RESEARCH ARTICLE

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

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ABSTRACT: Background : De cits in maintaining and manipulating sequential information online can occur even in patients with mild Parkinson's disease. The subthalamic nucleus may play a modulatory role in the neural system for sequential working memory, which also includes the lateral prefrontal cortex.
Objectives : The objective of this study was to investigate neural markers of sequential working memory de - cits in patients with de novo Parkinson's disease.
Methods : A total of 50 patients with de novo Parkinson's disease and 50 healthy controls completed a digit ordering task during functional magnetic resonance imaging scanning. The task separated the maintenance ("pure recall") and manipulation of sequences ("reorder & recall" vs "pure recall").
Results : In healthy controls, individual participants' task accuracy was predicted by the regional activation and functional connectivity of the subthalamic nucleus. Healthy participants who showed lower subthalamic nucleus activation and stronger subthalamic nucleus connectivity with the putamen performed more accurately in maintaining sequences ("pure recall"). Healthy participants who showed greater ordering-related subthalamic nucleus activation change exhibited smaller accuracy costs in manipulating sequences ("reorder & recall" vs "pure recall"). Patients performed less accurately than healthy controls, especially in "reorder & recall" trials, accompanied by an overactivation in the subthalamic nucleus and a loss of synchrony between the subthalamic nucleus and putamen. Individual patients' task accuracy was predicted only by the subthalamic nucleus connectivity. The contribution of the subthalamic nucleus activation or activation change was absent. We observed no change in the lateral prefrontal cortex.
Conclusions : The overactivation and weakened functional connectivity of the subthalamic nucleus are the neural markers of sequential working memory de cits in de novo Parkinson's disease. © 2020 The Authors. Movement Disorders published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society

Key Words: fMRI; Parkinson's disease; sequential working memory; subthalamic nucleus

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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 understanding temporal relations of events expressed out of chronological order.[4-7] In this study, we aimed to investigate neural markers of the deficits in de novo patients with mild PD using functional magnetic resonance imaging (fMRI). The use of a newly diagnosed and unmedicated cohort allows us to separate the contribution of the disease from that of chronic medication.

The cognitive and neural mechanisms that code and retrieve sequential information may differ from the mechanisms that code and retrieve item-specific information (eg, color).[8-10] Recently we described a neural system for sequential working memory comprising the lateral prefrontal cortex, posterior parietal cortex, subthalamic nucleus (STN), globus pallidus, and thalamus. The lateral prefrontal and posterior parietal regions were more activated and more strongly connected with the supplementary motor area when healthy adults processed sequential information. The effect of age exhibited as a widely spreading overactivation in the prefrontal and parietal regions and a weakened psychophysiological interaction between the prefrontal/parietal regions and supplementary motor area.[11]

Cognitive decline in PD correlates with the spread of misfolded α-synuclein from the brainstem to limbic and neocortical structures.[12] The etiology of PD-related decline may differ from that of age-related decline. In this study, we examined how the disease compromises the neural system for sequential working memory and alters behavioral performance in de novo patients with mild PD. To capture the neural processes of sequential working memory, we combined a digit ordering task (Fig. 1) with fMRI. In each trial, participants had to remember a sequence of 4 different digits in ascending order. In "pure recall" trials, the digits were presented already in ascending order, and there was no need for reordering. In "reorder & recall" trials, the digits were fully randomized, and participants always had to reorder them to generate a new sequence. The "pure recall" trials measured the temporary maintenance of sequences (including encoding,

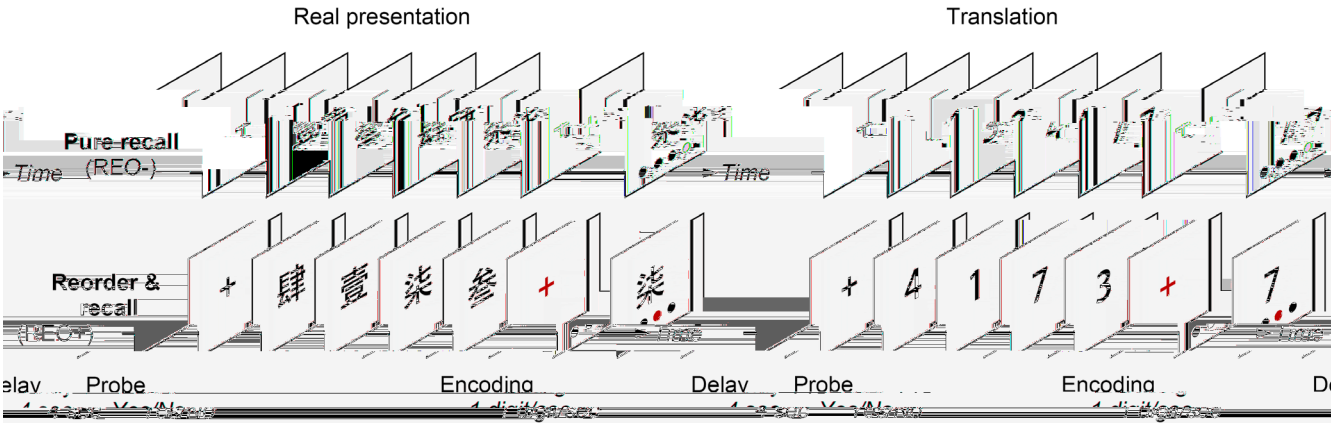

FIG. 1. Digit ordering task. The task included interleaved "pure recall" (REO–, 30 trials) and "reorder & recall" trials (REO+, 32 trials). In each trial, participants read a sequence of 4 different digits written in Chinese (1 digit/s). They had to remember the digits in ascending order through a short delay (4 seconds). In "pure recall" trials, the digits were presented in ascending order. In "reorder & recall" trials, the digits were randomized, and participants always had to reorder them. After the delay, participants saw a digit probe with 4 dots indicating 4 positions from left to right. They had to judge whether the red dot indicated the target position of the digit probe by pressing buttons with the right hand. [Color gure can be viewed at wileyonlinelibrary.com]

(7–8 minutes each). We measured all participants between 8 and 10 AM of the day to minimize the potential effects of circadian variations in the striatal dopamine release.[16,17]

Statistical Analysis of Behavioral Data

We controlled the quality of behavioral data by monitoring premature (trials with a reaction time shorter than 0.1 second) and inattentive responses (trials with a reaction time that was 3 standard deviations above the mean). Participants made no premature responses and very few inattentive responses (~1%).

First, we examined whether patients with PD responded less accurately (percentage of correct trials) or more slowly (mean reaction time of correct trials) than healthy controls using repeated-measures analyses of variance (ANOVAs) (1-tailed, $P < 0.025$ for Bonferroni correction). The ANOVA had a within-subject factor trial type ("reorder & recall," "pure recall"), and a between-subject factor group (PD, healthy control). Second, we examined whether individual patients' task

TABLE 1. Demographic, clinical, and neuropsychological data of patients with PD and healthy controls (means, standard deviations, and group differences)

Features/measures	De Novo PD, N = 50	Healthy control, N = 50	Group differences, P values
Male/female	25/25	25/25	1.00
Age, y	58.6 (9.0)	57.7 (5.5)	0.54
Education, y	13.1 (2.9)	13.0 (2.0)	0.87
Motor symptoms			
Hoehn and Yahr	1.9 (0.5)	—	—

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, η^2 = 0.14) and group ($F_{1,98}$ = 5.27, P = 0.024, η^2 = 0.05), and an interaction between group and trial type ($F_{1,98}$ = 3.93, P = 0.05, η^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 patients' "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

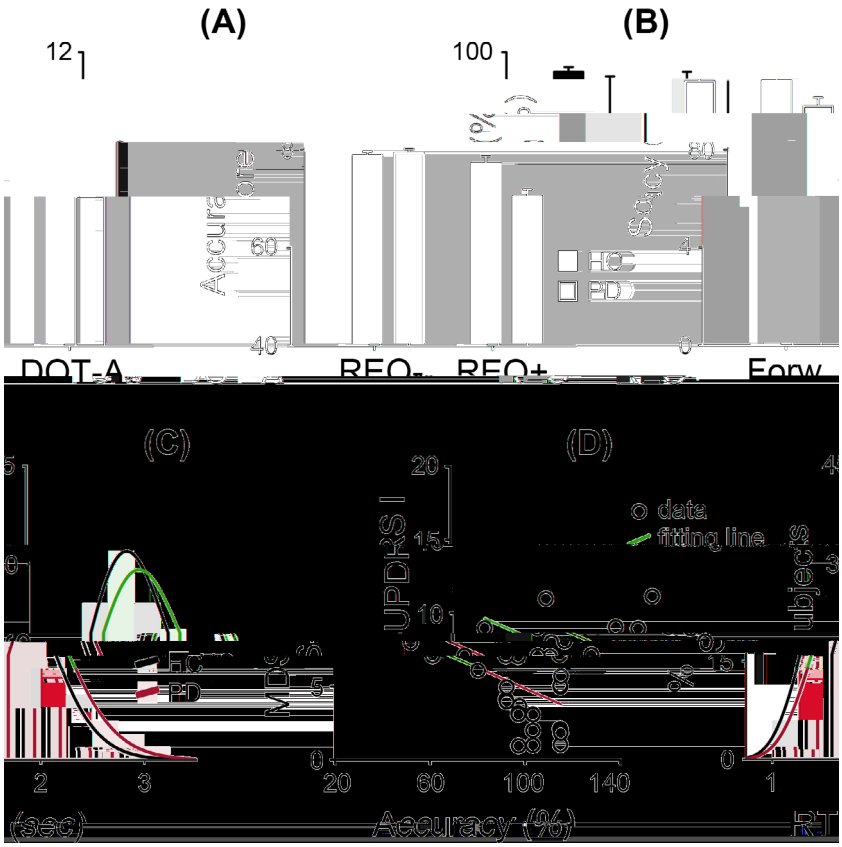

FIG. 2. Behavioral data in patients with Parkinson's disease (PD) and healthy controls (HC). (A) Mean scores and standard errors of the Adaptive Digit Ordering Test (DOT-A) and Digit Span Forward Test (Forw). (B) Mean accuracy and standard errors of the computerized digit ordering task for "pure recall & without reorder" (REO–) and "reorder & recall" trials (REO+). (C) Histogram of reaction times (RT) in "reorder & recall" trials with γ 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]

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

(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

disease may not influence the neural processes of sequential working memory in the same manner. Although the lateral prefrontal cortex exhibited age-related alteration in regional activation and inter-regional interaction,[11] it might not specifically contribute to the deficits in de novo PD.

The STN is an essential modulator of basal ganglia loops. It receives projections from the brainstem (including noradrenergic projections from the locus coeruleus and dopaminergic projections from the substantia nigra pars compacta), thalamus, external globus pallidus, and frontal cortex and projects back to the internal and external globus pallidus, striatum, and brainstem.[25,26] The observed STN dysfunction may result from the early affection of the locus coeruleus and substantia nigra pars compact in pathological stages 2 to 3 rather than direct damages to the prefrontal cortex in pathological stages 5 to 6.

STN has been associated with working memory. Some researchers found that patients with PD with STN deep brain stimulation responded faster and more accurately in visuospatial and emotional working memory tasks when the stimulation was switched ON versus OFF.[27–29] Other researchers observed the opposite: patients with PD made more errors and slower responses in visuospatial and verbal working memory tasks when the stimulation was switched ON versus OFF.[30,31] These studies revealed mixed results, probably because they looked at more advanced stages of PD when the cascade of α-synuclein pathology and the chronic effect of the medication lead to a more complicated situation. This study is an initial attempt to link the STN with sequential working memory in the early stages of PD. We proposed that the STN is involved in maintaining and manipulating sequences online and that the dysfunction of the STN contributes to sequential working memory deficits in de novo PD.

The temporary maintenance of sequences is often assumed to use a competitive queuing mechanism that comprises a parallel planning layer and a competitive choice layer.[32-34] The nodes in the parallel planning layer represent items in a to-be-recalled sequence. The order of the items is represented in terms of a primacy gradient of node activation. Namely, the node activation of the first item is strongest, and the node activations of the subsequent items decline monotonically toward the last item. The nodes in the competitive choice layers are excited by corresponding nodes in the parallel planning layer and inhibited by competitive nodes in the same layer. Recalling a sequence is realized via iterative processes. At each iteration, the most active node in the competitive choice layer is selected, and the corresponding node in the parallel planning layer is suppressed by the feedback projection from the competitive choice layer. At the next iteration, the second strongest node becomes the most active. The competitive queuing mechanisms are thought to reside in the prefrontal cortex, a notion supported by electrophysiological evidence from macaques[9,35-37] and magnetoencephalographic evidence from humans.[38] However, the direct evidence regarding the contribution of the basal ganglia is mostly missing.

The flexible manipulation of sequences is even less understood. Recently we proposed that rearranging sequential items may require a dynamic adjustment of node activations in the parallel planning layer, for example, inhibiting items that should be moved downward and enhancing items that should be moved upward in the new order.[11] The adjustment may be supported by a basal ganglia gating mechanism similar to that proposed for action selection. In Frank's model, the striatum modulates the execution of a particular action, whereas the STN modulates the decision threshold and reduces premature responding.[39] In other models, the STN supports the suppression of alternative competing actions when one action is selected.[40] However, the real picture may be more complicated than the computational models have anticipated given the afferent and efferent projections of the STN. To further understand its role (and that of other basal ganglia structures) in sequential working memory, perioperative intracranial electrophysiological recordings from the STN in PD might be helpful.[41]

In conclusion, we demonstrated the effect of PD on the neural system for sequential working memory in de novo patients with mild clinical symptoms. The neural system comprises the lateral prefrontal cortex, posterior parietal cortex, STN, globus pallidus, and thalamus. The STN plays a modulatory role in maintaining and manipulating sequences in healthy adults. Healthy participants who showed lower "pure recall" STN activation, greater ordering-related STN activation change, and stronger STN–putamen functional connectivity tended to perform better. In patients with PD, the STN was overactivated and lost synchrony with the putamen. Thus, the modulatory role of the STN was weakened mainly. Individual patients' performance correlated with the functional connectivity, but not the regional activation or activation change of the STN. It implies that downregulating STN activation and upregulating STN functional connectivity may be a potential strategy for enhancing sequential working memory in PD. ■

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