VIDEO

Enhancement of brain activation during trial-and-error sequence learning in early PD

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Abstract—*Background:* Although the pathophysiology remains unknown, most nondemented patients with PD have difficulty with frontal tasks, including trial-and-error sequence learning. If given time, they can perform cognitive tasks of moderate difficulty as well as controls. However, it is not known how brain function is altered during this time period to preserve higher cortical function in the face of PD pathology. *Method:* To evaluate this phenomenon, the authors matched sequence learning between PD and control subjects for the last 30 seconds of a PET scan. Learning during the initial 50 seconds of PET was unconstrained. *Results:* Learning indices were equivalent between groups during the last 30 seconds of the scan, whereas rates of acquisition, correct movements, and forgetting differed in the first 30 seconds. In normal controls sequence learning was associated with activations in the right prefrontal, premotor, parietal, rostral supplementary motor area, and precuneus regions. To achieve equal performance, the PD group activated greater volume within these same regions, and also their left sided cortical homologs and the lateral cerebellum bilaterally. *Conclusions:* Mildly affected patients with PD demonstrated only modest impairment of learning during the first 30 seconds of the task and performed equivalently with controls thereafter. However, the mechanism by which they achieved equiperformance involved considerable changes in brain function. The PD group had to activate four times as much neural tissue as the controls, including recruiting brain from homologous cortical regions and bilateral lateral cerebellum.

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Two thirds of patients with PD are not demented.[1] However, as many as 90% of nondemented patients with PD may demonstrate cognitive impairment after appropriate neuropsychological assessment.[2] The pathology responsible for this cognitive impairment is not known. Patients with PD have more difficulty learning a motor sequence than controls. However, if given time, and if the sequence is not too long, patients with PD can eventually achieve normal learning performance. The specific neural resources used by nondemented PD subjects to achieve normal performance have not been studied. Understanding the mechanism by which normal performance is preserved in early disease stages may have etiologic and therapeutic importance. Identifying those aspects of normal brain function that fail during learning can help expose the functional pathology underlying cognitive impairment in parkinsonism. Further, identifying how patients with PD alter brain function to compensate for parkinsonism may reveal brain function worth facilitating with novel treatment stratagems.

In this study we sought to identify the mechanism by which the brain conserves higher cognitive function by scanning patients with PD while they were in the process of achieving a degree of learning performance that was equivalent to age-matched normal control subjects. To accomplish this aim we utilized a modified equal performance design. Patients with PD were matched with controls such that all subjects made the same number of correct movements during the final 30 seconds of a ^{15}O-labeled water ($H_2{}^{15}O$) PET scan. During the initial 50 seconds, when most PET signal is acquired, learning between the two groups was not constrained.

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Materials and methods. *Subjects.* Table 1 shows the demographics of the eight patients with PD and eight normal control subjects matched such that the number of correct movements was equivalent from the 55-second through 75-second time bins. All subjects used English as a first language, were right-handed, and had scores > 27 on the Mini-Mental State Examination.[3] Patients and control subjects with prior histories of unrelated neurologic or

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Table 1 *Demographics*

Group	Age, y	Sex	Motor symptoms	Elements in sequence	Average correct movement 45–75 sec bins
Controls	70.025	M		5	4.17
	56.083	F		5	6.33
	55.417	M		6	7.00
	48.750	F		5	8.33
	56.417	M		6	8.67
	52.500	F		5	9.33
	56.667	F		4	9.67
	76.917	F		4	10.00
Mean	59.125	3M/5F		5.00	7.94
SD	9.473			0.76	1.98
PD	57.083	M	L	5	4.17
	62.500	M	L	4	6.17
	46.250	M	R	5	7.00
	77.167	F	L	4	8.17
	75.750	F	L	4	8.50
	48.500	M	R	6	9.67
	60.833	M	L	5	9.67
	58.917	F	L	5	9.83
Mean	60.875	5M/3F		4.75	7.90
SD	11.178			0.71	2.01
p Value*	0.74	0.20		0.51	0.97

Groups were matched such that number of correct movements was equivalent in the 45 through 75 second bins.
* *t*-Test or Fisher exact.

psychiatric illness, hypertension, cardiovascular disease, diabetes mellitus, or abnormal diagnostic MRI scans were excluded. Patients were included if they exhibited pure hemiparkinsonism (Hoehn and Yahr stage 1) without known causative factors and did not have dementia, supranuclear gaze abnormalities, or ataxia. Six patients with PD had left and two had right hemiparkinsonism. All patients with PD had greater than 20% improvement on the Unified PD Rating Scale[4] in response to dopamine replacement. All behavioral and imaging studies were performed following a 12-hour medication washout. All subjects signed informed consent in accordance with the North Shore University Institutional Review Board.

Tasks. We have previously described the tasks in detail[5] and present them visually in video 1 (see the *Neurology* Web site; go to www.neurology.org and scroll down the Table of Contents to find the title link for this article). Subjects moved a hand-held mouse on a digitizing tablet (12 inches × 18 inches, Numonics Corporation, Montgomeryville, PA). The position of the mouse was displayed as a cursor on a computer monitor. Subjects moved the cursor out and back from a central position to one of a set of radially arranged circles (targets) and then back to the central position again. The computer sampled hand positions at 200 Hz. All movements were made with the right hand. All subjects were right handed. Two of the eight patients with hemiparkinsonism had motor symptoms on the right. Therefore, six patients with PD were making movements with their clinically normal hand.

Control task for trial-and-error sequence learning task (TEseq_c). Eight radially arranged targets were presented on the screen. In synchrony with a 1-Hz tone, the targets turned black in counterclockwise order starting from the target at 3 o'clock. From the center, subjects made out and back movements to each successive target. They attempted to reverse their hand movement inside the peripheral target in synchrony with the tone (timing error, figure 1). If the cursor entered the correct target 250 msec before, during, or 250 msec after the tone, the target turned gray, providing the subject with positive reinforcement ("hit window," see figure 1B). If the cursor entered the wrong target, or entered the correct target but outside of the hit window, the target remained transparent, providing negative feedback. Although the task was paced at 1 Hz, movement was self-initiated.[6] Subjects needed to anticipate each target and move before hearing the tone, as in timed response tasks.[7]

Trial-and-error sequence learning task (TEseq). Like TEseq_c, TEseq also required self-initiated out and back cursor movements to radially arranged targets paced by a 1-Hz tone. Once again subjects received feedback from every movement. Thus, movement extent and frequency were the same for each TEseq and TEseq_c scan pair (kinematically controlled). Unlike TEseq_c, which had eight radially arranged targets, TEseq had four, five, or six radially arranged targets that corresponded to the lengths of the sequence to be learned (see figure 1). Unlike the control task (TEseq_c), the sequence was not revealed by targets turning black; instead, subjects had to determine the correct sequence of movements by trial and error, relying on positive and negative feedback from each movement (see figure 1A) (that is, relying on whether the target turned gray [correct] or remained transparent [incorrect] during the movement). The rules for each novel sequence were as follows: 1) the number of movements in the sequence was equal to the number of targets presented on the computer screen; 2) each target was visited once and only once during a sequence; and 3) the sequence cycled through its veridical order for the duration of the scan. Subjects were trained to adopt a specific strategy to learn the sequence[5] (see video 1 on the *Neurology* Web site; go to www.neurology.org). The strategy included making movements to a single target until it turned gray (was correct). Subjects were to consider this movement the first element in the sequence. They then made trial-and-error movements to targets, dividing their attention between counting tones so as to return to the first target at the proper time and learning new sequence elements. Subjects learned new elements by com-

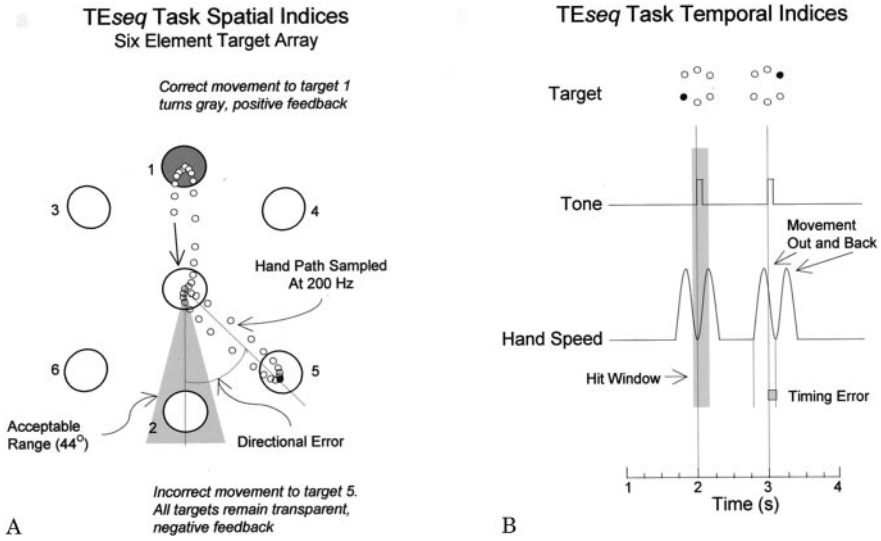

Figure 1. Spatial and temporal indices of trial-and-error sequence learning (TEseq) task. The plot of hand speed is biphasic because two sets of acceleration and deceleration are made; the outward movement from the center to the peripheral target, and the return movement from the peripheral to the center target.

bining feedback from each movement with deductions based on the sequence rules. This strategy would result in rapid sequence learning if all information could be held in working memory and applied. The load on working memory was particularly intense in the first seconds of the task (see video 1 on the *Neurology* Web site).

All subjects were given training and practice sessions before PET. These sessions were important for controlling movement and learning during PET. They ensured stable and equal levels of movement indices in the TEseq and TEseq_c tasks during PET. Thus, regions that remain activated after subtracting TEseq_c from TEseq scans reflect sequence learning rather than between-group differences in movement extent or velocity. These sessions were also used to determine the longest sequence each patient with PD was able to learn. This was defined as the longest sequence for which the patient hit all targets successfully at least once within each of three successive blocks of 80 movements. Finally, these sessions were used to evaluate healthy controls at multiple sequence lengths so that equal performance with patients with PD might be obtained during the last 30 seconds of the PET scan.

We computed the learning indices as follows. We defined a movement as correct when the directional error was less than 22 degrees on either side of the appropriate target midpoint (see figure 1A). To determine the other learning indices (e.g., acquire, retrieve, wrong, forget, and perseverate) we compared the target selected in the cycle of interest with both the veridical target order and the target selected in the preceding cycle. A correct movement in the cycle of interest with a wrong movement in the preceding cycle was scored correct and acquired. A correct movement in the cycle of interest with a correct movement in the preceding cycle was scored correct and retrieved. A wrong movement in the cycle of interest with a correct movement in the preceding cycle was scored wrong and forgot. A wrong movement in the cycle of interest with a wrong movement in the preceding cycle was scored wrong. A wrong movement in the cycle of interest with the same wrong movement in the preceding cycle was scored wrong and perseverate.

PET. All patients and controls fasted for 6 hours before PET scanning. All antiparkinsonian medications were discontinued at least 12 hours before the studies. All subjects underwent one pair of control scans (TEseq_c) and one pair of sequence learning scans (TEseq) of either 4, 5, or 6 target length. Each patient with PD underwent TEseq at the longest novel sequence that could be learned (see above). Each control subject underwent TEseq of sequence length such that the total number of correct movements during the final 30 seconds of the scan was matched between the groups (see table 1). Regional cerebral blood flow (rCBF) was measured using $H_2{}^{15}O$ with an 18-ring bismuth germanate GE Advance tomograph (General Electric, Milwaukee, WI) in three-dimensional mode that has reconstructed transverse and axial resolutions of 4.3 mm (full-width half maximum [FWHM]) at the center and an axial field of view of 14.5 cm as described by us elsewhere.[8] Motor tasks (Mseq and TEseq_c) were performed with the dominant right hand, and an IV catheter was placed in the left to administer $H_2{}^{15}O$. Relative rCBF was estimated using a modification of the slow bolus method of Silbersweig et al.[9]; the details of administration have been described elsewhere.[5,10]

Analysis. Psychophysics. Learning and movement indices were binned every 10 seconds for the duration of the PET scan. Between-group comparisons were evaluated using Student's *t*-tests or repeated measures analysis of variance as appropriate.

Images. Scans were prepared for analysis by a standard methodology using statistical parametric mapping (SPM99, MathWorks, Natick, MA)[11] software (MRC Cyclotron Unit, London, UK) in PROMATLAB (Mathworks) on a PC platform running Windows 2000 (Microsoft, Redmond, WA). Using SPM99, the original GE images for each subject were realigned and resliced (sinc interpolation) and then normalized into Talairach space (bilinear interpolation) to create images of 2 mm by 2 mm by 2 mm voxel size. Each scan was then smoothed using a Gaussian filter (FWHM 10 by 10 by 10 mm).

Means of the paired TEseq scans and the paired TEseq_c controls were created using the adjusted means: proportional scaling and average method in SPM. A single (mean) TEseq scan and a single (mean) TEseq_c scan for each subject was then entered into "PET/SPECT models: multi-group: conditions and covariates." Two groups were selected, eight subjects per group, two conditions per subject (TEseq and TEseq_c), and one (mean) scan per task. No covariates or nuisance variables were identified. The scans were normalized by proportional scaling and proportional threshold masking. The analysis threshold (proportion of global mean) was set at 0.8, and the calculation for the global mean was the within per image fullmean/8 mask.

Images were entered into this model in the following order: PD TEseq, PD TEseq_c, control TEseq, control TEseq_c. To determine those voxels where values of rCBF were greater during TEseq than during TEseq_c (voxel-by-voxel within-group subtraction analysis), the following contrasts were entered: 1 −1 0 0 (for the PD group analysis) and 0 0 1 −1 (for the control group analysis). To determine those voxels where the difference in values of rCBF between TEseq and TEseq_c (between-task difference) for the PD group was greater than the between-task difference for the control group, we entered the contrast 1 −1 −1 1 (voxel-by-voxel group-by-task interaction). To determine those voxels where the between-task difference for the control group was greater than the between-task difference for the PD group we entered the contrast −1 1 1 −1.

For the voxel-by-voxel within-group subtraction analysis statistical scores were thresholded at $p < 0.001$. Number of subjects, number of scans, and statistical threshold was equivalent between groups. We performed no correction for multiple independent comparisons on rCBF voxel changes as all regions activated have previously been identified by this and other sequence learning tasks.[10,12-15] These regions were considered to be hypothesis driven in that they comprise the distributed networks known to be acti-

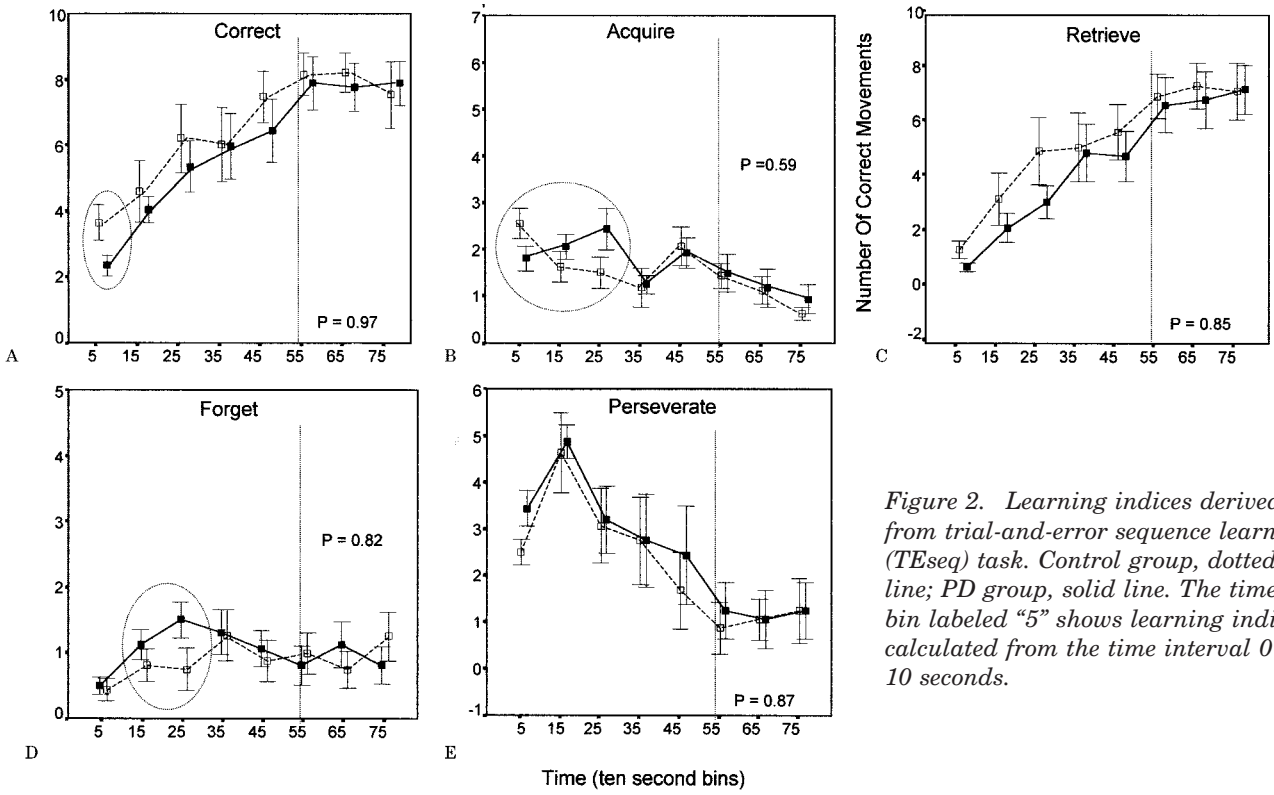

Figure 2. Learning indices derived from trial-and-error sequence learning (TEseq) task. Control group, dotted line; PD group, solid line. The time bin labeled "5" shows learning indices calculated from the time interval 0 to 10 seconds.

vated in sequence learning tasks and are therefore not independent of each other.[14]

For the voxel-by-voxel group-by-task interaction each voxel was thresholded at $p < 0.01$ without correction for multiple comparisons among the nonindependent regions associated with normal sequence learning (see above).

Results. *Behavioral results.* Learning indices. The number of correct movements in the 55-second through 75-second time bins was closely matched between the control and PD groups (figure 2A; F[1,14] = 0.002, $p = 0.97$). Thus, our fundamental design criterion that the two groups perform equivalently for at least the last 30 seconds of the scan was achieved. p Values for the repeated measures analysis across the 55-second, 65-second, and 75-second bins for correct, acquire, retrieve, forget, and perseverate are presented in figure 2 and illustrate no difference in these indices between PD and control groups.

Performance was not constrained across the 5-second through 45-second bins. The PD group made fewer correct movements in the first 10 seconds than the control group ($p = 0.02$, one-tailed t-test). The rate of new element acquisition in the PD group started off low in the first 10 seconds (see figure 2B) and then increased through 30 seconds, whereas the rate of new element acquisition in the control group started off high in the first 10 seconds and then declined ($p = 0.03$, t-test of slopes). The PD group forgot more sequence elements during the 25-second bin than the controls ($p = 0.04$, one-tailed t-test). Retrieval rates were no different between groups across the 5-second through 45-second bins (F[1,14] = 0.8, $p = 0.38$), nor were there any differences at any bin considered in isolation (see figure 2C).

Movement indices. To isolate brain function associated with learning but not movement, we subtracted a kinematically controlled movement task TEseq_c from TEseq. There were no differences between groups in motor indices (see figure 1). Movement times for the control and PD groups were 449.7 ± 55.6 (SD) msec and 443.7 ± 64.6 ($p = 0.8$ t-test), and timing errors were −8.0 ± 92.4 msec and 22.0 ± 64.6 msec ($p = 0.7$). This group of patients with mild PD made movements no different from controls.

PET results. Figure 3 identifies brain regions in which rCBF values during TEseq are greater than rCBF values during TEseq_c for each group (voxel-by-voxel within-group subtraction analysis). The figure is color coded such that brain regions activated in both groups are orange, brain regions activated by controls but not PD are red, and brain regions activated by PD but not controls are yellow. Brain regions activated by both groups (orange) included the right dorsolateral prefrontal cortex (DLPFC) (Brodmann area [BA] 9/10/46), bilateral premotor cortex (PMC) (BA 6/8), anterior sensory motor area (preSMA) (BA 6), precuneus (BA 7), and right parietal cortex (PC) (BA 7/40). The most striking finding was the widespread brain regions activated by the PD but not the control group (yellow): a total activation of 9,621 voxels (76,968 mm^3) in the PD group compared to 2,397 voxels (19,176 mm^3) in the control group. The increased PD activation included similar regions as activated by the control group (yellow around orange, yellow next to red), as well as regions not activated by the control group (yellow). The latter included a very large activation in left DLPFC extending from 6 mm through 38 mm relative to the anterior-posterior commissure (ACPC) line (BA 46/10/9), anterior cingulate (BA 32), left PC (BA 7/40), left insula/inferior frontal cortex (BA 47), and bilateral lateral cerebellum. See table 2 for more details.

The group-by-task analysis revealed no brain region in which the between-task difference was greater in the control group than in the PD group. By contrast, the between-task difference was greater in the PD group than the control group in left DLPFC, left insula/inferior frontal cortex, left PC, anterior cingulate, and preSMA; i.e., in those yellow regions in figure 3 identified as having PD but not control activation.

Other results. Of those voxels with significant activation (values of TEseq greater than values of TEseq_c in figure 3), the number of voxels in which the values of TEseq_c in the PD group were significantly different from the values of TEseq_c in the control group did not exceed the number expected by chance alone. Also, the group-by-task interaction showed that in the yellow regions, the between-task difference was significantly greater in the PD than in the control group. Therefore, when activations in figure 3 were observed in one group but not the other (yellow and red regions), they were the result of between-group differences in values of TEseq and not between-group differences in values of TEseq_c. Further, as behavioral movement indices were no different between groups (see above), we are confident in attributing between-group differences in brain activation in figure 3 to differences in motor sequence learning, and not to differences in

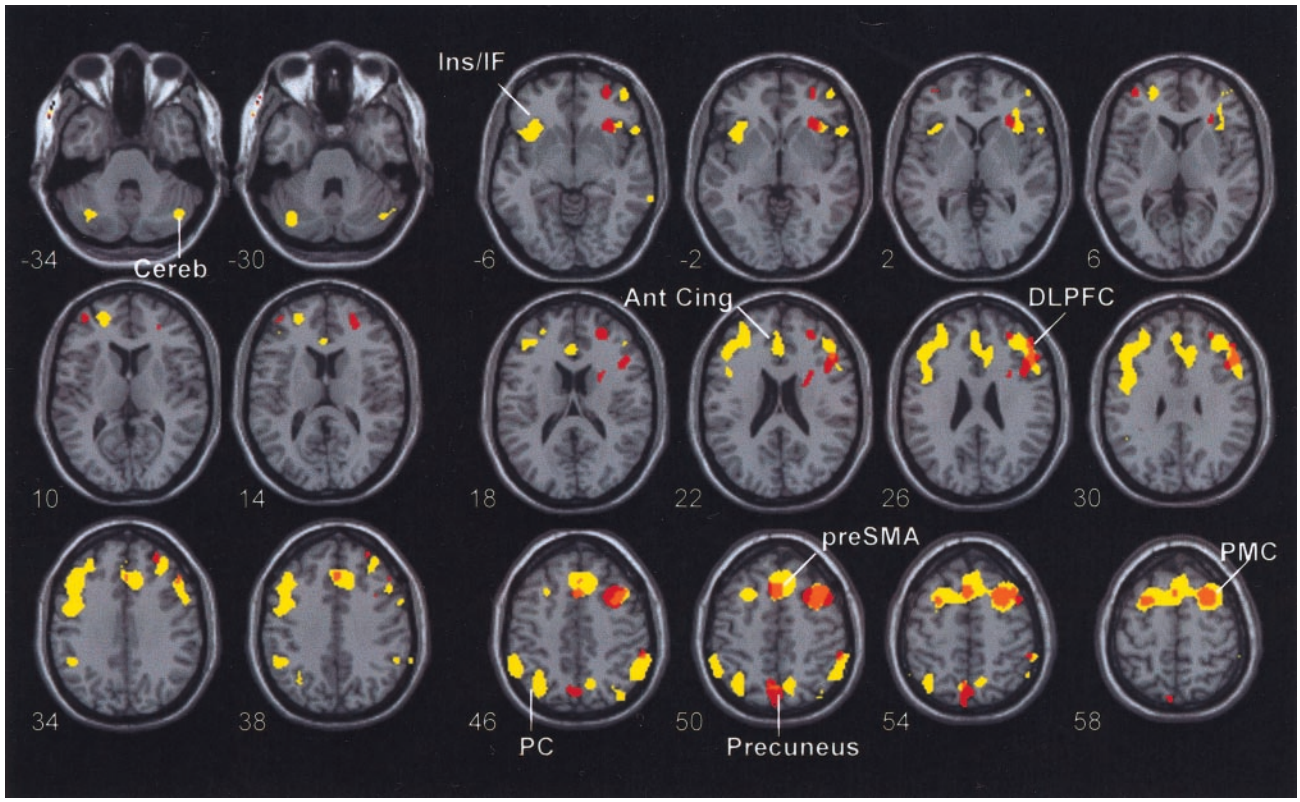

Figure 3. Brain regions activated by 8 patients with PD and 8 control patients to achieve equal learning performance. Voxels activated during sequence learning in PD and control groups are color coded and overlaid on a structural MRI in the space of the Talairach and Tourneaux[38] atlas. Numbers represent level of axial slice relative to the anterior-posterior commissure line. Left side of brain is on left side of scan. Yellow = PD but not control; orange = PD and control; red = control but not PD.

brain activation during movement or to differences in movement performance.

There were no differences in learning or movement indices between the right and left hemiparkinson patients with PD. The two right hemiparkinsonian patients were not outliers driving between-group differences in learning. In fact, the mean learning indices of the right hemiparkinsonian patients tended to be less impaired than, but not statistically different from, the mean values for the left hemiparkinsonian patients.

Discussion. A salient finding is that, in contrast with normal subjects, patients with mild PD exhibit widespread differences in brain function in the face of only modest differences in learning behavior. On the one hand, extensive bilateral brain changes were required to overcome the effects of mild PD pathology. On the other hand, these brain changes were effective in minimizing the behavioral differences, even in the early seconds of the scan. Compared to controls, the patients with PD made fewer correct movements over the first 10 seconds of the task, had different rates of new element acquisition over the first 30 seconds, and forgot more recently learned elements during the 30-second bin. The control group activated regions previously identified in motor sequence learning including preSMA, right DLPMC, bilateral PMC, precuneus, right PC, and right insula.[10,12-15] Under conditions of identical power for detecting brain activation, the PD group activated all these regions, but to a greater extent. In addition, these patients activated homologous DLPFC, PC, and insula in the left hemisphere, as well as anterior cingulate and bilateral lateral cerebellum.

If the learning strategy is successfully executed, subjects will observe and deduce many facts that need to be held in working memory (see Methods and video 1 [www.neurology.org]). Most facts are generated during the initial movements of the task, and subjects best able to utilize information gleaned from each movement learn the sequence most rapidly. Compared to controls, patients with PD had difficulty starting the task in that they acquired fewer elements in the initial 10 seconds and forgot more elements in the initial 30 seconds (see figure 2, A, B, and D). Thereafter, their learning indices were similar to those of controls, suggesting less of a problem with retrieval once the task was being executed. In agreement with some[16-18] but not other studies,[19] these data support the notion that a major problem with cognition in PD is task initiation rather than bradyphrenia. It must be noted, however, that because patients with PD acquired fewer sequence elements early in the scan, they had fewer elements to recall later in the scan. This confounds the assessment of PD patient retrieval, and conclusions on retrieval should be treated with caution. Further,

Table 2 *Local maxima of brain regions activated by trial-and-error learning in PD and control groups*

		PD				Control			
Brain region	BA	x,	y,	z	Z score	x,	y,	z	Z score
Regions activated by both groups									
PMC (right)	6/8	32	14	58	5.41	26	14	58	5.13
PMC (left)	6/8	−24	10	60	5.30	−26	8	60	4.07
PreSMA	6	4	22	52	6.59	0	16	52	5.01
Precuneus	7	12	−64	50	4.44	−6	−62	50	3.56
PC (right)	7/40	58	−40	48	3.47	58	−40	48	4.51
DLPFC (right)	46	48	26	26	4.08	48	24	24	4.16
Insula/IF (right)	47	58	18	−4	4.0	34	24	−4	3.91
Regions activated by PD but not control group									
PC (left)	7/40	−34	−60	50	5.41				
DLPFC (left)	9	−40	26	36	4.13				
DLPFC (left)	10	−22	50	12	4.17				
DLPFC (left)	46	−46	30	24	4.72				
Insula/IF (left)	47	−40	14	−4	3.81				
Anterior cingulate	32	0	32	22	4.38				
Lateral Cereb (left)		−38	−74	−28	4.87				
Lateral Cereb (right)		46	−68	−34	3.71				

BA = Brodmann area; PMC = premotor cortex; PreSMA = anterior sensory motor area; PC = parietal cortex; DLPFC = dorsolateral prefrontal cortex; IF = inferior frontal cortex; Cereb = cerebellum.

tasks of longer duration would be more suited to expose problems with retrieval.

In this equal learning comparison, the power to detect brain activation was identical between the groups as the number of subjects, number of scans, and statistical thresholds were the same for both (see figure 3). To achieve learning parity with controls, the PD group utilized homologous regions not activated by the control group including the left DLPFC, PC, insula, anterior cingulate, and bilateral lateral cerebellum, and activated a greater volume of tissue within regions that were activated by controls. These two mechanisms resulted in approximately four times as much brain activation in the PD group (9,621 voxels [76,968 mm^3]) compared to the control group (2,397 voxels [19,176 mm^3]).

Every region activated in this study has been previously shown to be part of the network associated with normal sequence learning and possible functions for each region have been discussed.[5,10,12,13,15,20-22]

After brain damage from trauma or disease, patients may regain function by activating nondamaged brain regions.[23] Functional recovery postdamage is often incomplete as the recruited region, which may be a contralateral homologous area, is less specialized for the behavior. By contrast, the left-sided regions and cerebellum activated by the PD group can be activated by healthy controls under different task constraints from the current study[5,10,12,13,15,20-22] (for example, if the sequence to be learned is more difficult than in the current study). Thus, these left-sided homotypical regions activated by the PD group may be specialized for the task of interest unlike other reports documenting recruitment of homotypical regions after trauma or disease. This may explain why the behavioral compensation in this mild group of patients with PD was so effective. The dramatic failure in learning that occurs when task difficulty is high or when parkinsonism is advanced may occur when activating regions from within the normal sequence learning networks can no longer compensate and other mechanisms to maintain function need to be utilized.

Patients with PD have most difficulty performing complex tasks that have a large executive or frontal component.[16,24] The notion that cognitive dysfunction in PD is primarily executive/frontal suggests that the disease process causes impaired function within frontal cortex, fronto-subcortical circuits, or both.[25,26] Dysfunction within the motor cortico-striatopallidal thalamo-cortical (CSPTC) loop[27] caused by nigrostriatal dopaminergic deficiency has been a successful hypothesis in explaining many of the motor abnormalities of PD, and has led to the speculation that nigrostriatal or ventral tegmental area (VTA)–frontal dopamine loss can also give rise to cognitive dysfunction through a failure of modulating frontal CSPTC loops. Indeed, decreased basal ganglia activation in PD compared to controls has been observed during performance of some frontal lobe tasks.[28] We also found reduction in basal ganglia activation in PD compared to controls using a simple intentional serial reaction time task (M_{RTL}).[10] However, in contrast to the TEseq task employed in the current study, M_{RTL} does not involve trial and error, and is

less demanding of working memory and other executive functions (see video 1 at www.neurology.org). Unlike M_{RTL}, TEseq in subjects does not activate basal ganglia, suggesting that striatal function is not an important component during the first few seconds of normal declarative learning in this trial-and-error task. Therefore, fronto-subcortical dysfunction involving lateral CSPTC loops may not be the direct cause of the cognitive difficulties in the PD group noted with this task (see figure 3).

Some of the results in this study support the notion of dysfunction within frontal lobes. The most striking behavioral abnormality was failure of new element acquisition in the first 30 seconds of sequence learning resulting in fewer correct movements. Sakai et al.[21] have shown that the earliest stage of sequence learning activates left DLPFC. The major difference in activation between the two groups was the large left DLPFC activation in the PD group (see figure 3, 18 mm through 38 mm above anterior-posterior commissure line). These findings suggest that patients with PD have an impairment of left frontal function in the first seconds of declarative sequence learning.

However, the between-group differences in brain function involved considerably more than the frontal lobes. Large areas in bilateral parietal lobe (medial and lateral), bilateral insula, and bilateral cerebellum were activated by TEseq in the PD but not the control group (see figure 3, Results). Although it is conceivable that these are all downstream effects secondary to abnormal function within the frontal lobe, it is also possible that the PD disease process responsible for cognitive dysfunction has a global effect on the cortex rather than an effect confined to the frontal lobe. This global effect hypothesis remains consistent with the behavioral observation that patients with PD have most difficulty with complex frontal tasks. Such tasks involve interaction between frontal and nonfrontal brain regions and performance may fail through a lesion that impairs cortical function globally. Indeed, we have recently demonstrated the critical relationship of parietal and temporal metabolic activity to classic neuropsychological assessments of cognitive functions that have large executive components.[29] Regions found to correlate with cognitive dysfunction in PD were in fact not frontal or fronto-subcortical, as would be expected if the cognitive disturbances were primarily caused by a lesion affecting function in the frontal cortex or in its subcortical afferents. Moreover, dopamine replacement therapy, which is successful in reversing motor symptoms in PD, has little if any effect on reversing cognitive symptoms.[30-33] This suggests that dysfunction within either the nigrostriatal or VTA-frontal dopamine systems is not likely to be the sole cause of cognitive dysfunction in PD. Nondemented patients with PD have abnormalities of noradrenergic,[34] serotonergic,[35] and cholinergic[36] modulatory systems in addition to the dopaminergic system. Anatomically, these systems extend globally throughout the entire cortex. Functionally, we have shown in man that acetylcholine has a high degree of specificity in modulating function in different brain regions responsible for executing a task.[37] Global cortical dysfunction caused by pathology within one or more of these modulatory systems might be responsible for the cognitive and functional brain abnormalities seen in PD.

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