Reward Processing in Health and Parkinson’s Disease: Neural Organization and Reorganization

It has been suggested that motivational processes mediated by dopaminergic neural systems may be relatively spared in Parkinson’s disease (PD) and activation of these pathways may be of therapeutic relevance. To investigate the behavioural and neural correlates of motivation in unmedicated PD patients, we used H$_2^{15}$O positron emission tomography to measure brain activation patterns related to the processing of monetary rewards of different magnitudes during a spatial search task in PD patients withdrawn from medication, and age-matched healthy controls. Both groups showed increased search efficiency with increasing reward, but demonstrated different patterns of neuronal activation. In healthy controls activity in prefrontal and rhinal cortices, and thalamic activity correlated with reward magnitude. In contrast, activity in the cerebellar vermis in PD patients increased with increasing reward magnitude, suggesting it was sensitive to motivational state. We interpret these relative increases in cerebellar activation as evidence for the presence of compensatory neural mechanisms in unmedicated PD patients.

Introduction

Parkinson’s disease (PD) is characterized by a loss of dopamine containing neurons in the substantia nigra pars compacta that innervate the striatum, with the loss of neurons in the ventral tegmental area innervating ‘limbic’ and neocortical regions being much less severe (Hornykiewicz and Kish, 1986). These dopamine systems have long been implicated in the processing of rewards (Wise, 1982; Schultz, 2002). It has recently been suggested that certain intact motivational processes may be of therapeutic benefit in PD (Charbonneau et al., 1996; Horvitz and Eyny, 2000; de la Fuente-Fernández et al., 2001). However, previous studies of reward processing in PD have produced contradictory findings, possibly related to the reward processes investigated, and the medication and mood status of patients (Charbonneau et al., 1996; Hart et al., 1998; Persico et al., 1998; Küng et al., 2000), and, therefore, it is important to examine whether reward processes, and the neural circuits underpinning them, are intact in PD.

In the current study, we set out to examine with H$_2^{15}$O positron emission tomography (PET) the neural structures involved in processing financial rewards of different magnitude in PD during the performance of a spatial search task. Previous research has shown that variations in the magnitude of biological rewards produce motivational shifts in performance (Dickinson and Balleine, 2002), and hence we hypothesized that, behaviourally, such an effect would be manifest with monetary rewards. The design enabled us to examine whether PD patients would show motivational effects similar to those of healthy controls, as well as to examine the neural correlates of such an effect.

Based on previous neuroimaging studies of monetary reward processing in healthy volunteers (e.g. Thut et al., 1997; Breiter et al., 2001; O’Doherty et al., 2001; Knutson et al., 2001; Elliott et al., 2003) we predicted that the striatum, thalamus, medial prefrontal cortices and temporal lobe structures, including the amygdala, would be activated in relation to financial rewards in healthy controls, and that the motivational properties of increasing reward magnitude would be mediated by these neural circuits. If motivational processes are relatively spared in PD, then we would predict a similar pattern of activation in PD patients to controls. If not, and PD patients show reduced motivation, then we would predict reduced activation in regions associated with reward processing: as previous imaging studies in PD have suggested areas of relative over-activation in PD, especially the cerebellar vermis, when striatal and frontal regions are underactivated (e.g. Jahanshahi et al., 1995; Rascol et al., 1997; Owen et al., 1998; Catalan et al., 1999; Hanakawa et al., 1999a; Thobois et al., 2000; Nakamura et al., 2001), we predicted that the cerebellar vermis would be relatively over-activated in PD in such a case.

Materials and Methods

Participants

We studied nine healthy controls (mean age 57 years, range, 45–69) and nine PD patients (mean age 58 years, range, 48–68) matched for age and pre-morbid verbal IQ as estimated using the National Adult Reading Test (NART; Nelson and Willison, 1991). All participants were right-handed. Participants were excluded if they had current or prior history of psychiatric or neurological disease other than PD, head trauma, hypertension, diabetes or medical conditions that may alter cerebral functioning, or a past or current history of alcohol or substance abuse. Healthy controls were initially screened by telephone and then assessed prior to scanning.

All Parkinsonian patients were referred from neurological clinics and assessed by a neurologist prior to scanning. They satisfied the UK Brain Bank criteria for clinically probable idiopathic PD (Gibb and Lees, 1988) and had a predominantly akinetic-rigid phenotype. In addition PD patients had to score >24 on the Mini-Mental Parkinson (Mahieux et al., 1995) to exclude co-existence of dementia, and be free of anticholinergic medication. The Geriatric Depression Scale (Yesavage, 1988) was also administered in the untreated patients to ensure that concomitant depression did not interfere with reward sensitivity in the untreated state. PET scans in this group were performed at least 12 h following withdrawal of anti-parkinsonian medication. In addition Unified Parkinson’s Disease Rating Scale (UPDRS) (Fahn and Elton, 1987) and Hoehn and Yahr (Hoehn and Yahr, 1967) scores were evaluated in the practically defined off state. Demographic features of all participants are detailed in Table 1.

Written informed consent was obtained from the participants according to the declaration of Helsinki after the nature and possible risks of the study were fully explained. The Ethics Committee of the Hammersmith Hospitals Trust gave approval for the study. Permission to administer radioisotopes was given by the Administration of Radioactive Substances Advisory Committee (ARSAC) of the Department of Health (UK).
Reward Paradigm

A spatial search task, based on one used in the CANTAB battery (Cambridge Neuropsychological Test Automated Battery; Cambridge Cognition, Cambridge, UK) was developed. A variant of this task has previously been used in neuroimaging studies of healthy volunteers (Owen et al., 1996) and neuropsychological studies of PD (Owen et al., 1997). The task was written in Microsoft Visual Basic 4 and ran on a Dell 486 PC fitted with a touch-sensitive screen that was suspended in the front of the participants within comfortable reach. The screen was controlled using Microtouch Mouse-emulation software.

Participants had to complete three trials of the task during each 90 s task condition, a valueless token or a monetary reward before it was presented. A pacing tone sounded every 3 s. When the participant heard the pacing tone, he touched a box on the screen. The box opened and revealed either an empty space, or (depending on the task condition), a valueless token or a monetary reward before it was covered up again. There were four different scan conditions, with differing reward magnitudes [zero (token), 5p (UK Sterling pence), 10p, 50p]. Per trial each box contained a token or reward only once. Hence in a particular trial four tokens or rewards had to be found (equal to the number of boxes per trial). The participants, therefore, had to remember which box previously had contained a token or reward on that trial, and avoid returning to it. When all four rewards or tokens had been found on a trial, a new configuration of boxes appeared on the screen for the participants to search. During a 90 s scan, three trials (12 boxes) were presented.

All participants received practice prior to scanning, in order to familiarize them with the task, and to rule out simple practice effects. Three further trials of the task were given while the participants were lying on the scanner couch immediately prior to scanning to ensure that they were able to perform the task successfully.

A complete PET study included 12 rCBF scans. Each condition (token, 5p, 10p, 50p reward) occurred three times with the value of the reward presented kept constant during any particular rCBF scan. The order of conditions was randomized both within and between participants to minimize time and order effects. Participants were explicitly instructed that they would be awarded the equivalent amount of financial reward that they found during the scanning session (~£24, rounded-up to £30). The level of task difficulty, four boxes per search, was deliberately kept low to ensure that PD patients showed a similar performance level to that of healthy controls, and to minimize the use of mnemonic strategies.

Two performance indices were recorded. Completion time was defined as a return to a previously successful box on a particular trial.

PET Data Acquisition

PET data were acquired with an ECAT EXACT HR+ 3-D camera (model 966, CTI, Knoxville, TN) with a total axial field of view of 23.4 cm (Spinks et al., 2000), allowing whole brain coverage. For each scan, ~185 MBq (5 mCi) of 15O-labelled water in 3 ml saline was flushed through an intravenous cannula into the participant over 20 s at a rate of 10 ml/min by an automatic pump. Scanning of emission data was started 30 s after the infusion of the radiolabelled tracer, ~5 s before the detection of radioactivity in the head, and lasted for 90 s. This was preceded by a 30 s scan to measure background radiation.

Between PET measurements an interval of 6 min was allowed for the decay of the radioactive tracer. All experimental tasks were started 30 s before the emission scan for the PD group and 15 s before the emission scan for the healthy control group. The extended preparation time for the patients was to ensure that all participants were at a similar point in the task during the scanning period. A transmission scan was performed with an external rotating point source of 137Cs, prior to the collection of emission data transmission scanning, to allow a measured attenuation correction. The emission data were reconstructed by 3-D filtered back projection (Ramp filter; Nyquist cut-off). This gives an isotropic reconstructed spatial resolution of 4.5 mm full-width at half-maximum (FWHM).

Statistical Parametric Mapping

Image analysis was undertaken on a SUN ULTRA 10 (Sun Microsystems Europe Inc., Surrey, UK) workstation using SPM99 software (Wellcome Department of Imaging Neuroscience, London, UK) implemented in MATLAB 5.3 (The MathWorks Inc., Sherborn, MA).

Scans were realigned using the mean image as a reference, normalized for global cerebral blood flow values and stereotaxically normalized into standard anatomical space using the template developed at the Montreal Neurological Institute. The images were smoothed using an isotropic Gaussian kernel (FWHM 12 mm for all directions). The contribution of global blood flow variance to local blood flow variance was removed by using analysis of covariance with global activity as the confounding variable. Additionally, scan order was entered as a covariate of no interest to control for any time or order effects (Brett et al., 1999).

Significant changes in activation within and between groups were localized using the General Linear Model. Appropriately weighted
linear contrasts identified activated areas on a voxel-wise basis (Friston et al., 1995). The following contrasts were constructed:

- Positive linear correlation between relative rCBF and amount of reward received. The latter was defined using the following formula: \((\text{No. of rewards collected per scan} \times \text{level of reward})/\text{No. of responses made per scan}/\text{response latency}) \times 100\). This parametric contrast allowed us to examine regions activated in relation to the relative ‘concentration’ of reward individuals received in each scan epoch.
- Conjunction analysis (Price and Friston, 1997) of the following subtraction contrasts: 50p versus tokens, 50p versus 10p, 50p versus 5p. This analysis allowed us to examine activation related to absolute levels of reward magnitude, independent of performance.

Contrasts were applied within and between groups. To provide a further between-group comparison we employed exclusive masking, which identifies areas that are activated to a greater extent in one group than in the other group.

For the initial within-group analysis we used a criterion for significance of \(P < 0.05\) at the voxel level, corrected for multiple non-independent comparisons. For the follow-up comparisons, we used the regions identified in the initial within-group analysis to guide a regions-of-interest analysis and report areas identified at a significance level of \(P < 0.05\) corrected for the regions of interest (Worsley et al., 1996). Activations which corresponded to the same anatomical regions (defined by the atlas of Talairach and Tournoux, 1988) as those identified in the initial within group analysis, but which fell outside our stringent defined regions of interest, are also reported for completeness. The results are displayed as statistical parametric maps (SPM\(^t_s\)) of significant focal changes in rCBF (Friston et al., 1995).

**Statistical Analyses of Performance Data**

Repeated measures analysis of variance (ANOVA) was applied to the completion time and search error data. In order to normalize the distributions and to reduce the heterogeneity of variances the latency data were subjected to a logarithmic transformation and the error scores were subjected to a square root transformation. Any remaining outliers were removed after the transformations and the missing values were substituted by the mean. All data analyses were performed using SPSS\(\text{TM}\) for Windows, version 10.

**Results**

**Performance Data**

Repeated measures ANOVA revealed a significant main effect of reward magnitude on completion times \([F(3,48) = 7.22, P < 0.001]\), but no effect of group \([F(1,16) = 0.01, P > 0.05]\) and no significant interaction term \([F(3,48) = 0.46, P > 0.05]\). Follow up linear trend analyses revealed linear decreases in completion times with increasing reward for both healthy volunteers \([F(1,8) = 12.183, P < 0.01]\) and PD patients \([F(1,8) = 11.494, P < 0.01]\). Data are represented in graphical format in Figure 2.

Concerning search errors, there was no main effect of reward level \([F(3,48) = 1.65, P = 0.191]\), no main effect of group \([F(1,16) = 0.04, P > 0.05]\), and no significant interaction term \([F(3,48) = 1.90, P > 0.05]\). The mean number of errors per condition in healthy volunteers were: token = 2, 5p = 3.9, 10p = 1.7, 50p = 1.6. The mean number of errors in PD were: token = 4.7, 5p = 3.7, 10p = 5.6, 50p = 4.9. The decrease in completion times with increasing reward, therefore, is not a manifestation of a speed-accuracy trade-off.

**rCBF data – Areas Showing Activity Correlating with Reward**

Several brain regions in the healthy control participants showed increases in activation that correlated with increasing levels of reward, including right medial and orbital frontal regions near the frontal polar cortex (Öngur et al., 2003), left rhinal cortex and right thalamus (Table 2). In PD patients, by contrast, there was an increase in cerebellar vermis activation that correlated with increasing levels of reward (Fig. 3, Table 2). The same areas were also identified in between group analyses (Table 2). In particular, PD patients showed relatively increased cerebellar activity in relation to reward.

**rCBF Data – Areas Showing Activity Changes Associated with High Reward versus No or Minor Reward Magnitudes**

The same brain areas identified in the parametric approach (see above) were also identified in the categorical approach within and between groups although only at a less stringent level of significance. The healthy volunteers showed rCBF activity changes in the left medial frontal (near the frontal pole) cortex, left rhinal cortex, and right thalamus when comparing the highest reward magnitude with minor reward magnitudes (Table 3). In PD patients, by contrast, the rCBF change was located in the cerebellum when comparing the highest reward magnitude with minor reward magnitudes (Table 3). The same areas were identified in between group analyses (Table 3).

**Discussion**

In this study, we set out to examine the neural correlates of the motivational modulation of behaviour induced by variations in reward magnitude, in patients with PD withdrawn from medication and in healthy volunteers. We have demonstrated a number of novel findings. Completion time improved with increasing reward magnitude in both unmedicated PD patients and healthy volunteers. In healthy volunteers, this effect was associated with increased rCBF in orbital and medial prefrontal and rhinal cortices, and the thalamus. By contrast, PD patients showed relative over-activation of the cerebellar vermis, which appeared to be modulated by motivational state, increasing with increasing financial rewards.
Motivational Modulation of Task Performance and Its Neural Correlates

Our data demonstrate motivational modulation of task performance by monetary rewards in control and Parkinsonian groups, even though the neural correlates of this effect appear to be different in the two groups. This finding may be important for therapeutic strategies in PD (Charbonneau et al., 1996; Horvitz and Eyny, 2000; de la Fuente-Fernández et al., 2001). In particular, Horvitz and Eyny (2000) have suggested that Parkinsonian deficits may be reduced in the presence of salient environmental stimuli. This may be related to the phenomenon of paradoxical movement (kinesia paradoxica) in PD.

Motivational shifts in performance have previously been shown in the animal literature (Flaherty, 1996; Dickinson and Balleine, 2002), and in humans (Eysenck, 1982), although the effect of reward on response vigour is generally more consistent than that on cognitive performance. The mechanisms by which reward improves performance are not well understood, but the following psychological processes have been suggested to be involved: emotional effects (Flaherty, 1996), attentional effects (Eysenck, 1982), and Pavlovian and instrumental incentive learning processes (Berridge and Robinson, 1998; Berridge, 2001; Dickinson and Balleine, 2002).

Although it is difficult to determine the relative contribution of these processes in our study, we can compare the neural correlates of increased motivation in our healthy volunteers to the neural structures shown to be necessary in other animals for various reward processes. Recent research has established that Pavlovian incentive learning is mediated by midbrain dopaminergic systems and their projections into the amygdala, midlateral thalamus and ventral striatum (McAlanon et al., 1993; Berridge and Robinson, 1998; Dickinson et al., 2000; Schultz, 2000; Cardinal et al., 2002). Instrumental incentive processes, by contrast, are mediated by cortical structures including the orbitofrontal and rhinal cortices (Gallagher et al., 1999; Schultz, 2000; Corbit et al., 2002; Cardinal et al., 2002). Hence, the activations seen in our study are likely composed of several reward processes. The neural systems identified in experimental animals, involved in approach behaviours and instrumental actions, are also activated in other neuroimaging studies in healthy controls during monetary reward processing (Thut et al., 1997; Breiter et al., 2001; O’Doherty et al., 2001; Knutson et al., 2001; Elliott et al., 2003). At a statistical threshold of $P < 0.05$ corrected for whole brain comparisons, we did not see activation in other areas associated with motivation, such as the ventral striatum and amygdala. Some previous imaging studies have shown such structures activated to monetary reward (Breiter et al., 2001; Knutson et al., 2001; Elliott et al., 2003), whereas others have not (Thut et al., 1997; O’Doherty et al., 2001). It is noteworthy that the areas activated in the current study are also seen during cue-induced craving (Grant et al., 1996; Bonson et al., 2002), and such cues can have marked performance effects (Ludwig et al., 1974). In addition, increases were seen both in relation to absolute reward magnitude in the subtraction analysis and increased reward ‘concentration’ per unit time in the parametric analysis, again suggesting they were related to a common motivational effect (Dickinson and Balleine, 2002). Taken together, these data strongly suggest that the activations seen in healthy volunteers in the present study are associated with the motivational effects of financial reward, rather than being epiphenomenal. As the areas activated in our paradigm are reciprocally connected (Insausti et al., 1987; Ray and Price, 1993; Carmichael and Price, 1995), and have previously been suggested to form a functional circuit involved in the processing of rewards (Baxter and Murray, 2000), our findings lead us to suggest that they may form an interconnected system mediating the motivational modulation of task performance.

Effects of Motivation in PD

Although motivational modulation of task performance was seen in PD (i.e. completion times were faster with increasing reward magnitudes), significant cortical and thalamic activity was not seen in PD patients, although it should be noted that the current study had limited statistical power. Previous activation studies in PD have linked similar reductions in activation to a reduction in task efficacy, which in turn was postulated to be due to a loss of dopaminergic neuromodulation (Jahanshahi et al., 1995; Rascol et al., 1997; Owen et al., 1998; Catalan et al., 1999; Hanakawa et al., 1999a; Thobois et al., 2000; Nakamura et al., 2001). It is likely that decreased monoaminergic neurotransmission contributed to reduced activations in our study, as reductions in cortical levels of both dopamine and

**Table 2**

Regions showing activity correlated with reward magnitude within and between groups (HC and PD)

<table>
<thead>
<tr>
<th>Area</th>
<th>Coordinates (mm)</th>
<th>Zmax</th>
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<tbody>
<tr>
<td>Healthy controls</td>
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<tr>
<td>Healthy controls (TA)</td>
<td></td>
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<tr>
<td>R orbital and medial PFC (BA 11)</td>
<td>18 57 –25</td>
<td>4.74</td>
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<tr>
<td>L rhinal cortex (BA 36)</td>
<td>–20 –38 –18</td>
<td>5.15</td>
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<tr>
<td>R thalamus</td>
<td>26 –31 4</td>
<td>5.39</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
<td></td>
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<tr>
<td>Cerebellar vermis</td>
<td>–2 –73 –20</td>
<td>4.88</td>
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<tr>
<td>Increases in HC relative to PD (interaction)</td>
<td></td>
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<tr>
<td>L orbital and medial PFC (BA 10)</td>
<td>–22 39 –5</td>
<td>3.44</td>
</tr>
<tr>
<td>L rhinal cortex (BA 36)</td>
<td>–22 –34 –17</td>
<td>2.81</td>
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<tr>
<td>R thalamus</td>
<td>–2 –23 12</td>
<td>2.27</td>
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<td>Increases in PD relative to HC (interaction)</td>
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<tr>
<td>Cerebellar vermis</td>
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<td>4.41</td>
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<tr>
<td>Increases in HC but not in PD (exclusive masking)</td>
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<tr>
<td>R orbital and medial PFC (BA 11)</td>
<td>16 51 –26</td>
<td>4.51</td>
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<tr>
<td>L rhinal cortex (BA 36)</td>
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<td>Increases in PD but not in HC (exclusive masking)</td>
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<tr>
<td>Cerebellar vermis</td>
<td>–2 –73 –20</td>
<td>4.88</td>
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</tbody>
</table>

*R = right, L = left.


* Opposite hemisphere to within-subject analysis. BA = Brodmann area derived from Talairach and Tournoux (1988).

* $P < 0.05$, corrected for multiple comparisons.

* $P < 0.01$, corrected for multiple comparisons.

* $P < 0.001$, uncorrected for multiple comparisons.

* $P < 0.05$, corrected for region of interest.

* $P < 0.01$, corrected for multiple comparisons.

* $P < 0.001$, corrected for region of interest.
noradrenaline in regions including the orbitofrontal, cingulate and rhinal cortices in PD have been reported (Scatton et al., 1983; Hornykiewicz and Kish, 1986; Ouchi et al., 1999).

By contrast to healthy controls, cerebellar (in the region of the vermis) rCBF was correlated with reward magnitude in PD patients suggesting that the cerebellum might be particularly involved in motivational modulation in PD patients showing reduced dopaminergic functioning (i.e. when unmedicated). It can be speculated that in the PD patients a dopamine-independent reward mechanism was at play, although it cannot be determined from the current data what psychological processes might have contributed to the motivational modulation.

That aspects of reward processing (e.g. hedonics and instrumental reward processes) can remain intact despite reduced dopamine levels has previously been reported in rats (Nader et al., 1997; Berridge and Robinson, 1998; Dickinson et al., 2000; Horvitz and Eyny, 2000). In particular, Salamone et al. (2001) have shown that animals still acquire and consume food, provided that the work requirement is relatively low, as in the current study, and rats with lesions to the (ventral) striatum can still show a motivational modulation of performance (Bowman and Brown, 1998). Nader et al. (1997) have proposed the existence of two anatomically separate motivational systems in the brain: one dopamine dependent and involving cortico-striatal-thalamocortical circuits, and one dopamine independent and involving the brainstem pedunculopontine tegmental nucleus (PPTg) (but see Berridge and Robinson, 1998). In the light of the current results, it is noteworthy that the PPTg and cerebellum are strongly interconnected (Hazzri and Parent, 1992) and that the cerebellum is involved in reward processing (Gibbs, 1992; Acheson et al., 2000; Knutson et al., 2001).

Hence, we suggest that cerebellar activation is able to support motivational modulation in PD patients withdrawn from medication. This finding may relate to Salamone’s suggestion (Salamone et al., 2001) that dopamine depleted animals are more dependent on the direct, sensory feedback provided by rewards. Indeed, visual cues are able to guide motor behaviour in PD (Oliveira et al., 1997; Praamstra et al., 1998; Lewis et al., 2000), a process involving the cerebellum (Hanakawa et al., 2000; Johnson et al., 2000).
al., 1999b). However, such compensatory processes will have limits. Indeed, there was a tendency to show increased errors in PD patients suggesting a subtle impairment in either activation or instrumental reward processes may have been present (although covarying for error scores in the analysis did not alter the findings; data not shown). It will be important in future work to determine if ventral striatal-related reward circuitry is active in medicated PD patients, together with a concomitant reduction in the use of cerebellar pathways.

Increased cerebellar activity during reward processing in PD may form part of a more general compensatory process in unmedicated PD patients. For example, the cerebellum has been suggested as a site that takes over functions following cortical damage (Vanderwolf et al., 1978), and in particular a role for cerebellar circuitry in compensatory processes in PD (including kinesia paradoxica) has been hypothesized by Keefe et al. (1989) and Glickstein and Stein (1991). To examine the generality of this process, we plotted the coordinates from previous imaging studies demonstrating relatively increased cerebellar activations in PD, compared with controls, during motor (Jahanshahi et al., 1995; Davis et al., 1997; Hanakawa et al., 1999a; Thobois et al., 2000; Nakamura et al., 2001), cognitive (Owen et al., 1998; Nakamura et al., 2001), and motivational tasks (Künig et al., 2000; present results). Figure 4 summarizes these. As can be seen there is a tight clustering of activation maxima, demonstrating consistency across studies and processing domains, in keeping with a generalized compensatory response. That such activations increase with increasing motivation may also have implications for rehabilitative strategies in PD.

**Does Increased Cerebellar Activation in PD Truly Represent a Compensatory Process?**

It could be argued that the relatively increased cerebellar activation seen in the present study, rather than reflecting compensatory processes, could reflect, for example, reduced baseline metabolism (Hu et al., 2000), reduced inhibition (Praamstra et al., 1998), a functional imbalance between regions (Stein and Aziz, 1999), or an artefact of altered task performance (Price and Friston, 1999). We find these explanations unlikely however, for a number of reasons.

First, the regions showing relatively increased rCBF during reward processing in PD appear different from those showing reduced basal metabolic activity (Hu et al., 2000). Secondly, our primary use of a correlational design overcomes some of the difficulties in interpreting subtractive contrasts (e.g. the pure insertion assumption, or increased baseline activity). Moreover, that there was a correlation between increasing amount of reward and cerebellar activation, together with a concomitant improvement in task efficiency, is very difficult to interpret in terms of task-irrelevant neural activity. Thirdly, the cognitive demands of the task were deliberately kept at a low level such that PD patients would not demonstrate any performance deficits (Owen et al., 1997). Further, the use of a pacing tone ensured that PD patients and controls made the same total number of movements during each 90 s scanning epoch.

It could be suggested that the improvement in performance with higher reward levels in PD patients indicates that the observed rCBF changes are related to facilitation of activity in regions involved in working memory, rather than those representing motivational processes. This is unlikely, however, because Cools et al. (2002) and Mattay et al. (2002) recently scanned untreated PD patients using working memory paradigms and neither study identified the cerebellar vermis to be activated during working memory in PD patients. Nor was the cerebellum significantly activated in controls who also showed a motivational modulation of performance.

To conclude, we have shown that monetary rewards can produce motivational modulation of task performance in PD patients when withdrawn from medication, together with relatively increased cerebellar vermis activation. Such activation likely reflects some kind of compensatory strategy, related to the guidance of behaviours by direct sensory cues. Whatever the nature of this process, it appears sensitive to motivational state, which may have implications for therapeutic strategies in PD.

**Notes**

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