The Role of the Subthalamic Nucleus in Sequential Working Memory in De Novo Parkinson's Disease

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When we schedule our day, we may arrange tasks in the order they come or prioritize a task that is due first. A critical ability involved in this scenario is the ability to maintain and manipulate sequential information online. This ability is sophisticated in humans and chimpanzees[1] but vulnerable to neurodegenerative diseases. In Parkinson's disease (PD), deficits in sequential working memory can occur even in patients with mild clinical symptoms,[2,3] which potentially lead to difficulties in planning sequential steps to solve problems and under-

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accuracy (arcsine transformed[18]) correlated with their severity of nonmotor (MDS-UPDRS Part I score) or motor symptoms (MDS-UPDRS Part III score) (2-tailed, $P < 0.025$ for Bonferroni correction).

MRI Acquisition and Preprocessing

Brain imaging data were acquired on a General Electric Discovery MR750 3.0T scanner with an 8-channel head coil. High-resolution T1-weighted images used an inversion recovery prepped-fast spoiled gradient recalled echo imaging sequence (192 sequential sagittal slices, 450-millisecond time of inversion, 7-millisecond time of echo, 12 ip angle, 256 × 256 mm^2 eld of view, 1-mm thickness, no gap, and 1 × 1 mm^2 in-plane resolution). Functional T2-weighted images used a standard echo-planar imaging sequence (33 interleaved ascending axial slices, 2000- millisecond time of repetition, 30- millisecond time of echo, 90 ip angle, 224 × 224 mm^2 eld of view, 4.2-mm thickness, no gap, and 3.5 × 3.5 mm^2 in-plane resolution).

fMRI data were preprocessed using SPM12 (revision 7219, www. l.ion.ucl.ac.uk/spm). The rst 5 images of each experimental block were discarded. Other images were realigned to a mean functional image, corrected for slice acquisition time difference, registered to the high-resolution T1-weighted image, normalized to the Montreal Neurological Institute and Hospital coordinate system,[19] resampled to voxels of 3 × 3 × 3 mm^3, smoothed with a Gaussian kernel of 6-mm full-width half-maximum, and ltered with a 128-second high-pass lter.

We controlled the quality of fMRI data preprocessing. A total of 5 participants from each group who had excessive head motion (total displacement >3 mm) or suboptimal spatial normalization (visual inspection) were excluded from fMRI data analysis. In the included participants, patients with PD did not move more than healthy controls.

Statistical Analysis of fMRI Data

First, we replicated the ordering-related regional activation and deactivation.[11] At the subject level, the general linear model convolved a design matrix with a canonical hemodynamic response function. The design matrix included correct and incorrect "reorder & recall" trials and "pure recall" trials as separate regressors. A comprehensive indicator of head motion was derived from estimated motion parameters and included as a nuisance regressor.[20] Each trial was time locked to its onset and modeled with its real duration. Classical parameter estimation was applied with a 1-lag autoregressive model. The ordering-related activation was de ned "rcanner554.tedts recall×3(inuscall)Tj /F16 1 Tf104.405 0 TD (")Tj /F14 1 Tf .5556 0 TD [(pur<)-266.1(recall)]TJ /F16

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Results

Behavioral Data

Figure 2 presents the behavioral data of the computerized digit ordering task and the 2 neuropsychological working memory tests. First, we replicated previous findings that patients with PD scored lower than healthy controls in the Adaptive Digit Ordering Test, but not in the Digit Span Forward Test (Fig. 2A and Table 1). Second, we observed a similar pattern in the accuracy of the digit ordering task (Fig. 2B) with main effects of trial type ($F_{1,98}$ = 16.02, P < 0.001, ^{2} = 0.14) and group ($F_{1,98}$ = 5.27, P = 0.024, ^{2} = 0.05), and an interaction between group and trial type ($F_{1,98}$ = 3.93, P = 0.05, ^{2} = 0.04). Participants were, in general, less accurate in "reorder & recall" than "pure recall" trials. Patients with PD were less accurate than healthy controls, especially in "reorder & recall" trials. However, we found no group difference in reaction time (Fig. 2C). Despite their motor symptoms, patients with PD were as fast as healthy controls. Third, we observed a negative correlation between individual patient's "reorder & recall" accuracy and their severity of nonmotor symptoms (MDS-UPDRS Part I score, r = 0.53, P = 0.002; Fig. 2D), when the severity of motor symptoms (MDS-UPDRS Part III score) was controlled. Patients with a lower task accuracy tended to report more severe nonmotor problems in daily living. The MDS-UPDRS Part III score itself did not correlate with task performance.

Replication of Ordering-Related Regional Activation and Deactivation

We replicated the ordering-related regional activation and deactivation across groups (Fig. 3A).[11] Regional activations were greater for "reorder & recall" than "pure recall" trials (whole-brain 2-sample t test, voxel-level P < 0.05 family-wise-error corrected) in the dorsomedial prefrontal cortex (BA8/6: peak in Montreal Neurological Institute and Hospital coordinate system [6, 15, 51], t = 15.66, 1687 voxels), dorsolateral prefrontal cortex (BA46/9: left [45, 6, 30], t = 12.55, 255 voxels; right [39, 33, 33], t = 9.73, 245 voxels), ventrolateral prefrontal cortex (BA44/45: left [45, 6, 27], t = 12.37, 172 voxels; right [54, 12, 18], t = 9.69, 116

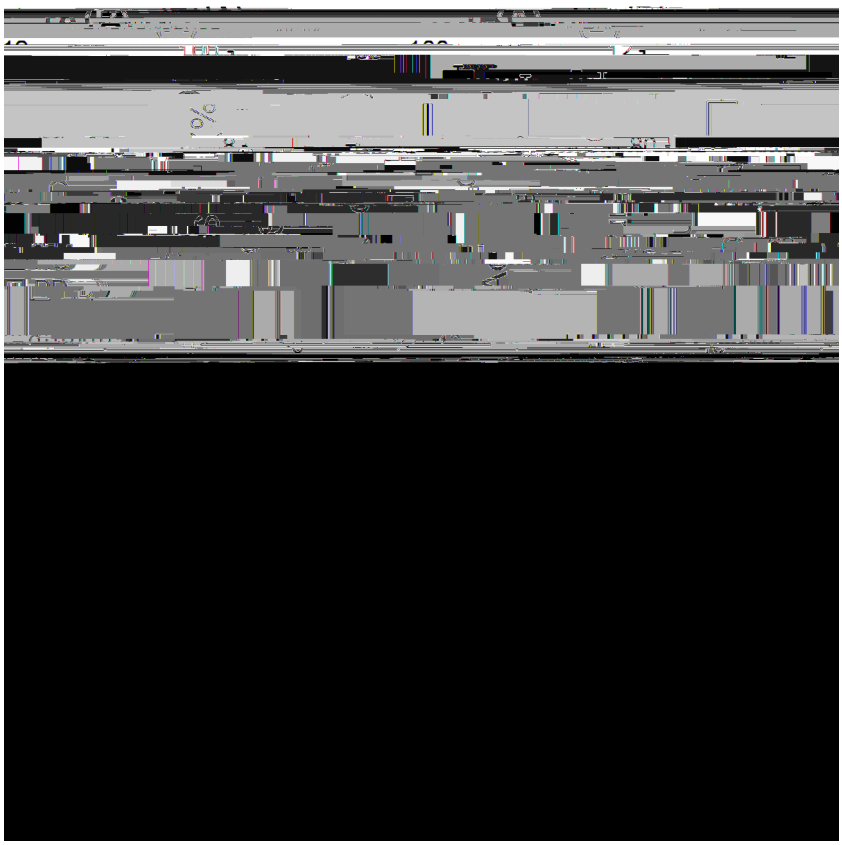

FIG. 2. Behavioral data in patients with Parkinson's disease (PD) and healthy controls (HC). (A) Mean scores and standard errors of the Adaptive Digit Ordering Test (DOT-A) and Digit Span Forward Test (Forw). (B) Mean accuracy and standard errors of the computerized digit ordering task for "pure recall & without reorder" (REO) and "reorder & recall" trials (REO+). (C) Histogram of reaction times (RT) in "reorder & recall" trials with distribution ts. (D) The "reorder & recall" accuracy (arcsine transformed) was negatively correlated with the severity of nonmotor symptoms (Movement Disorder Society–sponsored revision of Uni ed Parkinson's Disease Rating Scale Part I [MDS-UPDRS I] score). [Color gure can be viewed at wileyonlinelibrary.com]

FIG. 3. Group differences in regional activation. (A) Ordering-related regional activation (warm colors) and deactivation (cool colors). Color scales indicate t values. Coordinates are in Montreal Neurological Institute and Hospital space. (B) Means and standard errors of the percent signal change in the regions of interest for "pure recall" (REO) and "reorder & recall" trials (REO+) in patients with Parkinson's disease (PD) and healthy controls (HC). Asterisks indicate signi cant group differences (P < 0.05). L, left; mPFC, medial prefrontal cortex; d/vlPFC, dorsolateral/ventrolateral prefrontal cortex; PCC, posterior cingulate cortex; STN, subthalamic nucleus; GP, globus pallidus. [Color gure can be viewed at wileyonlinelibrary.com]

voxels), posterior parietal cortex (BA7/40: left [27, 69, 36], t = 16.27, 2042 voxels), STN (left [15, 18, 3], t = 7.40, 6 voxels; right [12, 15, 3], t = 6.64, 8 voxels), external globus pallidus (left [21, 3, 6], t = 8,22, 14 voxels; right [21, 6, 6], t = 6.92, 7 voxels), and thalamus (left [15, 6, 15], t = 10.39, 360 voxels; right [15, 6, 15], t = 9.94, 250 voxels). Regional deactivations were greater for "pure recall" than "reorder & recall" trials in the default mode network, including the medial prefrontal cortex ([6, 51, 15], t = 8.64, 347 voxels) and posterior cingulate cortex ([0, 48, 30], t = 7.10, 55 voxels).

Group Differences in the Subthalamic Nucleus and Globus Pallidus Activation

We observed group differences in the regional activation of the left STN and globus pallidus, but not other regions of interest (Fig. 3B). Note, we focused on the left regions because the ordering-related regional activation was left-lateralized in the independent fMRI data set.[11] In the left STN, we observed a main effect of group ($F_{1,88}$ = 3.94, P = 0.05, ^{2} = 0.04), an interaction between group and trial type ($F_{1,88}$ = 6.80, P = 0.01, ^{2} = 0.07), and a main effect of trial type ($F_{1,88}$ = 44.23, P < 0.001, ^{2} = 0.33). Patients with PD showed greater STN activation than healthy controls, especially in "reorder & recall" trials. In the left globus pallidus, there was an interaction between group and trial type ($F_{1,88}$ = 5.38, P = 0.02, ^{2} = 0.06) and a main effect of trial type ($F_{1,88}$ = 57.41, P < 0.001, ^{2} = 0.40), but no main effect of group ($F_{1,88}$ = 1.57, P = 0.21). Patients with PD showed greater globus pallidus activation than healthy controls in "reorder & recall" trials, but not in "pure recall" trials.

No other regions of interest showed a main effect of group or interaction between group and trial type. We exploratorily analyzed the right STN and globus pallidus and observed similar overactivations in PD.

Group Differences in STN Functional Connectivity

Having observed group differences in the regional activation of the STN and globus pallidus, we next sought group differences in their functional connectivity

(whole-brain 2-sample t test, cluster-level $P < 0.05$ family-wise-error corrected). We observed stronger time-course correlations between the left STN and putamen (left [27, 15, 9], $t = 5.74$, 41 voxels; right [30, 9, 6], $t = 6.06$, 54 voxels) and between the left STN and posterior cingulate cortex ([9, 42, 30], $t = 3.92$, 63 voxels) for healthy controls than patients with PD (Fig. 4A).

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