Temporal dynamics of basal ganglia under-recruitment in Parkinson's disease: transient caudate abnormalities during updating of working memory

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Using hybrid-blocked/event-related fMRI and the 2-back task we aimed to decompose tonic and phasic temporal dynamics of basal ganglia response abnormalities in working memory associated with early untreated Parkinson's disease. In view of the tonic/phasic dopamine hypothesis, which posits a functional division between phasic D2-dependent striatal updating processes and tonic D1-dependent prefrontal context-maintenance processes, we predicted that newly diagnosed, drug-naïve Parkinson's disease patients, with selective striatal dopamine deprivation, would demonstrate transient rather than sustained activation changes in the basal ganglia during 2-back performance. Task-related activation patterns within discrete basal ganglia structures were directly compared between patients and healthy elderly controls. The obtained results yielded uniquely transient underactivation foci in caudate nuclei, putamen and globus pallidus in Parkinson's disease patients, which indicates suboptimal phasic implementation of striatal D2-dependent gating mechanisms during updating. Sustained underactivation was only seen in the anterior putamen, which may reflect initial signs of tonic control impairment. No significant changes were exhibited in prefrontal cortex. The present findings resonate well with the tonic/phasic dopamine account and suggest that basal ganglia under-recruitment associated with executive dysfunction in early Parkinson's disease might predominantly stem from deficiencies in phasic executive components subserved by striatum.

Keywords: Parkinson's disease; hybrid fMRI; cognitive control dynamics; verbal working memory; Striatum

Abbreviations: BG = basal ganglia; DA = dopamine; fMRI = functional magnetic resonance imaging; PET = positron emission tomography; WM = working memory

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Introduction

Parkinson’s disease is a neurodegenerative disorder which beyond movement disabilities also entails cognitive difficulties. Despite the fact that Parkinson’s disease primarily arises from selective deterioration of dopaminergic neurons in the substantia nigra pars compacta and principally affects basal ganglia (BG) structures (Hornykiewicz and Kish, 1987), the resulting neuropsychological deficits show remarkable similarities with those observed in frontal lobe patients (Taylor et al., 1986). This disproportionate effect on so called executive functions is demonstrated very early in the disease (Lees and Smith, 1983; Owen et al., 1992) when severe dopamine (DA) depletion is largely restricted to the dorsal striatum (Kish et al., 1988), which implicates a crucial role of this structure in some critical aspect of normal executive functioning. However, the exact nature of this role and its degree of functional specificity/generality is not well understood.

Early positron emission tomography (PET) studies taxing planning and spatial working memory (WM) revealed under-recruitment of caudate nucleus and globus pallidus interna (GPI) in patients with Parkinson's disease relative to healthy controls (Owen et al., 1998; Dagher et al., 2001). However, since PET measures comprise the amalgamation
of brain activity from all cognitive operations occurring over prolonged task periods, inferences about specific component processes giving rise to BG underactivity are unfeasible. More recently, event-related functional magnetic resonance imaging (fMRI) studies, enabling better temporal resolution than PET, have yielded evidence of Parkinson’s disease-related transient striatal underactivity specifically associated with difficulties during task-set shifting (Monchi et al., 2006a) and ‘online’ manipulation of information within WM (Lewis et al., 2003; Owen, 2004). Still, the neurocognitive significance of BG underactivation and its contribution to executive dysfunction in early Parkinson’s disease remains underspecified. Although standard event-related fMRI allows transient activity elicited by particular trials to be measured and interrogated for Parkinson’s disease-related abnormalities, it cannot provide information regarding potential changes in sustained activity associated with tonic control components. Recent studies in healthy subjects using ‘hybrid’ blocked/event-related fMRI designs, which permit separation of transient and sustained activity, have shown that enhanced sustained responses are functionally coupled with trial-independent tonic control processes engaged throughout task performance (Donaldson, 2004). It remains possible that task-induced sustained underactivation represents a yet unexplored characteristic of abnormal BG responses in Parkinson’s disease.

Functional neuroimaging studies in healthy subjects have yielded findings of striatal involvement in both tonic and phasic executive control. Although several studies have reported transient caudate activation during phasic executive processes like response inhibition (Wager et al., 2005), set-shifting (Brass et al., 2003) and manipulation (Lewis et al., 2004), other imaging evidence has shown sustained caudate activation associated with maintenance-related tonic control processes (Huettel et al., 2004; Chang et al., 2007; Marklund et al., 2007a, b). For example, in a recent hybrid-blocked/event-related fMRI study employing the n-back paradigm a sustained activation pattern was elicited in the caudate which dynamically modulated with incremental executive load from 1-back to 2-back (Marklund et al., 2007a, b). Sustained delay-period activity in striatum has also been evidenced in monkey electrophysiological recordings (Hikosaka et al., 1989; Apicella et al., 1992).

At a fundamental level, understanding the precise nature of deficient striatal mechanisms that give rise to cognitive impairments in early unmedicated Parkinson’s disease requires taking into account detailed properties of normal DA neuromodulation (Cohen et al., 2002; Frank and O’Reilly, 2006). Biologically plausible computational modeling of mechanistic principles assumed to underlie dynamic DA modulation in ‘normally’ operating working memory (Durstewitz et al., 1999; Seamans et al., 2001), together with molecular imaging studies exploring the relative functional and regional importance of key DA receptor-families (for review, see Croll et al., 2006), promise to shed light on putative striatal roles in executive control and how compromised BG integrity relates to cognitive deficits in Parkinson’s disease.

The tonic/phasic model of DA neurotransmission (Grace, 1991; Bilder et al., 2004; Grace et al., 2007) has recently been proposed as a promising theoretical gateway for exploring the dysexecutive characteristics observed in Parkinson’s disease (Cools, 2006). This model is based on the opposing, but complementary principles by which the two key DA receptor subclasses in the brain; D1 and D2, are believed to subserve efficient information processing in the brain (Bilder et al., 2004); with D1 receptors being particularly abundant in prefrontal cortex (PFC), and D2 receptors having their primary site of occupancy in the dorsal striatum (Hall et al., 1994). According to the tonic/phasic hypothesis, D1 receptors are involved in tonic DA activation modes serving to promote stable neural representations and processing states, whereby they are deemed critical for WM and active maintenance processes mediated by sustained activation in PFC (Bilder et al., 2004). In contrast, D2 receptors are assumed to preferentially engage in phasic DA neurotransmission serving to promote adaptive behaviour and cognitive flexibility. In computational models BG structures are given a key role in purportedly D2-dependent gating mechanisms that control information going in and out of WM and come into play when there is great demand on rapid updating of WM or shifting between operational modes (Frank et al., 2001). The tonic/phasic DA model has received indirect empirical support from electrophysiological animal work (Williams and Goldman-Rakic, 1995), pharmacological challenges in humans (Mehta et al., 2003; Tost et al., 2006), and molecular imaging studies directly assessing regional DA function in vivo (for review, see Croll et al., 2006). However, the local relationship between DA transmission and brain activity is not well understood and presumably vary between brain regions and specific demands on cognitive tasks. Nonetheless, intriguing evidence suggest a close link between various parameters of DA and brain activity at local BG sites. A positive coupling has been established between local DA release and neural activation in nucleus accumbens (Knutson and Gibbs, 2007) and PET findings of striatal DA release during performance of an executive task (Monchi et al., 2006a) corresponded closely to striatal blood oxygen level-dependent (BOLD) signal increases reported for the same task (Monchi et al., 2006b).

In view of these suggestive empirical findings and the functional division of the DA system into tonic and phasic neuromodulatory components, with compelling evidence of D2-dependent striatal contributions to phasic executive control (Croll et al., 2006), it may be hypothesized that regionally selective striatal DA loss in early Parkinson’s disease would predominantly yield transient BG underrecruitment related to suboptimal implementation of phasic control processes essential for cognitive flexibility and updating. This would confer with the particular sensitivity in Parkinson’s disease to cognitive tasks involving...
Striatal underactivation in Parkinson’s disease

The main objective of the present study was to explicate the relationship between BG underactivation and tonic/phasic executive components of WM in newly diagnosed Parkinson’s disease patients who had never been exposed to DA drug therapy. By using drug-naïve patients, potential confounds of previous medication, such as effects on number of DA receptors, can be avoided. This issue has generally not been considered in prior imaging research on Parkinson’s disease. For the purpose of decomposing the temporal dynamics of WM-related brain activity the running 2-back paradigm was deemed especially suitable since it reliably activates striatal circuitry in healthy subjects (Marklund et al., 2007a; Dahlín et al., 2008) and provides ideal task characteristics for separating neural correlates of context maintenance and updating (Marklund et al., 2007b).

In accordance with the tonic/phasic DA model, we predicted that Parkinson’s disease patients would predominantly exhibit transient striatal response abnormalities (especially in the caudate) associated with the phasic executive component of updating, with less pronounced changes in sustained responses. Yet, it remains unresolved whether profound striatal DA deprivation causes disturbances in tonic executive components that involve BG structures. The fact that not only D2 receptors but also D1 receptors are densely expressed in dorsal striatum (Volkow et al., 1996) may tentatively have implications for the neurofunctional impact of striatal DA loss on BG BOLD signals that go beyond transient underactivity. A critical component in 2-back that relies on tonic control is context maintenance which evokes sustained frontostralial activation in healthy young adults (Marklund et al., 2007b).

Using hybrid-blocked/event-related fMRI and the 2-back task we aimed to disentangle tonic and phasic executive components of BG under-recruitment in de novo Parkinson’s disease by way of contrasting the relative contributions of sustained versus transient activity with respect to their ability to account for abnormal fMRI BOLD signal patterns. Task-related activation patterns within regions of interest (ROIs) were directly compared between patients and healthy elderly controls. To the knowledge of the authors, no prior imaging study has specifically examined sustained activity changes in patients with Parkinson’s disease. The relative degree to which BG activation of sustained and transient nature are affected by executive challenges in de novo Parkinson’s disease might have theoretical implications for biologically based models attempting to explicate the relationships between striatal DA deficiencies and cognitive impairments in Parkinson’s disease.

Material and Methods

Subjects

Twenty newly diagnosed Parkinson’s disease patients (mean age = 64.9 years; SD = 10.8; nine males) that had not yet started any (DA replacement) treatment and 21 healthy control subjects (mean age = 69.1 years; SD = 2.5; eight males), matched for gender and education level, were enlisted to participate in the study after having given written informed consent. All patients fulfilled diagnostic criteria for definite Parkinson’s disease and were in the early phase of the disease (Gibb and Lees, 1988). Mini-Mental State Examination scores (Folstein et al., 1975) in patients were in the range of 28–30 and they all exhibited a pathological dopamine transporter (DAT) SPECT acquired using DaTSCAN™, while normal uptake was found in all healthy control subjects (Amersham Bio-Sciences, GE Healthcare, WI, USA). Motor functioning was assessed using the Electronic tapping test (Dilks et al., 2006) and yielded significantly lower scores in Parkinson’s disease patients than controls for the left hand, and a trend towards significant difference was found for the right hand (Table 1). Eighteen of the Parkinson’s disease patients and 10 control subjects also underwent extensive neuropsychological assessment. The current study was approved by the ethics committee at Umeå University of Northern Sweden.

Neuropsychological tests

Cognitive functioning was assessed using forward and backward digit span, mental control, paired associative learning and the logical memory subtest of the Wechsler Memory Scale (Wechsler, 1987), the free and cued selective reminding test (Buschkue, 1984), the brief visuospatial memory test (Benedict et al., 1996), verbal fluency tests, the Boston naming test (Benton et al., 1983), the Benton judgment of line orientation test (Benton et al., 1983), the Wisconsin Card Sorting Test (WCST) (Heaton et al., 1993) and the Trail Making Test versions A and B (TMTA and TMTB) (Reitan, 1958).

Experimental protocol and procedures

Prior to the scanning session, all subjects were given thorough instructions regarding the 2-back task paradigm they were to perform in the scanner. They were also allowed sufficient practice on the task on a computer outside the scanner. In the 2-back task a sequence of single word items was presented on a screen one at a time (duration 2.5 s per word), with varying intervals between consecutive presentations, including some inter-stimulus-intervals (ISIs) of up to more than 20 s to tax active maintenance processes. Subjects were instructed to make a target/foil judgment for every presented word, and respond ‘yes’ when the word matched the one presented two items earlier (i.e. target trial), and ‘no’ when it was different (i.e. foil trial). They were told to indicate ‘yes’ and ‘no’ responses by pressing keys on a pair of scanner-compatible keypads (Lumitouch reply system, Lightwave Medical Industries, Canada) with their right or left index finger, respectively. The experimental protocol lasted for approximately 6 min (357 s), and comprised four task blocks of 63 s each. Task blocks were
interleaved with 21 s fixation blocks, and scanning sessions also began and ended with such blocks. During these ‘off’ task periods, subjects were instructed to do nothing apart from keeping their gaze fixed at a small circle presented at the centre of the screen. At the end of these fixation blocks an instructional cue was displayed on the screen for 2.5 s informing subjects that the 2-back task was now beginning. Each task block consisted of eight consecutive trials, with the first two items requiring ‘no’ responses (since no 2-back item had yet been presented), which were then followed by three target and three foil items, the presentation order of which was intermixed and balanced out across task blocks. The stimulus material was projected on the centre of a semitransparent screen that subjects viewed through a tilted mirror attached to the head coil. Behavioral performance [i.e. accuracy data and response time (RT) data] were recorded using a PC running E-Prime 1.1 (Psychology Software Tools, Inc., PA). For the RT data all trials with RTs below 300 ms were excluded from because they were considered as outliers.

**fMRI data acquisition and analysis**

The fMRI acquisition was conducted using a 1.5 T Philips Intera scanner (Philips Medical Systems, The Netherlands). Functional T$_2^*$-weighte images were collected with a single-shot gradient echo EPI sequence used for BOLD) imaging. The sequence had the following parameters: repetition time: 3000 ms, echo time: 50 ms, flip angle: 90°, field of view: $22 \times 22$ cm, $64 \times 64$ matrix and 4.40 mm slice thickness (voxel size $3.44 \times 3.44 \times 4.40$ mm$^3$). Every repetition time, 33 slices were acquired. To eliminate signals arising from progressive saturation, five dummy scans were performed prior to the image acquisition. In the scanner, cushions were used to reduce head movement and headphones were used to dampen scanner noise and for communication with the subjects.

The obtained fMRI data were transferred to a PC and converted to Analyze format. Preprocessing and statistical analyses were performed with Statistical Parametric Mapping (SPM2) (Wellcome Department of Imaging Neuroscience, London, UK) adopting a ROI approach. The pre-processing step included slice timing correction, realignment with respect to the first image volume in the series, unwarping to reduce residual movement-related variance, normalisation to an EPI template in the Montreal Neurological Institute (MNI) space, and finally smoothing using an isotropic Gaussian filter kernel with a full width at half maximum of 8.0 mm.

The 2-back task was performed in four task blocks, each containing eight word items presented with varying ISIs, with a fixation cross-hair presented at the centre of the screen in between trials. Task blocks were interspersed with 21 s baseline periods during which a circle was continuously presented at the centre of the screen. The regressors modelling event-related responses and epoch-related responses, respectively, are inevitably correlated with each other to some extent in hybrid designs, which makes it mandatory to design the experiment in such a way that it minimizes this correlation, since a high degree of correlation between regressors yields low parameter estimation efficiency (Visscher et al., 2003). In order to de-correlate the event and epoch regressors within task blocks the stimulus onset asynchrony (SOA) was ‘jittered’ between 2.5 and 25 s in a pseudorandomized fashion according to an approximate Poisson distribution (i.e. for ~60% of the items, the SOA was 2.5 s, for 30% of the items, the SOA was 20 s, and for a few items, the SOA was 22.5 s (9%) or 25 s (1%) long). By this procedure the correlation between event and epoch-related regressors was kept below 0.6, which conurs with a reasonably efficient estimation and separation of transient and sustained neural responses.

Sustained and transient effects were modelled separately in the framework of the general linear model (Friston et al., 1995) as implemented in SPM2. Event-related transient responses were modelled as regressors containing delta functions representing onsets of word stimuli, whereas epoch-related sustained responses were modelled with boxcar functions representing entire task blocks (Friston et al., 1998). Both regressor types were convolved with a canonical haemodynamic response function.

Applying the general linear model to the imaging data resulted in least square estimates of the regressors on a subject-specific level. Task-induced sustained and transient effects were calculated as linear combinations of the individual regressors and stored as subject-specific contrast images. Since 2-back accuracy in two subjects of the control group was 4 SDs below average performance level they were dropped from further analyses. To maintain equivalent group sizes the Parkinson’s disease patient with poorest performance was also eliminated from further analyses. Hence, contrast images of 38 subjects (i.e. 19 Parkinson’s disease patients and 19 age-matched healthy controls) were included in the regression analyses conducted in SPM to assess activation changes associated with Parkinson’s disease. Subject-specific contrasts were entered into a second-level model using two sample t-tests to examine differential activations between groups for each contrast of interest. This method is equivalent to a random effects analysis treating subjects as a random variable (Holmes and Friston, 1998).

We employed an ROI approach to limit the scope of our analyses since we were mainly interested in effects occurring in BG structures. We defined six (left and right) BG-ROIs which together covered caudate nucleus (1956 voxels), putamen (2073 voxels) and GPi (573 voxels), with the anatomical demarcation of each ROI being specified with the help of the WFU-pickatlas (Maldjian et al., 2003) as implemented in SPM2. Given the strong a priori hypothesis predicting reduced activation within rather small BG-ROIs in Parkinson’s disease patients and an interest for increasing sensitivity since we specifically focused on de novo Parkinson’s disease (that were somewhat younger than controls) we accepted a liberal statistical threshold set to $P < 0.005$ (uncorrected). Bonferroni correction for multiple comparisons was deemed excessively stringent and not applicable since its requirement for total independence of measures between ROIs was not satisfied. The results from an independent analysis, conducted to test for covariance among BG ROIs in each group separately confirmed that activation in many regions were significantly correlated with one another, especially for transient activity in the control group. To ensure that the direction of effects was one-way (i.e. Parkinson’s disease < controls) as predicted by our hypotheses, the reverse contrast (i.e. Parkinson’s disease > controls) was examined for occurrences of greater sustained or transient responses in patients relative to controls at $P < 0.05$ (uncorrected) within each ROI. With respect to this reverse contrast a very lenient threshold provides a good test of discriminant validity and anatomical generality pertaining to the hypothesis of BG underactivation in early Parkinson’s disease patients. Additional supplementary ROI analyses were performed in lateral PFC. For this exploratory analysis we created spherical (5 mm radius) PFC-ROIs in left and right ventrolateral (VLPFC) and dorsolateral (DLPFC) regions based on the peak activation coordinates demonstrated
in whole-brain SPMs of sustained and transient responses relative to baseline combined across all subjects (including patients and controls; see Fig. 1). PFC-ROIs centres were for transient effects (VLPFC: MNI $x$, y, z-coordinates, left and right: $-32, 26, -2$ and $32, 26, -2$; DLPFC: $-36, 40$ and $34, 54, 33$), and sustained effects (VLPFC: $-54, 12, 2$, and $46, 24, -2$; DLPFC: $-48, 30, 32$, and $48, 36, 32$). This allowed an exploratory interrogation of WM-related PFC response abnormalities in newly diagnosed Parkinson’s disease patients that had not yet started DA replacement treatment. Previous findings of Parkinson’s disease-related activity changes in PFC have involved medicated patients (Lewis et al., 2003). For these exploratory analyses Bonferroni correction for multiple comparisons was used.

To index functional consequences of underactivity at distinct BG foci we calculated correlations between magnitude of sustained and transient responses and 2-back performance measures (RT and accuracy). Further exploratory analyses correlated BG underactivity foci with two executive behavioural indices derived from neuropsychological testing. Reasoning that there might be differences in the patterns of brain–behaviour relations between ‘normal’ (albeit age-affected) BG recruitment vis-à-vis early pathological BG under-recruitment in Parkinson’s disease, not only quantitatively but also qualitatively, these correlational analyses were conducted within each group separately. Newly diagnosed, unmedicated Parkinson’s disease patients have been associated with disproportionate impairments on WCST (Lees and Smith, 1983), especially with respect to perseverative errors, which makes this score particularly interesting for probing the neurofunctional impact of BG underactivity on cognitive flexibility. Brain–behaviour correlations were also calculated for TMTB score (time to completion) which measures shifting and maintenance of complex motor set. Bonferroni correction for multiple comparisons was applied for these brain-behavioural analyses ($P < 0.05$ four tests per ROI yielding a $P < 0.01$). Results are reported both with and without this multiplicity adjustment.

![Fig. 1](http://brain.oxfordjournals.org/) Sustained brain activity during 2-back relative to resting baseline, thresholded at $P < 0.0001$ after false discovery rate correction (top), transient brain activity during 2-back relative to resting baseline, thresholded at $P < 0.000001$ after family-wise error correction (middle), and overlap (yellow) between sustained (green) and transient (red) responses (bottom) from whole brain analyses combining all subjects.

### Results

#### Neuropsychological tests

The mean scores and standard deviation for the neuropsychological data in the two groups are displayed in Table 1. We performed $t$-tests to compare scores between groups which only yielded significant differences on WCST; Parkinson’s disease associated with greater number of trials ($P < 0.05$) and nonperseverative errors ($P < 0.05$, equal variances not assumed). Overall, Parkinson’s disease patients performed normally, although a tendency towards relatively poorer performance was observed for the majority of executive functioning scores.

#### Behavioural data

No significant group difference was observed with respect to 2-back performance accuracy (percent correct).

### Table I Mean scores and SD for demographic and neuropsychological data in patients with Parkinson’s disease and healthy controls

<table>
<thead>
<tr>
<th></th>
<th>Parkinson’s disease patients</th>
<th>Controls</th>
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<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>18 (9 male)</td>
<td>10 (4 male)</td>
</tr>
<tr>
<td>Age</td>
<td>65.1 (11.1)</td>
<td>69.1 (3.0)</td>
</tr>
<tr>
<td>Education</td>
<td>11.4 (4.1)</td>
<td>11.4 (2.9)</td>
</tr>
<tr>
<td><strong>Neuropsychological measures</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buschke selective reminding test (17/10)</td>
<td>44.3 (4.4)</td>
<td>45.8 (2.6)</td>
</tr>
<tr>
<td>Logical memory A (13/7)</td>
<td>12.2 (3.1)</td>
<td>10.9 (2.5)</td>
</tr>
<tr>
<td>Logical memory B (13/6)</td>
<td>6.9 (3.5)</td>
<td>6.2 (2.5)</td>
</tr>
<tr>
<td>Associative learning</td>
<td>13.8 (4.1)</td>
<td>13.3 (3.4)</td>
</tr>
<tr>
<td>Brief visuospatial memory test</td>
<td>22.2 (5.0)</td>
<td>20.9 (6.6)</td>
</tr>
<tr>
<td>Digit Span Foward</td>
<td>10.1 (2.0)</td>
<td>9.2 (2.1)</td>
</tr>
<tr>
<td>Digit Span Backward</td>
<td>6.7 (2.1)</td>
<td>6.5 (2.1)</td>
</tr>
<tr>
<td><strong>Psychomotoric</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Electronic tapping test right hand</td>
<td>54.6 (10.0)</td>
<td>60.00 (71)</td>
</tr>
<tr>
<td>Electronic tapping test left hand</td>
<td>46.7 (14.2)</td>
<td>56.4 (78)**</td>
</tr>
<tr>
<td><strong>Executive functions</strong></td>
<td></td>
<td></td>
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<tr>
<td>Mental control (17/10)</td>
<td>7.5 (1.7)</td>
<td>6.5 (2.1)</td>
</tr>
<tr>
<td>WCST (total score)</td>
<td>40.5 (11.1)</td>
<td>46.4 (5.9)</td>
</tr>
<tr>
<td>WCST (trial)</td>
<td>24.4 (19.3)</td>
<td>13.4 (6.2)**</td>
</tr>
<tr>
<td>WCST (errors)</td>
<td>23.5 (11.1)</td>
<td>17.6 (5.9)</td>
</tr>
<tr>
<td>WCST (perseverative responses)</td>
<td>14.2 (7.2)</td>
<td>11.4 (6.3)</td>
</tr>
<tr>
<td>WCST (perseverative errors)</td>
<td>12.0 (5.6)</td>
<td>9.5 (4.6)</td>
</tr>
<tr>
<td>WCST (nonperseverative errors)</td>
<td>11.5 (6.9)</td>
<td>8.1 (2.8)**</td>
</tr>
<tr>
<td>WCST (concept formation)</td>
<td>33.5 (15.6)</td>
<td>41.6 (8.4)</td>
</tr>
<tr>
<td>WCST (number of categories)</td>
<td>2.3 (1.5)</td>
<td>3.1 (1.4)</td>
</tr>
<tr>
<td>Trail making test A (total secs)</td>
<td>46.6 (16.3)</td>
<td>42.3 (15.7)</td>
</tr>
<tr>
<td>Trail making test B (total secs)</td>
<td>108.0 (491)</td>
<td>104.3 (35.2)</td>
</tr>
<tr>
<td><strong>Verbal function</strong></td>
<td></td>
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<tr>
<td>Verbal fluency: FAS</td>
<td>47.6 (15.2)</td>
<td>44.2 (4.5)</td>
</tr>
<tr>
<td>Verbal fluency: Category</td>
<td>44.3 (98)</td>
<td>43.6 (8.3)</td>
</tr>
<tr>
<td><strong>Visuospatial function</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The Benton judgement of line orientation</td>
<td>24.9 (4.0)</td>
<td>24.8 (3.7)</td>
</tr>
</tbody>
</table>

**$P < 0.05$; **$P < 0.05$ (equal variances not assumed).
patients performing a WM task involving manipulation. Apart from the fact that patients participating in the present study were drug-naïve, this inconsistency might be due to differences in disease severity since we only included newly diagnosed patients. Another plausible explanation is that manipulation relies more heavily on DLPFC than updating.

### Brain–behaviour correlational analyses

In Parkinson’s disease patients there was no evidence of associations between magnitude of transient underactivity and RT or accuracy measures recorded during 2-back performance ($P > 0.1$). The absence of activation–RT correlations clearly indicates that reduced BG responses in Parkinson’s disease cannot easily be attributed to motor programming difficulties during response execution. In contrast, in healthy controls who elicited differentially greater transient responses in the same foci, the activation magnitude generally showed positive correlations with RT indices, but negative correlations with accuracy. For example, responses at the right transient caudate focus was positively correlated with RT ($R^2 = 0.46, P < 0.05$), while negatively correlated with accuracy ($R^2 = -0.58, P < 0.05$). This indicates that in healthy controls transient responses at foci showing Parkinson’s disease-related underactivity in BG-ROIs increased with item-related processing time tentatively dependent on degree of decision uncertainty. For the sustained putamen underactivity focus, controls’ responses showed negative correlation with RT ($R^2 = -0.53, P < 0.05$) and a similar trend for accuracy ($R^2 = -0.44, P < 0.06$). No correlations were found between age and the reported transient and sustained effects in ROIs.

Brain–behaviour relationships between magnitude of response in underactivated BG ROI foci and non-flexibility in WCST performance as measured by perseverative errors revealed negative correlation in the Parkinson’s disease group, but not the control group, between transient left caudate activation and number of perseverative errors in WCST ($R^2 = -0.48, P < 0.05$). This finding suggests, albeit indirectly, a functional association between striatal under-recruitment in newly diagnosed, drug-naïve Parkinson’s disease patients and impaired cognitive flexibility. In healthy controls a negative correlation was found between sustained right putamen activation and TMTB time ($R^2 = -0.67, P < 0.05$) indicating a role of this structure in motor set

### Neuroimaging data

#### Hypothesis-Driven BG ROI analysis

Direct comparisons of task-related sustained and transient activation patterns between Parkinson’s disease patients and controls within each ROI revealed mainly transient abnormalities. Only the right anterior putamen exhibited sustained response changes related to context maintenance with patients showing underactivity relative to controls (Table 2, Fig. 2A). Parkinson’s disease-related transient underactivity was found in left hemispheric caudate and GPi (Fig. 2B and C), and right hemispheric caudate and putamen (Fig. 2D and E) associated with matching, response selection and/or updating processes (Table 2). Importantly, the reverse contrasts examining ROIs for greater activation in patients relative to controls yielded no significant effects at $P < 0.05$ (uncorrected, voxel extent = 10) in either sustained or transient responses.

#### Supplementary exploratory PFC ROI analyses

None of the ROIs in VLPFC and DLPFC were found to demonstrate significant group differences in either sustained or transient responses. Prefrontal effects were absent even at the lenient threshold of $P < 0.05$ (uncorrected, voxel extent = 10 voxels). This contrasts with previous imaging findings of Lewis and co-workers (2003) who demonstrated DLPFC underactivity in medicated Parkinson’s disease patients performing a WM task involving manipulation. Apart from the fact that patients participating in the present study were drug-naïve, this inconsistency might be due to differences in disease severity since we only included newly diagnosed patients. Another plausible explanation is that manipulation relies more heavily on DLPFC than updating.

### Table 2 Brain activity differences between patients with Parkinson’s disease and healthy controls in the basal ganglia ROIs

<table>
<thead>
<tr>
<th>Region</th>
<th>Transient effects (Parkinson’s disease &lt; controls)</th>
<th>Sustained effects (Parkinson’s disease &lt; controls)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$(x, y, z)$</td>
<td>$t$</td>
</tr>
<tr>
<td>L Caudate</td>
<td>-18, 22, 14</td>
<td>2.78</td>
</tr>
<tr>
<td>L Globus Palidus</td>
<td>-22, -8, -6</td>
<td>2.92</td>
</tr>
<tr>
<td>R Caudate</td>
<td>10, 20, -8</td>
<td>2.88</td>
</tr>
<tr>
<td>R Putamen</td>
<td>28, -16, 6</td>
<td>2.73</td>
</tr>
</tbody>
</table>

The opposite contrasts of sustained and transient effects (Parkinson’s disease > controls) did not reveal any significant effects at a statistical threshold of $P < 0.05$ (uncorrected). $K$ = number of voxels.
preparation that was not found in Parkinson's disease. However, since none of these effects survived a strict Bonferroni multiplicity adjustment they can only be regarded as trends in the direction of our hypotheses.

Discussion

The present study dissociated sustained and transient activity elicited during a 2-back WM task to elucidate the relative degree to which abnormal BG activation in *de novo* Parkinson’s disease might reflect deficiencies in tonic and phasic components of executive control. The results were broadly consistent with predictions based on the tonic/phasic model of DA function suggesting a particularly close link between striatum, especially the caudate, and D2-dependent neurotransmission, assumed to mediate cognitive flexibility and phasic executive processes such as response inhibition and updating (Cools, 2006). Consistent with prior findings Parkinson’s disease was associated with marked reduction of activation in BG structures recruited in healthy controls performing the same WM task. We found no abnormalities in patients’ PFC activation. Investigating the temporal signature of diminished responses among discrete BG structures established that transient activity was weakened in left dorsal caudate, right ventral caudate, right putamen and left GPi. Only one BG structure, the right anterior putamen, demonstrated reduced sustained activity in Parkinson’s disease patients relative to controls.

This non-uniform temporal pattern of BG hypoactivation suggests that neurocognitive consequences of striatal DA dysfunction in (early) Parkinson’s disease cannot readily be attributed to general decline in tonic engagement of BG regions (although such effects may occur with incremental executive demands and/or detrimental performance). Instead, the principal impact of DA depletion on BG activity, in the context of 2-back, appears to be diminished transient activity in caudate and its main output layer, the GPi, which may reflect early signs of a faltering ability to engage phasic executive processes responsible for gating access of behaviourally relevant input to WM. The absence of behavioural deficits in 2-back accompanying the attenuated brain responses in Parkinson’s disease patients warrants some consideration. Even at the earliest stages of the disease DA deficiencies will impede striatal executive processing to suboptimal levels albeit under the relatively modest demands of 2-back this can probably be behaviourally compensated for. A (dys)functional interpretation of transient caudate underactivity in terms of executive deficits also received support from the brain–behaviour correlational trend observed between magnitude of decrease and number of perseverative errors on WCST. In the following sections the current findings are discussed with respect to each BG substructure taking into account implications from functional and neurochemical neuroimaging evidence in Parkinson’s disease and healthy subjects.

**Caudate nuclei**

Corroborating evidence of caudate involvement in phasic (rather than tonic) executive components of WM comes...
from many imaging studies in healthy subjects (Manoach et al., 2003; Kelly et al., 2004). For instance, bilateral increases in caudate activation has been associated with successful response inhibition, but not WM maintenance (Hester et al., 2004). However, we suggest that the current finding of transient caudate underactivity in de novo Parkinson’s disease might relate more specifically to phasic mechanisms underlying updating, rather than control of response execution. Neurocomputational modelling work attempting to delineate the functional interactions between PFC and BG in WM processes emphasize phasic updating (rather than tonic maintenance) as the key mechanism by which striatum contributes to executive control of WM (Frank et al., 2001). Recent biophysically detailed models have highlighted the importance of BG involvement in accounting for the more ‘fine-grained’ DA modulations required when partial updating takes place within actively maintained context representations (Cohen et al., 2002). Updating in two-back implies analogous requirements when shuffling representation–action associations within WM. By means of ‘focusing’ otherwise undifferentiated phasic DA bursts at pinpointed cortical destinations, the BG might accomplish selective gating among representational elements. Contemporary models extend (and go beyond) previous theoretical frameworks that posited a central role of BG circuitry in action selection (Mink, 1996; Graybiel, 1998). In prior models the striatum was assumed to operate at the interface of the perceptuomotor cycle by means of integrating widely distributed cortical inputs in the service of guiding and validating the selection of currently most appropriate response. Current theories of DA embrace a conceptually broader perspective on the modulatory role of striatum in ‘selection’, entailing filtering and assimilating context-relevant stimulus information based on its predictive value for future goal attainment (Cohen et al., 2002).

Functional links between the caudate and DLPFC are evidenced by anatomical evidence of reciprocal connections between these areas in nonhuman primates (Alexander and Crutcher, 1990). Among the five parallel cortico-striatal-pallido-thalamo-cortical loops defined by Alexander and co-workers (1990), the dorsal caudate and DLPFC are considered core structures within functionally integrated frontostriatal circuitry devoted to executive cognition. This notion has presumably encouraged interpretations of Parkinson’s disease patients’ frontal-like executive impairments in terms of abnormal processing within PFC (e.g. Morris et al., 1988; Brown and Marsden, 1990). As of yet, no consensus has been reached regarding whether the earliest stages of Parkinson’s disease involve compromised PFC functioning or not. However, there is mounting evidence indicating that executive deficits in early stage Parkinson’s disease might selectively be attributable to striatal D2 deficiencies rather than intrinsic PFC disturbances (cf. Frank and O’Reilly, 2006). The notion of frontal dysfunction in early Parkinson’s disease largely rests on the assumption that initial stages of the disease are accompanied by reduced mesocortical DA inflow to PFC (Scatton et al., 1982). However, several in vivo molecular imaging studies suggest that DA function in PFC is within normal ranges in newly diagnosed Parkinson’s disease (Piccini et al., 2003; Sawamoto et al., 2004) and might even be upregulated at the earliest stages of the disease (Rakshi et al., 1999). In agreement with proposals of relatively spared prefrontal DA function in early Parkinson’s disease (Jellinger, 2001), the present findings revealed no changes in PFC activation in unmedicated de novo Parkinson’s disease. It should be noted that the occurrence of normal sustained activity in the caudate in the present study does not exclude that other tonic executive processes (or altered demands on n-back or context maintenance) relying on this region are unaffected by Parkinson’s disease.

**GPI**

While the striatum constitutes the main input nuclei of the BG, Gpi represent the key output nuclei from where the end-products of BG computations are transferred to their cortical destinations. In contrast to the massive DA depletion occurring in dorsal striatum, animal models suggest that DA projections to Gpi are relatively spared in early Parkinson’s disease (Parent et al., 1990). Still, DA function in Gpi appears to become upregulated at the onset of Parkinson’s disease, as indicated by PET measures of a 50% regional increase in [18F]dopa uptake (Whone et al., 2003), which presumably reflects an adaptive physiological mechanism attempting to compensate for reduced striatal DA (Brooks and Piccini, 2006).

Despite apparent early-stage differences in DA deficiencies between the caudate and Gpi, previous imaging studies of WM in Parkinson’s disease have shown similar degrees of underactivation in these structures (e.g. Owen et al., 1998). The present data extend on prior findings by suggesting that striato-pallidal underactivation in Parkinson’s disease might preferentially reflect transient, rather than sustained, response abnormalities within circuitry associated with phasic executive components of WM. In particular, the caudate and Gpi might play important roles in the control over WM contents, especially when it comes to gating or restructuring task-relevant information in the service of constraining behavioural output or updating sensorimotor integration. This would concur with neuroimaging findings in healthy young subjects showing co-recruitment of caudate and Gpi in such diverse functions as filtering out behaviourally irrelevant information (McNab and Klingberg, 2007), temporal-order sequencing of meaningful events (Tinaz et al., 2006), and dual-task coordination (Erickson et al., 2005) suggesting a common denominator that might reflect gating and updating-processes putatively modulated by phasic striatal D2 neurotransmission (Cropley et al., 2006).
Putamen
This motor-related section of striatum distinguished itself from the caudate and Gpi by exhibiting sustained underactivity (right anterior portion) in addition to diminished transient activity (right posterior portion). Prior empirical data supporting an association between anterior putamen and tonic control comes from studies using in vivo molecular imaging methods relating putamen DA function to WM capabilities. Studies in early Parkinson’s disease have shown correlation between reduction of \[^{18}\text{F}]\text{dopa}\) uptake in anterior putamen and verbal WM impairment (Cheesman et al., 2005), while in healthy subjects, DA synthesis capacity in the putamen (along with caudate) was recently found to correlate positively with WM capacity (Cools et al., 2008). Some functional imaging studies have reported sustained activity in putamen during delays in WM tasks (Cairo and Liddle, 2004; Chang et al., 2007) whereas other studies have not (Landau et al., 2008). In young healthy subjects sustained responses in bilateral putamen were exhibited in the sustained attention to response task (Fassbender et al., 2004), and left anterior putamen has shown common activation for successful response inhibition and verbal WM rehearsal (Hester et al., 2004). Tentatively, this implicates that present findings of sustained underactivity in putamen may represent early signs of impeding tonic control deficiencies at more advanced stages of Parkinson’s disease. However, as opposed to PET indices of DA hypofunction in the caudate, which are known to be robustly correlated with executive deficits in early Parkinson’s disease (Marie et al., 1999; Brück et al., 2001), regional putaminal DA loss is not typically associated with cognitive impairments (cf. Cropsey et al., 2006).

These inconsistent findings might argue against a dedicated role of putamen in purely cognitive aspects of tonic control, whereby the Parkinson’s disease-related sustained underactivity may instead reflect some anticipatory or preparatory aspect related to motor control. One possibility is that anterior putamen plays a role in WM processes encompassing tonic control of motor set. Sustained activity in the striatum has previously been linked with maintenance of prospective motor codes during spatial WM tasks (Postle and D’Esposito, 1999, 2003). Such an interpretation concurs with the notion that correlations between putamen DA function and executive abilities, exemplified by cognitive shifting, do not generally reflect ‘pure cognitive’ switches (Rinne et al., 2000), but are principally observed for tasks requiring motor actions following switches (e.g. Lozza et al., 2004). It could be that sustained activity in putamen (and presumably the caudate) might encompass action-biasing mechanisms reflected as preparatory tonic control signals carrying prospective response codes mapping onto ‘go’ and ‘no go’ contingencies assigned to the items held 2-back and 1-back, respectively, in WM. On a higher-level a similar mechanism may exert tonic control over competing motor sets in set-shifting paradigms.

Conclusion
Taken together, the present finding that de novo untreated Parkinson’s disease yields predominantly unique transient underactivation in caudate nuclei, putamen and Gpi during 2-back performance indicates that phasic control mechanisms might be disproportionately affected by selective striatal DA deficiencies. This would resonate well with computational WM models assigning an updating role to BG and agrees with predictions based on the tonic/phasic DA hypothesis.

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