Dysfunction of the Default Mode Network in Parkinson Disease

A Functional Magnetic Resonance Imaging Study

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Objective: To examine the integrity of the default mode network in patients with Parkinson disease (PD). Previous functional neuroimaging experiments have studied executive deficits in patients with PD with regard to task-related brain activation. However, recent studies suggest that executive performance also relies on the integrity of the default mode network (ie, medial prefrontal cortex, posterior cingulate cortex, precuneus, and lateral parietal and medial temporal cortices), characterized by a deactivation of these cortical areas during the performance of executive tasks.

Design: We used functional magnetic resonance imaging to investigate cortical deactivations during a card-sorting task (retrieval and manipulation of short-term memory contents) compared with a simple sensory-motor matching task. In addition, a functional connectivity analysis was performed.

Setting: Tertiary outpatient clinic.

Participants: Seven patients with mild to moderate PD (not taking medication) and 7 healthy controls.

Main Outcome Measure: Cortical deactivations.

Results: Both groups showed comparable deactivation of the medial prefrontal cortex but different deactivation in the posterior cingulate cortex and the precuneus. Compared with controls, patients with PD not only showed less deactivation of the posterior cingulate cortex and the precuneus, they even demonstrated a reversed pattern of activation and deactivation. Connectivity analysis yielded that in contrast to healthy individuals, medial prefrontal cortex and the rostral ventromedial caudate nucleus were functionally disconnected in PD.

Conclusions: We describe specific malfunctioning of the default mode network during an executive task in PD. This finding is plausibly linked to dopamine depletion and may critically contribute to the understanding of executive deficits in PD.

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Patients with Parkinson disease (PD) demonstrate deficits in executive tasks that include planning and set shifting. However, the underlying disease-related mechanism is not completely understood. Using functional imaging, neuronal substrates of those deficits were mainly found in the frontostriatal circuitry. Depending on the involvement of the dorsal caudate nucleus (NC), both hypoactivity and hyperactivity of prefrontal areas have been reported in unmedicated patients with PD when compared with controls.

Whereas those studies focused on differences in brain activations in the sense of an increase in activity during executive task performance, recent findings suggest that for the successful performance of an executive task, the integrity of a network showing task-related deactivations might be just as relevant. This network is commonly referred to as the “default mode network” (DMN), encompassing the medial prefrontal cortex (mPFC), posterior cingulate cortex (PCC), precuneus, and lateral parietal and medial temporal cortices. According to leading hypotheses, deactivation of these areas could signal a reduction in inhibitory processes (dissociation) but also the ability to redirect attentional processes from self-reflection to goal-directed behavior (ie, internal to external reference). As for executive task performance, the dynamic regulation of disinhibition and shifting attention to external goals both seem essential.

There is a vivid discussion on the role of DMN dysfunction in normal aging and in neuropsychiatric diseases, such as dementia, depression, or schizophrenia. In PD, the DMN has been poorly investigated. Although the functionality of the DMN might be specifically perturbed in this disease. Parkinson disease is hallmarked by a loss of dopaminergic neurons projecting to the striatum. It is widely accepted that this leads to a relative functional disconnection of the striato-thalamo-frontal loop ultimately resulting in impaired modulation of frontal...
activity.\textsuperscript{18} Tracer studies in monkeys consistently described that the mPFC, in contrast to the orbitofrontal cortex, has major projections to the rostral part of the ventromedial NC.\textsuperscript{19,20} Given the pivotal role of dopamine in the striato-thalamo-frontal loop,\textsuperscript{18,21} we hypothesized that dopamine depletion in the ventromedial NC might lead to a functional disconnection of the DMN, consequently resulting in a failure to appropriately modulate DMN activity when facing an executive task.

In contrast to a previous study investigating activity increases,\textsuperscript{21} herein we focused on decreases in blood oxygen level–dependent (BOLD) signal during executive trials of the Montreal card-sorting task.\textsuperscript{21} We categorized the trials in 2 main conditions. In executive trials, sorting the test card required retrieval and manipulation of short-term memory contents. The control task was a simple sensory–motor matching task. We predicted impaired deactivation of the DMN in patients with PD relative to controls. Beyond quantitative differences in activation, we predicted disturbed functional connectivity between the mPFC and the ventromedial NC.

### METHODS

#### SUBJECTS

Seven right-handed patients with PD at Hoehn and Yahr stages 1 to 2 (age range, 56-70 years) participated in this study. All patients met the “core assessment program for surgical intervention therapy” criteria for the diagnosis of idiopathic PD.\textsuperscript{22,23} All patients stopped taking all antiparkinsonian medication 12 to 18 hours before scanning. Their mean score on the motor subset of the Unified Parkinson’s Disease Rating Scale prior to scanning (not taking medication) was 23.1. Patients were screened for dementia and depression using the Mini-Mental State Examination and the Beck Depression Inventory, respectively. Seven right-handed control subjects (age range, 47-60 years) with no history of neurological or psychiatric disorder also participated in this study. For both the patients and the control subjects, the exclusion criteria were a score of less than 27 on the Mini-Mental State Examination and a score of more than 15 on the Beck Depression Inventory. All participants gave informed consent after reading the protocol, which was reviewed and approved by the Research Ethics Committee of the Montreal Neurological Institute. Although our cohort of patients with PD did not show clinically overt executive deficits, they demonstrated a relative impairment in the executive task investigated herein.\textsuperscript{21}

#### COGNITIVE TASK

The Montreal card-sorting task used in this study has been described in detail in previous publications of our group.\textsuperscript{21,24} Four reference cards are permanently on display in the top half of a computer screen, displaying 1 red triangle, 2 green stars, 3 yellow crosses, and 4 blue circles, respectively. On each trial, a new test card is presented below the reference cards and the subject has to match the test card to a specific reference card. The test card contains a certain number of stimuli (1-4), being 1 of 4 shapes (triangle, star, cross, or circle) in 1 of 4 colors (red, green, yellow, or blue). The response is indicated by pressing 1 of 4 buttons with the right hand, using 1 of 4 fingers, each corresponding to a specific reference card. The screen briefly (2.3 seconds) becomes bright if the response was correct and dark if the response was incorrect. The trial categories in this task mainly differ in terms of executive demand. In executive trials, the match of each test card to a specific reference card is determined by a varying classification rule based on a single shared attribute (color, shape, or number). In control trials, the test card on each trial is a replica of 1 of the 4 reference cards and the participant is only required to match the test card to its twin within the 4 reference cards. The executive trials can be further subdivided in terms of working memory load and set-shift demand as described in previous publications.\textsuperscript{21,24} The task was performed in a blocked design, with 8 minutes per block in a pseudorandom sequence of executive (n=4) and control (n=2) blocks. Behavioral measures of executive performance (arcsin-transformed error rate and the mean latency [in milliseconds] to a correct response) were assessed per executive block.

#### FUNCTIONAL MAGNETIC RESONANCE IMAGING AND PREPROCESSING

Using a 1.5-T Siemens Sonata magnetic resonance imaging (MRI) scanner (Siemens, Malvern, Pennsylvania), a T1-weighted, 3-dimensional volume was acquired, followed by acquisitions of echo planar T2*-weighted images with BOLD contrast in 6 runs containing 200 volumes, each acquired every 2.5 seconds. Volumes contained 24 slices, and voxels were cubic with an edge length of 4.7 mm. Images were processed and analyzed using SPM2 software (http://www.fil.ion.ucl.ac.uk/spm; Wellcome Trust Centre for Neuroimaging, London, England). The first 2 scans of each run were discarded to allow for steady-state magnetization. The remaining images were realigned to the first image and spatially

### Table 1. Deactivations During Executive Relative to Control Trials

<table>
<thead>
<tr>
<th>Region</th>
<th>Cluster</th>
<th>Peak Voxel</th>
<th>Side</th>
<th>Extent a</th>
<th>t Value</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>Millimeters</th>
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<tbody>
<tr>
<td>Healthy Controls</td>
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<td>M 55</td>
<td>6.87</td>
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<tr>
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<tr>
<td>Precuneus</td>
<td>M 37</td>
<td>5.48</td>
<td>−4</td>
<td>−64</td>
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<td>Patients With PD</td>
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<tr>
<td>mPFC</td>
<td>M 17</td>
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<td>−4</td>
<td>28</td>
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Abbreviations: M, midline; mPFC, medial prefrontal cortex; PCC, posterior cingulate cortex.

a Cluster extent is reported in number of voxels. P<.05 corrected for multiple comparisons at cluster level.
normalized to a standard template (MNI 305). The normalized images were spatially smoothed with a gaussian kernel of 8 mm at full width at half maximum to reduce intersubject differences in anatomy and enable the application of the gaussian random field theory.

DEACTIVATION

A first-level analysis was performed individually for each subject based on the general linear model.23 Executive, control, and error trials were separate regressors by modeling the onsets of each trial as delta functions convolved with a hemodynamic response function. Regression coefficients for all regressors were estimated using least squares. Using the appropriate linear contrast (executive trials: −1; control trials: 1; error trials: 0), contrast images were computed for each participant, representing BOLD signal decreases in executive relative to control trials. Contrast images were entered into 1-sample t tests (within-group analysis) and a multiple regression analysis (between-groups analysis) with the variables “group” and “age.” We used age as a nuisance variable to regress out potential age confounds.

To further explore the relationship between task performance and DMN activity, we performed separate post hoc analyses of covariance. We defined the suprathreshold clusters of the earlier-mentioned between-group analysis as volumes of interest and used the respective mean BOLD signal change of each executive block as dependent variables. As independent variables, we entered the factor “group” (1, −1) and blockwise behavioral measures “error” (arcsin-transformed error rate) and “latency” (mean latency [in milliseconds] to correct response).

FUNCTIONAL CONNECTIVITY ANALYSIS

To identify brain regions showing either a prophasic or an antiphasic interrelationship with the activity in the mPFC, we performed a post hoc multiple regression analysis using the mPFC time series as a variable of interest. Global (whole-brain) signal change over time was entered as a second (ie, nuisance) variable. First, the individual deactivation images of every subject (controls and patients) were entered into a 1-sample t test to obtain the common maximum of deactivation within the mPFC (x, y, and z = 0, 38, and −8 mm). The individual time series of mPFC activity (first regressor) was extracted using an 8-mm sphere centered at the local maximum that was nearest to the common maximum. The global signal time series (second regressor) was automatically generated by SPM2 (SPM.xGx.rg). The 2 regressors were entered into a multiple regression model and regression coefficients were estimated for each voxel. Contrast images for positive and negative correlation with mPFC activity (linear contrasts: +1 0; −1 0) were computed for each participant. Resulting statistical maps were entered into 1-sample (within-group) and unpaired, 2-tailed (between-group) t tests. For the statistical threshold in the between-group comparison, we applied a small-volume correction with a 10-mm sphere centered in the rostral ventromedial NC, based on our a priori hypothesis.

We considered a statistical threshold of P < .05 (corrected for multiple comparisons at cluster level, height threshold t > 3.5, no extend threshold) to be significant. Methods and results of behavioral analyses are published elsewhere.21

RESULTS

DEACTIVATION

In healthy controls, executive trials compared with control trials led to a decrease in BOLD signal (ie, deactivation) in the mPFC, PCC, and precuneus (Table 1) (Figure 1).

Figure 1. Cerebral deactivations as indexed by blood oxygen level–dependent decreases during executive relative to control trials. The statistical T maps are superimposed on sections (corresponding stereotactic coordinates are stated in millimeters) of the T1-weighted magnetic resonance imaging template implemented in MRicro (http://www.sph.sc.edu/comd/rorden/micro.html). Controls (CT) show deactivation of the medial prefrontal cortex, posterior cingulate cortex, and precuneus. Patients with Parkinson disease (PD) show deactivation of the medial prefrontal cortex only. Controls show more deactivation of the posterior cingulate cortex and precuneus. The bar graphs plot the contrast estimates (CEs) and 90% confidence intervals (CIs) per group and condition for the respective peak voxels within the posterior cingulate cortex and precuneus.
Patients with PD also showed deactivation of the mPFC (Table 1) (Figure 1) but significantly less deactivation of the PCC and precuneus (Figure 1). In fact, patients with PD demonstrated a reversed pattern of activation and deactivation in these regions, as depicted in a diagram of the contrast estimates per group and condition (Figure 1). There were no areas showing more deactivation in patients than in controls.

In the post hoc analyses of covariance exploring the relationship between DMN activity and performance, we found that the factor “group” had no significant influence on the respective correlation slopes (Figure 2). Pooling both groups, we found significant positive correlations between errors and BOLD signal change in both the precuneus and PCC. Additionally, there was a significant positive correlation between latency and BOLD signal change in the PCC. On a block-by-block basis, this means the more deactivated those areas were, the better the performance. PD indicates Parkinson disease.

FUNCTIONAL CONNECTIVITY WITH mPFC

In healthy controls, multiple regression analysis revealed a positive correlation of mPFC activity with the mPFC itself, the ventral anterior cingulate and medial orbitofrontal cortex, the precuneus, and the ventromedial NC bilaterally (Table 2) (Figure 3). Patients with PD showed a positive correlation of mPFC activity with itself, the ventral anterior cingulate and medial orbitofrontal cortex, the precuneus, and the right ventrolateral prefrontal cortex (Table 2) (Figure 3). Compared with healthy controls, patients showed less positive correlation with mPFC activity in the left ventromedial NC (Table 3). There were additional trends toward less positive correlation with mPFC activity in the left ventromedial NC and in the precuneus. No brain region showed more positive correlation with mPFC activity in patients than in controls.

Healthy controls demonstrated a negative correlation between activity of the mPFC and activity of the rostral supplementary motor area, the left ventral premotor cortex, and the left superior parietal lobule (Table 2). Additionally, the right superior parietal lobule showed a nonsignificant trend (Figure 3, right upper panel). In patients with PD, only the prestriate cortex showed a negative correlation with mPFC activity (Table 2). Despite seemingly divergent patterns of negative correlation, no between-group difference survived correction for multiple comparisons.
The goal of this study was to assess the functional integrity of the DMN in unmedicated patients with PD. The comparison of patients with PD and healthy controls unveiled 2 major findings. First, patients with PD not only failed to deactivate parts of the DMN to a normal extent, they even demonstrated a reversed pattern of activation and deactivation in those areas. Second, beyond quantitative differences, functional connectivity of the DMN was perturbed in patients with PD with a relative disconnection of the ventromedial NC and mPFC. Herein, we address the question of how DMN dysfunction may be linked to dopamine depletion in PD and how this potentially contributes to executive deficits in patients with PD.

What is the role of DMN deactivation in normal cognition and how is DMN dysfunction related to executive impairments in PD? Brain activity patterns in healthy controls showed a specific network (the mPFC, PCC, and precuneus) being engaged during control trials and disengaged during executive trials. Moreover, post hoc analysis corroborated the relevance of DMN deactivation in terms of performance. This is in general agreement with the 2 major hypotheses on the functional role of the DMN. Deactivation of these areas could signal a reduction in inhibitory processes (disinhibition) but also the ability to redirect attentional processes from self-reflection (ie, internal reference) to goal-directed behavior (ie, external reference).10-12 In the light of the present findings in PD, however, a recently proposed extension of the second hypothesis has particular appeal.13 There is evidence from functional imaging studies that the frontal part of the DMN is engaged in attending self-referring memory contents26 and the parietal part, in allocating visuospatial attention according to anticipation.27 Both studies suggest a role for these regions in the respective screening of internal and external environments according to endogenous (internally driven screening) as opposed to exogenous factors, such as visuospatial precues (externally driven screening). As Raichle and colleagues10 pointed out in their original article on the DMN, such a screening function has great evolutionary significance but would be counterproductive when focused attention is demanded during a cognitive task. This theory is underscored by observations in autistic patients, who failed to disengage mainly the frontal part of the DMN (internally driven screening of internal environments),28 whereas patients with attention-deficit/hyperactivity disorder show DMN dysfunction mainly in the parietal part of the DMN (internally driven screening of external environments).29,30 In this context, the executive trials of the present task generally increased externally driven demands.

Our results in patients with PD suggest both an inability to disengage the parietal part of the DMN during executive trials and an inability to engage the parietal part of the DMN during control trials. These observations critically differ from findings in normal aging,14 as patients with PD showed a reversed pattern of activation and deactivation. In this context, potential aging effects were regressed out in our analysis. It might still be possible, however, that the DMN in PD undergoes a non–disease-
specific or compensatory change associated with decrease in task performance. Our results suggest that patients with PD are less able to engage internally driven screening of external environments during low externally driven demand. This would be in accordance with a precueing experiment providing either exogenous or endogenous advance information about the spatial position of target cues. Patients with PD were reported to profit from exogenously derived (externally driven), but not from endogenously derived (internally driven), advance information. In sum, patients with PD fail to appropriately modulate internally driven screening of external environments.

The failure to deactivate the DMN in PD during executive trials was not as specific or dependent on the involvement of the rostromedial NC as the change of prefrontal activity observed in these patients when studying increased BOLD signal linked to working memory and set shifting. Indeed, all the analyses presented herein were also performed on a condition-by-condition basis (using the original nomenclature of the Montreal card-sorting task). All of them generated results very similar to those reported herein and this is why they are not reported herein.

Is there any direct link between dopamine depletion in PD and DMN dysfunction? In accordance with functional MRI data in humans and tracer studies in monkeys, we found that the mPFC is functionally connected to the ventromedial NC. In comparison with healthy controls, patients with PD showed a relative impairment of this connection. Based on neuropathological studies in patients with moderately advanced PD, we suggest that the disruption of this connection may be linked to an underlying dopaminergic depletion in the ventromedial NC. This assumption is further corroborated by a functional MRI study showing that dopaminergic medication strongly modulates striatal connectivity in humans. We therefore suggest that dopamine depletion in the ventromedial NC may critically contribute to the inability of our patients to appropriately modulate DMN engagement. However, this inference is generally limited because of the relatively small number of subjects and the fact that we were primarily interested to assess DMN function in a state of dopaminergic depletion and did not investigate DMN function in patients with PD taking medication.

Table 3. Between-group Analysis

<table>
<thead>
<tr>
<th>Region</th>
<th>Side</th>
<th>Extent</th>
<th>t Value</th>
<th>x</th>
<th>y</th>
<th>z</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deactivation</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>PCC</td>
<td>M</td>
<td>22</td>
<td>5.39</td>
<td>12</td>
<td>−16</td>
<td>44</td>
</tr>
<tr>
<td>Precuneus</td>
<td>M</td>
<td>25</td>
<td>4.24</td>
<td>−4</td>
<td>−68</td>
<td>24</td>
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<td>Positive Correlation</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Ventromedial NC</td>
<td>L</td>
<td>4</td>
<td>3.77</td>
<td>−12</td>
<td>16</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: L, left; M, midline; mPFC, medial prefrontal cortex; NC, caudate nucleus; PCC, posterior cingulate cortex.

Figure 3. Demand-independent connectivity with the medial prefrontal cortex (mPFC). Positive (blue) and negative (yellow) correlation with mPFC activity. Suprathreshold voxels in the corresponding color are superimposed on the T1-weighted magnetic resonance imaging template implemented in MRIcro (http://www.sph.sc.edu/comd/rorden/mricro.html). Controls: mPFC activity positively correlates with the activity of the mPFC, precuneus, and ventromedial caudate nucleus bilaterally and negatively correlates with the activity of the rostral supplementary motor area, left ventral premotor cortex, and superior parietal lobule. Patients: mPFC activity in patients positively correlates with the activity of the mPFC, precuneus, and left ventrolateral prefrontal cortex. Compared with healthy controls, patients showed less positive correlation with mPFC activity in the left ventromedial caudate nucleus. Stereotactic coordinates are stated in millimeters. L indicates left; PD, Parkinson disease; and R, right.
In conclusion, we describe prominent dysfunctions of the DMN that distinguish patients with PD from healthy subjects, but also other neuropsychiatric disorders and normal aging. Disturbed connectivity with the ventromedial NC seems an underlying factor of this dysfunction, which might be linked to local dopamine depletion. In our opinion, getting to the bottom of dopamine-related DMN dysfunction in further experiments will offer a great new opportunity to better understand executive deficits in PD.

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