75 years) recruited from Lübeck and the surrounding area were examined as controls. Functional MRI data of two healthy participants (one male, one female) were discarded because one participant showed large head movements during scanning (>10 mm) and the other reported that observing and executing the facial expressions elicited subjective experience of other emotions than joy (see below). Functional MRI data of these two participants were replaced with functional MRI data from two additional age- and sex-matched control participants.

All participants were native German speakers, had normal or corrected-to-normal vision and no history of neurological or neuropsychiatric disease; none reported to have received any dopaminergic or anti-parkinsonian drug treatment. All participants gave their written informed consent before participation and the study was approved by the local ethics committee (University of Lübeck, Germany).

Overview of design

To compare processing of facial gestures in *Parkin* mutation carriers and healthy controls at the behavioural and cerebral level, we conducted a behavioural emotion recognition test and a functional MRI experiment. The behavioural test required participants to name blends of emotional facial expressions in a forced-choice paradigm. In the functional MRI experiment, participants were asked to execute and observe neutral and affective dynamic facial expressions, but no explicit emotion recognition was required. This way, we could assess emotion recognition ability and brain activity independently. We also intended to manipulate facial expressivity and pleasantness independently by including a highly positive expressive facial gesture (a smile) along with a slightly positive gesture (a lip protrusion indicating a kiss). However, post-scan joy ratings indicated that participants experienced 'kiss' gestures as equally joyful as 'smile' gestures, thus these two conditions were fused to one condition (see below). Results of the behavioural task will be reported first although all participants underwent functional MRI scanning before completing the behavioural task.

Table 1 Overview of clinical data of *Parkin* mutation carriers

Code	Sex	Age	Mutation	UPDRSIII	BDI
b25	M	34	delEx7	0	0
b39	M	44	delEx7	3	0
b45	M	45	delEx7	4	1
b36	M	46	1072delT	1	8
b28	F	43	delEx7	2	0
b962	F	43	1072delT	5	0
b29	F	45	1072delT	2	5
b27	F	48	1072delT	1	1

BDI = Beck Depression Inventory; F = female; M = male; UPDRSIII = Unified Parkinson Disease Rating Scale, subscale motor abilities.

Behavioural experiment

To measure the participants' ability to decode emotions from facial expressions, we used a set of facial stimuli taken from the Facial Expression of Emotions: Stimuli and Test (FEEST; Young *et al.*, 2002). Each stimulus of this set is a computer-transformed blend ('morph') of two different, 'neighbouring', emotional facial expressions of one actor 'J.J'. The set includes five different blends (90–10%, 70–30%, 50–50%, 30–70%, 10–90%) for each pair of neighbouring emotions in the series surprise–fear–sadness–disgust–anger–happiness–surprise, giving a total of 30 different stimuli. Stimuli were presented on a computer screen with five replications in randomized order, giving a total of 150 trials. During each trial, participants were asked to choose the emotion that best described the facial expression on the screen from a set of six target emotions (surprise, fear, sadness, disgust, anger and happiness). Written German labels ('Überraschung', 'Furcht', 'Trauer', 'Ekel', 'Wut' and 'Freude') for these six emotions were provided throughout the experiment next to each other at the bottom of the computer screen in a pseudorandomized order that was balanced across participants. Participants indicated their choice by verbally naming the selected emotion. Participants were asked to respond quickly, and each facial expression disappeared after 5 s, but there was no upper limit of response time. Choices were entered into a computer by a lab member (B.S.) the next face appeared immediately after the response was given. Stimuli were presented in five runs with a short break in between. Data collection was preceded by 30 test trials to familiarize participants with the task. Both 90–10% ('clear-cut') and 70–30% ('fuzzy') morphs were included in the analyses, and a response was defined as 'correct' if the label chosen by the participant corresponded to the emotion that was dominant in a given morph and as 'incorrect' otherwise. Thus, a total of 10 trials were derived for each emotion at either level of difficulty.

Functional magnetic resonance imaging experiment

Stimuli

For the functional MRI experiment, short video clips of different facial gestures were used as stimuli. Video clips were recorded from 24 actors in an in-house multi-media centre (RWTH Aachen University, Germany). Actors were filmed in portrait format, including their head and shoulders but not their arms, in front of a grey background with a commercial video camera (Sony DVX 2000, spatial resolution 720 × 576 pixels). The actors' hair was fixed and covered with a black scarf. For each video clip, the actor was asked to relax, then to express a facial gesture for 3 s (indicated by a visual sign by a lab member), and then to relax again. After recording, video clips were cut such that each sequence started ~1 s before onset of the facial gesture and terminated ~1 s after offset of the facial gesture, resulting in a total length of 5 s for each video clip. Each actor produced several instances of six affective facial expressions (surprise, fear, sadness, disgust, anger and happiness) and a number of communicative and meaningless facial gestures (lip, cheek and eye movements). After recording, all videos were categorized according to facial gesture by 30 naive observers. Three types of gestures were selected for the current study: 'smile' (the actor showing a smile), 'kiss' (the actor showing a lip protrusion) and 'neutral' (the actor showing a relaxed expression). Only positive facial gestures were selected in order to keep stress for the participants during scanning as low as possible. For each of the 24 actors, the most accurate expression of each category was selected (i.e. the video with the highest recognition rate by the naive observers), giving a total of 72 videos. In addition to these 72 original video clips, a scrambled version was produced of each clip by randomization of down-sampled pixels (1/40 of the original resolution) of the foreground of each frame (i.e. the actor's head and shoulder). In the resulting video clips, the shape of the actor was retrieved, but the facial gesture was no longer visible (Fig. 1).

Experimental design

The functional MRI experiment was designed in a 2 × 3 factorial design, the first factor being the participant's task [the participant was either asked to express a given facial gesture ('do') or to observe the facial gesture shown by the actor ('view')] and the second factor being the type of facial gesture (neutral, kiss or smile) that was to be executed or observed. Video clips were presented in blocks of four 5-s video clips of the same experimental condition (do-neutral, do-kiss, do-smile, view-neutral, view-kiss, or view-smile), giving six 20-s blocks for each experimental condition. These blocks were presented with a stimulus onset asynchrony of 28.8 s (corresponding to 12 scans), thus each block was followed by a 8.8 s baseline (black fixation cross on grey background). Blocks of videos were presented in randomized order. After every sixth video block an additional 33.6 s baseline (corresponding to 14 scans) was inserted. Scanning was divided in two runs, each lasting ~10 min, with a short break in between (Fig. 1).

Participants were instructed to execute a facial gesture ('do') whenever they saw a scrambled video and to attentively watch the actor ('view') whenever they saw an unscrambled video. Scrambled (rather than unscrambled) videos were used in the 'do' condition in order to clearly separate brain activity associated with the execution of a facial gesture from brain activity associated with the perception of a facial gesture. A coloured fixation cross (blue, red or green) superimposed on the actor's scrambled face from 1 s after video onset to 1 s before video offset indicated the participant which facial gesture (neutral, kiss or smile) they were to execute.

After scanning, participants were asked to rate how much joy they had experienced during each condition on a visual analogue scale (1, not at all, to 7, very intense). Additionally, participants were asked to indicate if they had experienced any other emotion than joy during any condition.

Data acquisition

Two hundred and sixty-two echo-planar T_2*-weighted images (EPI, 33 horizontal slices, tilt angle −30°, slice thickness 3 + 1 mm gap, in plane resolution 3 × 3 mm^2, echo time 30 ms, repetition time 2.4 s) were acquired with a 3.0 T scanner (Philips) during each functional imaging run. Functional imaging was preceded by 16 functional scans not included in the analysis to allow for T_1 saturation and participant habituation. Additionally, a T_1-weighted anatomical image

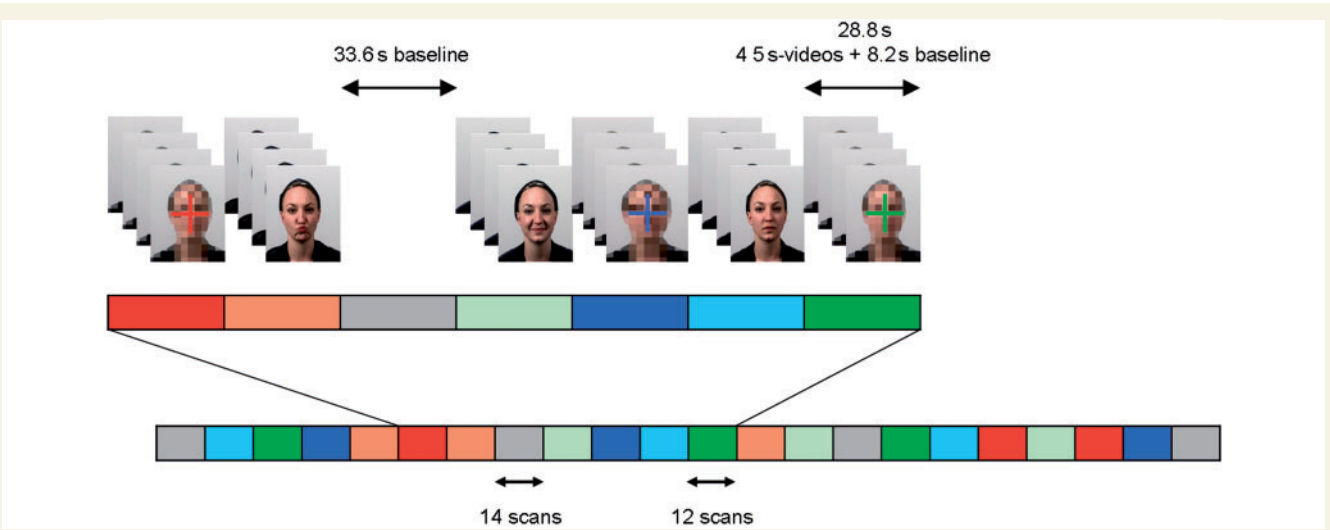

Figure 1 Design of the functional MRI study. The bar at the bottom represents one experimental run. Each participant underwent two runs. Colours indicate the six experimental conditions (green, do-smile; light green, view-smile; red, do-kiss; light red, view-kiss; blue, do-neutral; light blue, view-neutral). Note that 'smile' and 'kiss' conditions were fused in the analysis (see text).

(magnetization-prepared rapid acquisition gradient echo, 1-mm isotropic voxels) was acquired from each participant that was used for spatial normalization of individual data.

Analysis of functional magnetic resonance imaging and behavioural data

Functional MRI data were analysed with SPM5 (The Wellcome Department of Imaging Neuroscience, Institute of Neurology, University College London, UK) following a standard procedure. Pre-processing included slice acquisition time correction, concurrent spatial realignment and unwarping concurrent spatial realignment and correction of image distortions (Anderson *et al.*, 2001), normalization into standard anatomical space (Montreal Neurological Institute, 3-mm isotropic voxels) and spatial smoothing (8-mm Gaussian kernel).

A linear model that accounted for first-order autocorrelations and low-frequency drifts (high pass cut off period 600 s) was used to estimate blood oxygen level-dependent signal amplitudes during each experimental condition for each participant. Each block was modelled as box car function (representing the full length of a video block, 20 s) convolved with a standard canonical haemodynamic response function as implemented in SPM5. Condition-wise averaging of the estimated parameter maps resulted in six parameter maps for each participant, one for each experimental condition (do-neutral, do-kiss, do-smile, view-neutral, view-kiss, view-smile). Since joy ratings in *Parkin* mutation carriers and controls did not differ for 'kiss' and 'smile' gestures (see 'Results' section), parameter estimates for 'kiss' and 'smile' were averaged to one stimulus condition (positive facial gestures), separately for 'do' and 'view' conditions. The resulting four parameter maps for each participant (do-neutral, do-positive, view-neutral, view-positive) were used for group analysis.

A $2 \times 2 \times 2$ ANOVA with between-subject factor group and within-subject factors task ('do' or 'view') and type of facial gesture ('neutral' or 'positive') was used for group analysis. Unequal variance was assumed for all conditions.

Manipulation check

First, we wanted to test whether the experimental paradigm used in the current study reliably reproduced patterns of brain activity reported in previous studies. In particular, we wanted to test whether both execution and observation of facial gestures reliably activated putative mirror neuron areas in the ventrolateral premotor cortex. For this purpose, we used a conjunction analysis across 'do' and 'view' contrasts, which tests the logical *AND*, i.e. the null hypothesis that any of the two contrasts ('do' or 'view') does not show an effect. In other words, for an effect to be significant at the conjoint level it has to be significant in each and every contrast ('conjoint' conjunction in SPM terminology, Nichols *et al.*, 2005). For this initial analysis, we combined data across all participants (i.e. group statistics were computed across *Parkin* mutation carriers and controls neglecting any possible group differences). Three conjunctions were computed: (i) 'do-neutral' AND 'view-neutral'; (ii) 'do-positive' AND 'view-positive'; and (iii) 'do-positive-minus-neutral' AND 'view-positive-minus-neutral'.

Group comparison

Next, we searched for brain activity that was significantly altered during processing of facial gestures in *Parkin* mutation carriers relative to controls. For this, we used a conjunction analysis that tests the null hypothesis that both contrasts show no effect. Since in this analysis it is assumed that all contrasts included in the conjunction show consistent effects, for the conjoint effect to be significant all contrasts have to survive a threshold that decreases with the power of the number of contrasts included ('global' conjunction in SPM terminology, Friston *et al.*, 2005). Although some authors have argued that this conjunction tests a less stringent hypothesis than the 'conjoint' conjunction (Nichols *et al.*, 2005), we opted for this analysis for the group comparison because a 'global' conjunction is more sensitive than a 'conjoint' conjunction analysis (Friston *et al.*, 2005). Since we assumed unequal variance across conditions, the global conjunction analysis required that 'do' and 'view' contrasts were orthogonalized relative to one another. All 'do' contrasts were orthogonalized relative to 'view' contrasts because we reasoned that any effects in visuomotor regions (our main hypothesis) would be stronger for 'do' than for 'view' contrasts (Leslie *et al.*, 2004). Three global conjunctions were computed: (i) 'parkin-do-neutral' versus 'controls-do-neutral' AND 'parkin-view-neutral' versus 'controls-view-neutral'; (ii) 'parkin-do-positive' versus 'controls-do-positive' AND 'parkin-view-positive' versus 'controls-view-positive'; and (iii) 'parkin-do-positive-minus-neutral' versus 'controls-do-positive-minus-neutral' AND 'parkin-view-positive-minus-neutral' versus 'controls-view-positive-minus-neutral'.

All group comparisons were computed in both directions, i.e. increased or decreased activity in *Parkin* mutation carriers relative to controls. To test our main hypothesis that *Parkin* mutation carriers show stronger than normal increase of activity in the right ventrolateral premotor cortex, we used a false discovery rate (Genovese *et al.*, 2002) of $P = 0.05$ within a region of interest that included the pars opercularis of the right inferior frontal gyrus as defined by the automated anatomic labelling (AAL, Tzourio-Mazoyer *et al.*, 2002) Atlas. A false discovery rate of $P = 0.05$ for the whole brain was used to assess statistical significance of altered brain activity outside the right inferior frontal gyrus pars opercularis.

Correlation analysis

Finally, we were interested whether the level of activity in any brain region that showed altered brain activity during facial gesture processing in *Parkin* mutation carriers relative to controls would be positively correlated with an individual's ability to decode emotional facial expressions. This would provide evidence that an increased (or decreased) level of activity in the respective region facilitates decoding of facial emotional expressions. To test this, we extracted parameter estimates for each condition and participant (do-neutral, do-positive, view-neutral, view-positive) from the peak of each activated cluster and fused them to one contrast for each participant (positive-minus-neutral). Two different types of regression analyses were performed. First, we asked whether there was a relation between activity in a given region and each participant's ability to decode emotional facial expressions. To ensure that correlations would not simply be due to differences between groups, group averages were removed from the data in this analysis. Secondly, we asked whether the relation between activity and emotion recognition ability would be altered in *Parkin* mutation carriers. In order to test this, we performed separate regression analyses for the two groups and tested whether the slope of regression would differ between groups (please note that for this analysis it is irrelevant whether group differences are removed). In addition to the regression analysis with emotion recognition data, we performed similar regression analyses for post-scan joy ratings. For this, we fused post-scan joy ratings to a single value for each participant that corresponded to the contrast of brain activity used for the correlation analysis activity ('positive-minus-neutral').

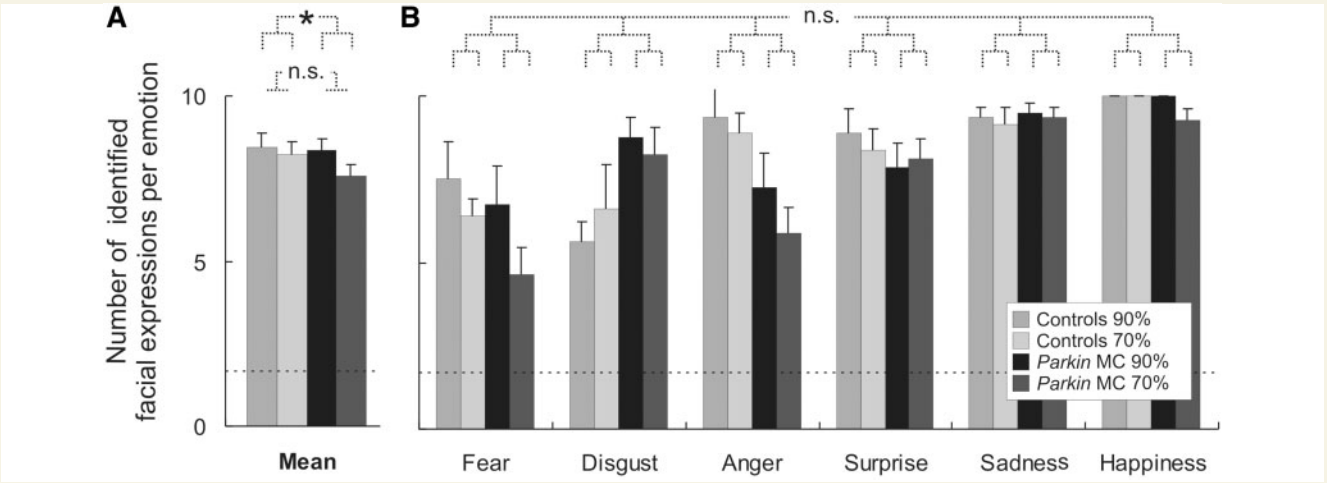

Figure 2 Facial emotion recognition in controls and *Parkin* mutation carriers. (**A**) Average emotion recognition rates did not differ significantly between *Parkin* mutation carriers and controls; however, mutation carriers showed a significantly larger decrease in emotion recognition from clear-cut (90–10%) to fuzzy (70–30%) morphs. (**B**) There was no significant group × level × emotion interaction, indicating that the slight impairment of *Parkin* mutation carriers was not limited to any specific emotion. The asterisk indicates a significant effect (*$P < 0.05$); n.s = not significant. *Parkin* MC = *Parkin* mutation carriers.

Results

Emotion recognition

Both controls and *Parkin* mutation carriers showed above-chance emotion recognition accuracy for both clear-cut (90–10%) and fuzzy (70–30%) morphed emotional facial expressions (Fig. 2; clear-cut morphs, controls 85% correct, *Parkin* mutation carriers 84% correct; fuzzy morphs, controls 82% correct, mutation carriers 76% correct; chance 16%). There was no overall statistically significant difference between *Parkin* mutation carriers and controls [$T(14) = -0.7$], but *Parkin* mutation carriers showed a significantly greater decline from clear-cut to fuzzy emotional expression than controls [$T(14) = 2.0$, $P = 0.03$, one-tailed]. A $2 \times 2 \times 6$ ANOVA with between-subject factor group and within-subjects factors difficulty (clear-cut versus fuzzy morphs) and type of emotion did not reveal a significant group-by-level-by-emotion interaction [$F(5,70) = 1.3$, $P = 0.30$]. Thus, *Parkin* mutation carriers showed a particular impairment for fuzzy facial expression that was not limited to any specific emotion.

Self-reported joy

First, we asked whether the six experimental conditions elicited similar joy responses in *Parkin* mutation carriers and controls at the subjective level and found that this was the case. Pair-wise group comparisons of post-scan joy ratings revealed no significant differences between *Parkin* mutation carriers and controls for any condition [$F(1,14) < 4.0$, $P > 0.05$ for all pair-wise comparisons, Fig. 3]. This was confirmed by a $2 \times 2 \times 3$ ANOVA with factors group, task and type of facial gesture that revealed no significant main effect of group [$F(1,14) = 0.7$, $P > 0.30$], no significant group-by-facial gesture interaction [$F(1,14] = 1.0$, $P > 0.30$] and no significant group-by-task-by-facial gesture interaction [$F(1,14] = 0.8$, $P > 0.30$]. Thus, *Parkin* mutation carriers did not differ from controls in how much joy they experienced during the different experimental conditions.

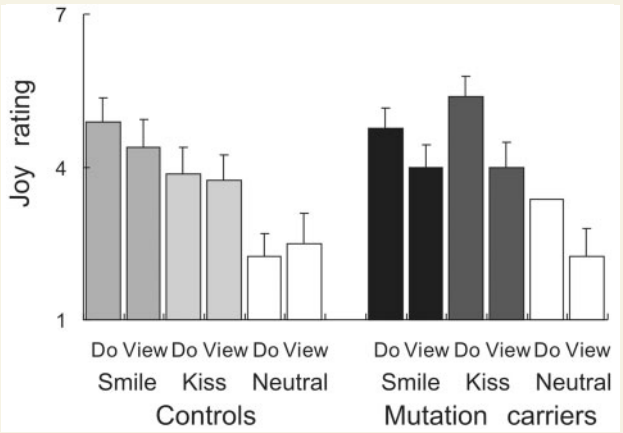

Figure 3 Post-scan joy ratings. *Parkin* mutation carriers did not differ significantly from controls in self-reported joy in any condition.

Next, we tested whether the three different types of facial gestures (neutral, kiss, smile) elicited the intended increasing joy responses in both groups. Both groups showed the expected significant increase in joy ratings from 'neutral' to 'kiss' gestures [*Parkin* mutation carriers, $T(7) = 3.4$, $P = 0.006$; controls, $T(7) = 2.0$, $P = 0.04$], but there was no additional increase in joy ratings from 'kiss' to 'smile' facial gestures [*Parkin* mutation carriers, $T(7) = -0.8$; controls, $T(7) = 1.5$, $P = 0.09$]. Due to this lack of significant differences in joy ratings for the two positive facial gestures, we fused functional MRI data for the 'kiss' and 'smile'

conditions to two conditions (do-positive and view-positive) (see below).

As intended, data fusion led to significant differences between the resulting types of facial gestures in both groups [*Parkin* mutation carriers, $T(7) = 4.0$, $P = 0.003$; controls, $T(7) = 2.9$, $P = 0.01$, note that these comparisons do not constitute valid statistics and *T*- and *P*-values are reported for descriptive purposes only]. Importantly, joy ratings remained very similar across groups, i.e. no significant pair-wise differences between groups, [$F(1,14) < 3.0$, $P > 0.10$ for all pair-wise comparisons], no significant main effect of group [$F(1,14) = 0.8$, $P > 0.30$], no significant group-by-facial gesture interaction [$F(1,14) = 0.3$, $P > 0.50$] and no significant group-by-task-by-facial gesture interaction in a $2 \times 2 \times 2$ ANOVA [$F(1,14) = 0.4$, $P > 0.50$].

Common brain activity during execution and observation of facial gestures

Next, we wanted to test whether the experimental paradigm used in the current study reliably reproduced patterns of brain activity

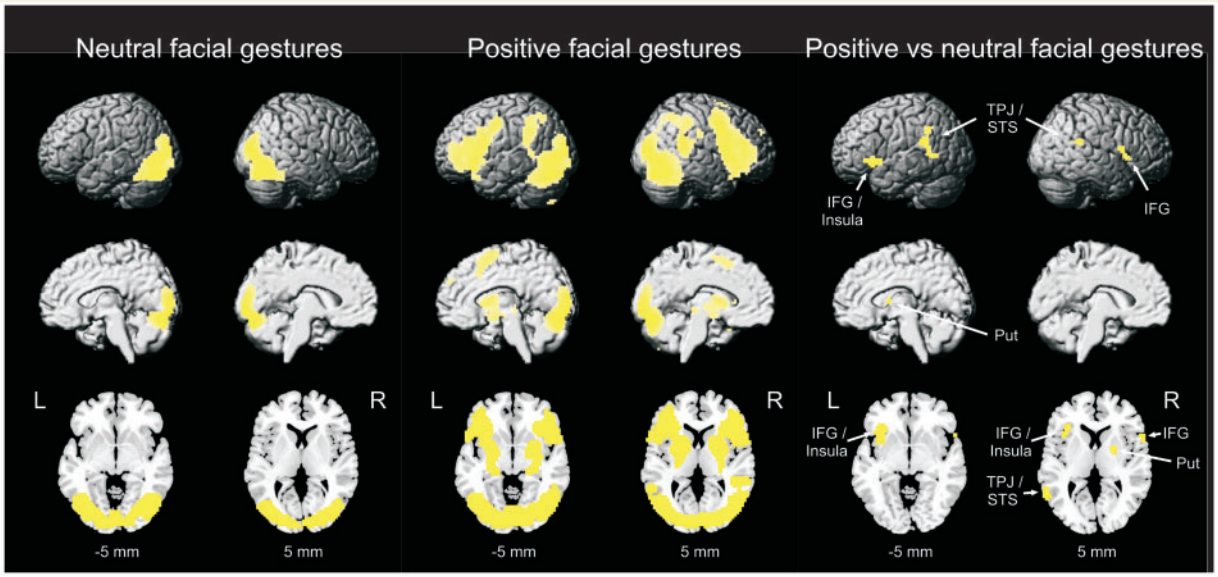

Figure 4 Common BOLD activity during execution and observation of facial gestures in all participants. Statistical parametric maps for execution of facial gestures and for observation of facial gestures were individually thresholded at a false discovery rate of 0.05 (corrected for the whole volume) and inclusively masked such that only voxels are highlighted that show significant activity in both conditions. Only clusters that comprise at least 10 voxels in both contrasts are shown. IFG = inferior frontal gyrus; Put = putamen; STS = superior temporal sulcus; TPJ = temporoparietal junction.

Table 2 Common brain activity during execution and observation of positive versus neutral facial gestures in all participants

Location of cluster	Coordinates at peak	*T*-value at peak	Cluster size (*k*)	Percentage of voxels per anatomical structure	
Temporoparietal junction L	−60 −42 24	4.2	88	40	Superior temporal gyrus L[a]
				25	Supramarginal gyrus L
				18	Middle temporal gyrus L
				14	Inferior parietal gyrus L
Frontoinsular cortex L	−36 18 −3	4.3	78	59	Insular L[a]
				23	Inferior frontal gyrus, pars opercularis L
				13	Inferior frontal gyrus, pars orbitalis L[a]
Frontoinsular cortex R	63 9 9	4.1	26	69	Inferior frontal gyrus, pars opercularis R
				15	Precuneus R
				12	Rolandic operculum R[a]
Temporoparietal junction R	66 −42 21	4.2	16	81	Superior temporal gyrus R[a]
				19	Supramarginal gyrus R
Basal ganglia R	24 0 9	4.2	14	79	Putamen R[a]
				21	Pallidum R

Ordering of clusters is by size. Anatomical structures are labelled with the AAL atlas (Tzourio-Mazoyer *et al.*, 2002). Statistical parametric maps for execution of facial gestures and for observation of facial gestures were individually thresholded at a false discovery rate of 0.05 (corrected for the whole volume) and inclusively masked such that only voxels are highlighted that show significant activity in both conditions. Listed are clusters that comprise at least 10 voxels in both contrasts and anatomical structures that contain at least 10% of all voxels in a cluster. Coordinates are in MNI space.

a The anatomical structure that contains the highest activated voxel.

L = left hemisphere; R = right hemisphere.

reported in previous studies. For this initial analysis, we neglected possible group differences and treated all participants as belonging to a single group. Processing of neutral facial gestures (versus baseline) led to significant activity in a large cluster that comprised lateral and medial occipito-temporal cortex in both hemispheres (Fig. 4). Processing of positive facial gestures (versus baseline) additionally activated two large fronto-temporal clusters that comprised prefrontal, premotor, insular and anterior temporal cortex, part of the basal ganglia and the amygdala. In addition, three smaller lateral parieto-temporal clusters and two smaller frontomedial clusters were observed, comprising supplementary motor and premotor cortex (Fig. 4). Direct comparison of positive and neutral facial gestures revealed stronger activity during processing of positive facial gestures in bilateral inferior frontal cortex, extending into the insula and orbitofrontal cortex in the left hemisphere, and extending into the precentral gyrus and rolandic operculum in the right hemisphere. Additionally, this comparison revealed stronger activity during processing of positive facial gestures in the left and right temporoparietal junction and in the basal ganglia (Fig. 4 and Table 2).

Altered brain activity in *Parkin* mutation carriers

Having ensured that our experimental paradigm reliably reproduced the pattern of overlapping activity during execution and observation of facial gestures reported in previous studies, we proceeded to search for altered brain activity in *Parkin* mutation carriers relative to controls. As predicted, a region-of-interest analysis of the pars opercularis of the right inferior frontal gyrus revealed a significantly stronger than normal increase of brain activity in *Parkin* mutation carriers during processing of positive facial gestures in this area [inferior frontal gyrus pars opercularis, Brodmann area 44/6, $x = 60$, $y = 15$, $z = 6$, $T(14) = 2.9/2.2$ (T execution/observation), conjoint cluster size $k = 20$, Fig. 5]. No other stronger than normal increase of brain activity was observed in *Parkin* mutation carriers. The reverse comparison revealed a significantly weaker than normal increase of brain activity in *Parkin* mutation carriers in the right fusiform gyrus during processing of neutral facial gestures [Brodmann area 18/19, $\times = 21$, $y = -78$, $z = -15$, $T(14) = 4.3/3.7$, conjoint cluster size $k = 7$; Fig. 5. Note that this activity was not predicted and is reported for completeness only] and in the left lateral orbitofrontal cortex during processing of positive versus neutral facial gestures [inferior frontal gyrus pars orbitalis, Brodmann area 47, $x = -42$, $y = 30$, $z = -18$, $T(14) = 3.4/3.4$, conjoint cluster size $k = 3$, Fig. 5]. Parameter estimates in the ventrolateral premotor cortex and the lateral orbitofrontal cortex indicate similar levels of activity during execution and observation within either group (Fig. 5).

Correlation between altered brain activity and emotion recognition ability/self-reported joy

Finally, we asked whether altered brain activity in *Parkin* mutation carriers would be linked to an individual's ability to decode

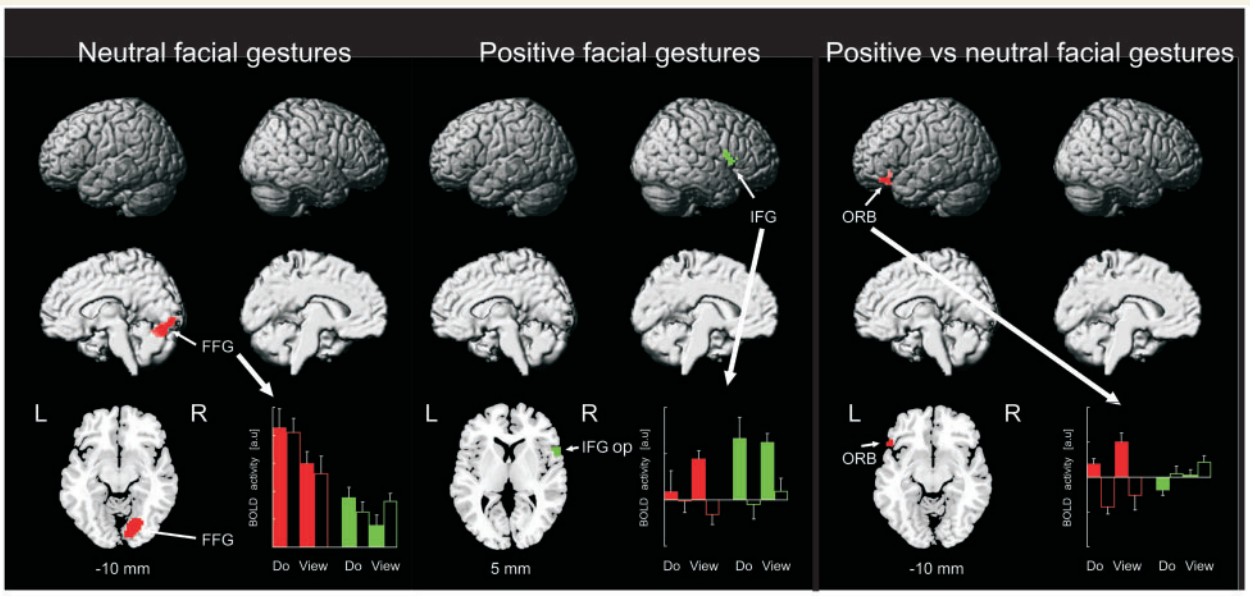

Figure 5 Altered BOLD activity during processing of facial gestures in *Parkin* mutation carriers relative to controls. For visualization, conjoint statistical parametric maps for execution and observation of facial gestures are thresholded at a voxel-wise height threshold of $P = 0.005$, but only clusters are shown whose most significantly activated voxel does not exceed a false discovery rate of 0.05 (see text). The histogram at the bottom of each panel shows activity at the most significantly activated voxel in each map. Red bars = controls; green bars = *Parkin* mutation carriers; filled bars = positive facial expressions; open bars = neutral facial expressions. Error bars indicate standard error of the mean. FFG = fusiform gyrus; IFG op = inferior frontal gyrus, pars opercularis; ORB = inferior frontal gyrus, pars orbitalis.

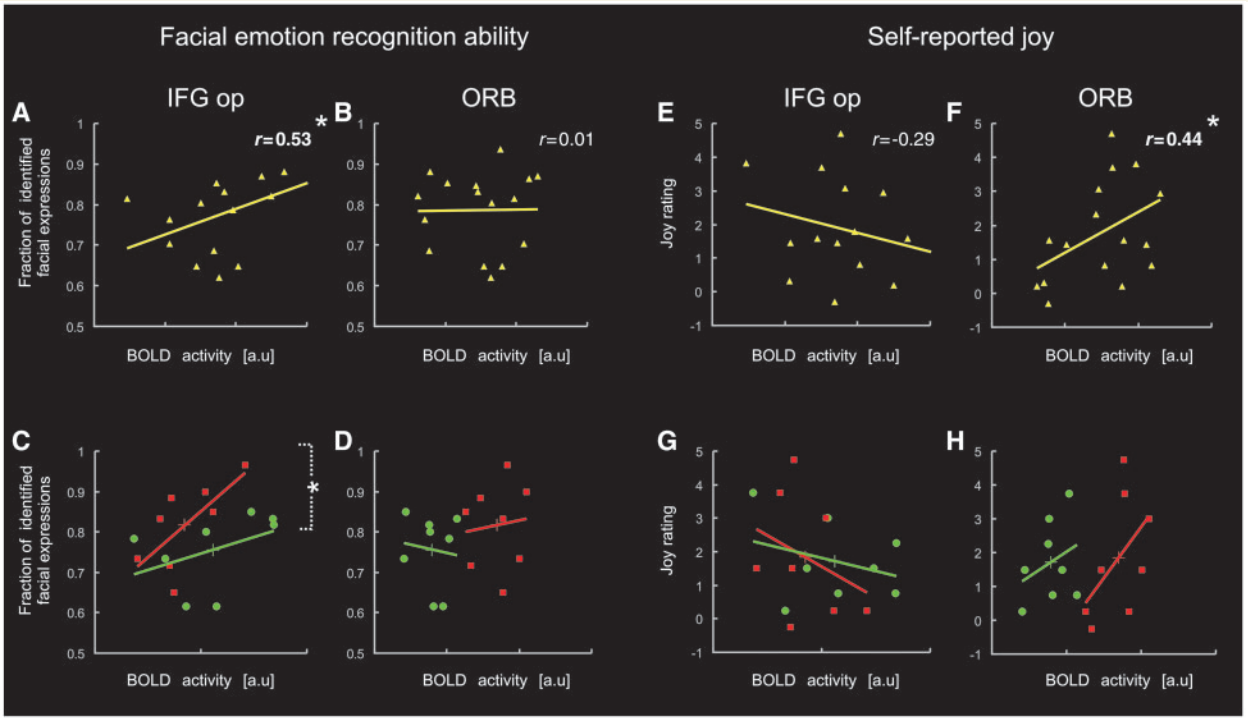

Figure 6 Correlation of BOLD activity and facial emotion recognition ability/self-reported joy. (**A** and **B**) Overall correlation between BOLD activity and facial emotion recognition accuracy in all participants (group differences are removed from BOLD and behavioural data). (**C** and **D**) Slope between BOLD activity and facial emotion recognition accuracy in controls (red squares) and *Parkin* mutation carriers (green circles). Projections of the group means (indicated by the plus) on the *x*- and *y*-axes, respectively, indicate the group mean of BOLD/behavioural data. (**E** and **F**) Overall correlation between BOLD activity and post-scan joy ratings in all participants (group differences are removed from BOLD and behavioural data). (**G** and **H**) Slope between BOLD activity and post-scan joy ratings in controls (red squares) and *Parkin* mutation carriers (green circles). Projections of the group means (indicated by the plus) on the *x*- and *y*-axes, respectively, indicate the group mean of BOLD/behavioural data. *X*-axes represent the contrast of parameter estimates 'positive-minus-neutral', averaged across 'do' and 'view'. *Y*-axes represent emotion recognition scores for fuzzy morphs (70–30%)/post-scan joy ratings (scale 1–7, 'positive-minus-neutral', see text), averaged across 'do' and 'view'. Asterisks indicate a significant correlation (**A**, **B**, **E** and **F**) or a significant difference between slopes for controls and *Parkin* mutation carriers (**C**, **D**, **G** and **H**).

emotional facial expressions. In this analysis, we focused on the two spots in the ventrolateral premotor cortex and the lateral orbitofrontal cortex, respectively, that showed altered activity in Parkin mutation carriers. We found a significant positive correlation between brain activity ('positive-minus-neutral') and emotion recognition scores across all participants in the ventrolateral premotor cortex [$r = 0.52$, $T(1,13) = 2.3$, $P = 0.02$, Fig. 6A]. Notably, separate regression analyses for *Parkin* mutation carriers and controls revealed a significantly flatter slope of regression between inferior premotor activity and emotion recognition scores in *Parkin* mutation carriers than in controls [*Parkin* mutation carriers, slope = 0.8, controls slope = 2.3, $T(1,12) = -1.8$, $P = 0.04$; Fig. 6C]. In other words, individuals in the *Parkin* group had to produce a greater increase in brain activity in the ventrolateral premotor cortex in order to gain a similar increase in facial recognition ability as individuals in the control group. No significant correlation between brain activity and emotion recognition scores was observed in the lateral orbitofrontal cortex ($r = 0.01$, not significant, Fig. 6B and D). To test for the possibility that lateral orbitofrontal activity was more closely related to affective evaluation of facial gestures than to physical decoding, we also correlated brain activity ('positive-minus-neutral') in the ventrolateral premotor cortex and the lateral orbitofrontal cortex with post-scan joy ratings ('positive-minus-neutral'). In the ventrolateral premotor cortex, we found no correlation between brain activity and post-scan joy ratings ($r = -0.40$, not significant; Fig. 6E and G). However, there was a significant positive correlation between brain activity and post-scan joy ratings across all participants in the lateral orbitofrontal cortex [$r = 0.54$, $T(1,13) = 2.4$, $P = 0.02$; Fig. 6F]. The slope of regression between lateral orbitofrontal activity and post-scan joy ratings was similar in *Parkin* mutation carriers and controls [*Parkin* mutation carriers, slope = 1.4, controls slope = 3.0, $T(1,12) = -0.8$, not significant; Fig. 6H].

Discussion

The current study investigated facial emotion recognition ability and brain activity during processing of facial gestures in asymptomatic *Parkin* mutation carriers relative to controls. As predicted,

Parkin mutation carriers were slightly impaired in facial emotion recognition. This slight impairment did not seem to be limited to any particular facial expression. Furthermore, *Parkin* mutation carriers showed a stronger than normal increase of activity in the right ventrolateral premotor cortex (inferior frontal gyrus pars opercularis, Brodmann area 44/6) pars opercularis of the right inferior frontal gyrus (inferior frontal gyrus pars opercularis, Brodmann area 44/6) during processing of affective facial gestures, whereby a stronger increase in inferior frontal gyrus pars opercularis activity during processing of facial gestures predicted less impairment at the behavioural level. In addition, mutation carriers showed a weaker than normal increase of activity during facial emotion processing in the left lateral orbitofrontal cortex (inferior frontal gyrus pars orbitalis, Brodmann area 47), which was unrelated to facial emotion recognition ability. This suggests that compensatory activity in putative human mirror neuron areas during processing of affective facial gestures might have a beneficial effect on facial emotion recognition ability in subclinical *Parkin* mutation carriers.

The ventrolateral premotor cortex

The pars opercularis of the inferior frontal gyrus forms part of the human ventrolateral premotor cortex and is thought to be homologue to monkey premotor area F5, that part of the monkey cortex where 'mirror neurons' were first detected (di Pelligrino *et al.*, 1992). Overlapping blood oxygen level-dependent (BOLD) activity in this area during imitation/production and mere observation of facial expressions in functional MRI studies in humans has been interpreted as evidence that similar visuomotor 'mirror neurons' exist in the human brain (Carr *et al.*, 2003; Leslie *et al.*, 2004; Hennenlotter *et al.*, 2005; van der Gaag *et al.*, 2007), and that these neurons might not only be involved in action understanding, but also in decoding of facial expressions (Adolphs *et al.*, 2000; Gallese, 2003; Decetey and Jackson, 2004; Baastiansen *et al.*, 2009; Iacoboni, 2009). In line with these studies, we found a significant overlap of BOLD activity during execution and observation of affective facial gestures in bilateral ventrolateral premotor cortex in our participants.

In line with our hypothesis, direct comparison of asymptomatic *Parkin* mutation carriers and healthy controls revealed that activity in this area was significantly enhanced during processing of affective facial gestures in *Parkin* mutation carriers. This provides evidence that compensatory mechanisms in asymptomatic *Parkin* mutation carriers are not limited to motor-related activity associated with finger movements (Buhmann *et al.*, 2005; van Nuenen *et al.*, 2009*a*), but extend to ventrolateral premotor activity associated with facial gestures. Importantly, a stronger than normal increase of activity in this area in *Parkin* mutation carriers was not only observed during execution, but also during observation of affective facial gestures. This suggests that similar compensatory mechanisms might be effective during execution and perception of facial gestures and thereby supports 'mirror neuron' theories of facial gesture processing (see Jacobs *et al.*, 1995 for an early related account).

The second important finding of the current study is the positive correlation between ventrolateral premotor activity and emotion recognition ability across participants. Notably, this positive relation was observed even though brain activity was measured during processing of positive facial expressions only, while emotion recognition scores reflected an individual's ability to identify a large range of different emotions. This suggests that increased neural activity in the ventrolateral premotor cortex during facial gesture processing indeed facilitates facial emotion recognition. Importantly, however, the slope of regression between ventrolateral premotor activity and emotion recognition ability was flatter in *Parkin* mutation carriers than in controls. This means that individuals in the *Parkin* group had to produce a greater increase in brain activity in the ventrolateral premotor cortex, or, to 'work harder', in order to gain a similar increase in facial recognition accuracy as individuals in the control group.

The lateral orbitofrontal cortex

In addition to the stronger than normal increase of activity in the right ventrolateral premotor cortex, *Parkin* mutation carriers showed a significantly weaker than normal increase of activity during processing of affective facial gestures in the left lateral orbitofrontal cortex (inferior frontal gyrus pars orbitalis/Brodmann area 47). Although activity in this region is sometimes observed during processing of affective social signals (Sprengelmeyer *et al.*, 1998; Wildgruber *et al.*, 2004; Ethofer *et al.*, 2009; Lotze *et al.*, 2009) this region appears to be primarily involved in value representation and stimulus evaluation (Kringelbach and Rolls, 2004). In line with this interpretation we found a positive correlation between lateral orbitofrontal activity and the participants' joy ratings, but not with their ability to decode facial emotional expressions.

Interestingly, three previous studies have reported reduced grey matter or altered neural activity in patients with Parkinson's disease in clusters remarkably close to the peak of weaker than normal lateral orbitofrontal activity in the current study (Le Jeune *et al.*, 2008: $x = -36$, $y = 31$, $z = -5$; Ibarretxe-Bilbao *et al.*, 2009: $x = -36$, $y = 40$, $z = -18$; Lotze *et al.*, 2009: $x = -54$, $y = 24$, $z = -9$; current study: $x = -42$, $y = 30$, $z = -18$). Only the first of these studies (Le Jeune *et al.*, 2008) found a positive relation between lateral orbitofrontal activity (glucose metabolism measured with PET) and facial emotion recognition in patients with Parkinson's disease. The other two studies assessed recognition of emotional gestures, but did not find a significant correlation between BOLD activity during observation of emotional gestures and emotional gesture recognition ability (Lotze *et al.*, 2009) or grey matter volume and facial emotion recognition ability (Ibarretxe-Bilbao *et al.*, 2009; note, however, that these authors report a positive correlation between grey matter loss in more distributed regions of the orbitofrontal cortex and emotion recognition impairment). Thus, orbitofrontal grey matter and neural activity seem to be altered in Parkinson's disease but these changes might not have a direct impact on social emotion recognition ability in these patients.

Two different compensatory mechanisms?

The pattern of findings described above raises the question why *Parkin* mutation carriers show stronger than normal activity in the

right ventrolateral premotor cortex (where activity was positively linked to emotion recognition ability), but weaker than normal activity in left orbitofrontal cortex (where activity was positively linked to self-reported joy). One matter that makes it difficult to tackle this question is the fact that the non-motor loops that connect the basal ganglia with human prefrontal cortex are considerably less well understood than basal ganglia–cortical motor loops.

The ventrolateral premotor cortex—presumably including Brodmann area 44/monkey area F5—is generally assumed to be part of the motor basal-ganglia cortical gating loop (DeLong and Wichmann, 2007) that projects from premotor, motor and somatosensory cortex via the putamen back to the supplemental motor area (Alexander *et al.*, 1986). The stronger than normal activity in the inferior frontal gyrus pars opercularis in the current study can thus be interpreted as a compensatory response caused by nerve degeneration in the putamen.

The situation is less clear for the orbitofrontal cortex. This is partly due to the fact that most current knowledge about cortico-basal ganglia–cortical gating loops stems from studies in non-human primates (or even rodents) and that human orbitofrontal cortex—and particularly Brodmann area 47 where weaker than normal activity was observed in the current study—cannot easily be mapped onto monkey prefrontal cortex (Kringelbach and Rolls, 2004). This area has been discussed to be part of at least two alternative cortico-basal ganglia–cortical gating loops. Lotze *et al.* (2009) suggested that this area forms part of the 'lateral orbitofrontal gating loop' described by Alexander *et al.* (1986) that receives input from the lateral orbitofrontal cortex and superior and inferior temporal cortex and projects, via the *head of the caudate nucleus*, back to the inferior frontal gyrus pars orbitalis. This assumption is supported by a diffusion tensor imaging study in healthy human participants, which found anatomical connections from the anterior putamen/head of the caudate nucleus to Brodmann area 47 (Lehericy *et al.*, 2004). Alternatively, as pointed out by Kringelbach and Rolls (2004), Brodmann area 47 might be part of a cortical area that in fact is homologue to medial orbitofrontal cortex in monkeys. If this was true, then this area might be part of the 'anterior cingulate gating loop' of Alexander *et al.* (1986). This loop receives inputs from medial prefrontal, enthorinal, perirhinal and temporo-polar cortex as well as the amygdala and hippocampus and projects, via the ventral striatum, back to medial prefrontal cortex. Interestingly, behavioural studies have often ascribed emotion recognition deficits in Parkinson's disease to this latter loop (which is often referred to as 'mesolimbic gating loop') (e.g. Sprengelmeyer *et al.*, 2003; Clark *et al.*, 2008; Gray and Tickle-Degnen, 2010). Both the caudate nucleus and the ventral striatum have been found to be affected in Parkinson's disease (e.g. Morrish *et al.*, 1996; Hilker *et al.*, 2001; Kumajura *et al.*, 2010), but the current study does not permit to directly link one of these basal ganglia sites to the observed weaker than normal activity in the lateral orbitofrontal cortex.

It is possible that non-motor basal ganglia–cortical gating loops have less capacity to compensate for dopaminergic nerve degeneration than motor basal ganglia–cortical gating loops. Thus, reduced (rather than amplified) lateral orbitofrontal activation might be observed already at very early stages of the disease. Another intriguing possibility is that dopaminergic imbalance leads to heightened (rather than diminished) sensitivity in the 'mesolimbic gating loop' early in the disease and that the lower level of inferior frontal gyrus pars orbitalis activation in *Parkin* mutation carriers is in fact a compensatory response to such heightened sensitivity. In line with this reasoning, a recent PET study demonstrated that dopaminergic activity of the 'mesolimbic' system is heightened, rather than diminished, at least in some stages of Parkinson's disease (Kumakura *et al.*, 2010), and there is first evidence that heightened amygdala activity resulting from deep brain stimulation in the substantia nigra can have a detrimental effect on facial emotion recognition (Le Jeune *et al.*, 2008). However, this evidence is clearly still very limited and further studies a needed to examine these questions in more detail.

Limitations

The current study demonstrates altered processing of affective facial gestures in asymptomatic *Parkin* mutation carriers at the behavioural and cerebral level and thereby extends previous studies that have shown altered motor-related activity in these individuals. However, the current study also shares some limitations with previous studies that used asymptomatic mutation carriers as a human model for presymptomatic Parkinson's disease. First, all *Parkin* mutation carriers investigated in the current study were members of one family living in a rural area in northern Italy. To keep logistical effort reasonable, other studies have used a similar approach (Hilker *et al.*, 2001, 2002; Khan *et al.*, 2002, 2005; Scherfler *et al.*, 2004; Buhmann *et al.*, 2005). However, until findings from these and the current study have been replicated in a larger sample, including individuals from different pedigrees, the possibility remains that the altered pattern of cerebral processing observed in those and the current study did not result from the gene mutations in question, but from some other genetic or environmental factors shared by all mutation carriers in a particular study. Secondly, altered patterns of brain activity in the current study could not be directly linked to altered dopamine metabolism in circumscribed nodes of the basal ganglia. Current developments in PET technology and data analysis permit detailed investigations of dopamine metabolism at high spatial resolution (e.g. Kumakura *et al.*, 2010). Future studies should aim to integrate these techniques with functional MRI in the same individuals to examine the neurobiological processes underlying altered patterns of cerebral processing in the presymptomatic and clinical stages of Parkinson's disease in more detail.

Conclusion

The current study provides evidence for altered processing of affective facial gestures in the presymptomatic stage of Parkinson's disease. Most importantly, our findings demonstrate for the first time a link between increased activity in the ventrolateral premotor cortex (inferior frontal gyrus pars opercularis, Brodmann area 44/6) and facial emotion recognition ability in

these individuals and thereby provide direct evidence for a compensatory effect of increased ventrolateral premotor activity on facial emotion recognition deficits. A breakdown of this mechanism might lead to the impairment of facial expressivity and facial emotion recognition observed in manifest Parkinson's disease. In addition, we observed significantly weaker than normal activity in *Parkin* mutation carriers in lateral orbitofrontal cortex (inferior frontal gyrus pars opercularis, Brodmann area 47), an area that is probably associated with stimulus evaluation and value representation. Further studies combining PET and functional MRI are needed to track the neurobiological processes underlying these changes in cortical activity.

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