Compensatory Neural Mechanisms in Cognitively Unimpaired Parkinson Disease

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Objective: Cognitive impairments in Parkinson disease (PD) are thought to be caused in part by dopamine dysregulation. However, even when nigrostriatal dopamine neuron loss is severe enough to cause motor symptoms, many patients remain cognitively unimpaired. It is unclear what brain mechanisms allow these patients to remain cognitively unimpaired despite substantial dopamine dysregulation.
Methods: Thirty-one cognitively unimpaired PD participants off dopaminergic medications were scanned using functional magnetic resonance imaging while they performed a working memory task, along with 23 controls. We first compared the PD off medication (PD_OFF) group with controls to determine whether PD participants engage compensatory frontostriatal mechanisms during working memory. We then studied the same PD participants on dopaminergic medications to determine whether these compensatory brain changes are altered with dopamine.
Results: Controls and PD showed working memory load-dependent activation in the bilateral putamen, anterior–dorsal insula, supplementary motor area, and anterior cingulate cortex. Compared to controls, PD_OFF showed compensatory hyperactivation of bilateral putamen and posterior insula, and machine learning algorithms identified robust differences in putamen activation patterns. Compared to PD_OFF, the PD on medication group showed reduced compensatory activation in the putamen. Loss of compensatory hyperactivation on dopaminergic medication correlated with slower performance on the working memory task and slower cognitive speed on the Symbol Digit Modality Test.
Interpretation: Our results provide novel evidence that PD patients maintain normal cognitive performance through compensatory hyperactivation of the putamen. Dopaminergic medication downregulates this hyperactivation, and the degree of downregulation predicts behavior. Identifying cognitive compensatory mechanisms in PD is important for understanding how some patients maintain intact cognitive performance despite nigrostriatal dopamine loss.

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At the time of diagnosis, approximately 60 to 85% of Parkinson disease (PD) patients are considered cognitively unimpaired.[1–4] Within 3 years, a third of these patients progress to mild cognitive impairment[5,6]; however, the neural processes that distinguish cognitively unimpaired and impaired patients are poorly understood.[7] Studies investigating early PD neuropathology suggest that mild cognitive impairment results from neurotransmitter dysregulation and, in particular, from downstream effects of nigrostriatal dopamine neuron loss.[8] What brain mechanisms allow some patients to have preserved cognitive performance when dopamine neuron loss is sufficient to manifest motor symptoms?[9] One hypothesis is that compensatory neuronal activity is present in regions affected by early dopamine neuron loss.[10] Characterizing potential compensatory mechanisms is paramount for understanding, and ultimately treating, PD cognitive impairments. In particular, this could lead to identification of potential therapeutic

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targets for improving cognitive performance in impaired individuals.[11]

Working memory, the ability to maintain and manipulate information in temporary storage for task-relevant goals, is central to many higher-order cognitive functions,[12,13] and working memory deficits are often the earliest cognitive sequelae in PD patients.[14] Dopamine is critical for normal working memory,[15,16] and administration of dopamine-receptor blocking medications to normal adults leads to deficits in working memory ability.[17] Functional magnetic resonance imaging (fMRI) of healthy individuals has identified a frontostriatal network, involving the caudate, putamen, and dorsolateral prefrontal cortex (PFC), that is activated during a wide range of working memory tasks.[16,18–20] Several fMRI studies in PD have identified frontostriatal modulation associated with impairments in cognitive performance,[21] including reduced striatal activity during working memory and other executive tasks.[22–25] Striatal under-recruitment has been implicated as a possible mechanism for PD-related executive dysfunction.[26,27] However, few studies have investigated frontostriatal activity in cognitively unimpaired patients. In particular, it remains unclear whether these patients engage the putamen and caudate more to achieve similar levels of performance as controls.[22,28] It is also not known whether cortical hubs within cognitive control networks, such as the PFC or the insula, are differently engaged in cognitively unimpaired patients.[29,30] Crucially, little is known about the influence of dopaminergic medication on the striatum and extrastriatal cognitive networks and the subsequent impact on cognitive processing in PD. The stringent off–on medication design traditionally used in PD motor studies is rarely applied to cognitive studies.

Here we use fMRI to determine whether cognitively unimpaired PD patients engage compensatory frontostriatal activation during a working memory paradigm. To test this hypothesis, we compared PD subjects off dopaminergic medications (PD_OFF) with cognitively matched healthy controls (HC). Additionally, we used a stringent off–on design in these same patients to investigate how dopaminergic medications alter performance and brain activation. We hypothesized that unimpaired cognitive performance in PD patients when off dopaminergic medications would be associated with compensatory hyperactivation in frontostriatal regions and, critically, that activation in these regions would be modulated when patients are on dopaminergic medications, suggesting a mechanism for dopamine-mediated alterations in working memory function. Finally, we used multivariate classification analysis to determine brain regions where activation patterns during working memory can most accurately differentiate between groups.

Subjects and Methods

Participants

Our sample included a total of 54 right-handed participants with normal or corrected-to-normal vision. Participants were recruited from the Stanford Movement Disorders Clinic and from the surrounding community. Participants included 31 PD patients with no cognitive impairment, defined as no more than 1 test exceeding 1.5 standard deviations (SD) below age- and education-matched normative values on comprehensive neuropsychological testing that included at least 2 tests for each of the 5 cognitive domains[31] (Table 1). All patients were diagnosed with PD by a board-certified neurologist with specialty training in movement disorders (K.L.P.) based on UK Parkinson's Disease Society Brain Bank criteria.[32] For further confirmation of diagnostic accuracy, we only included participants with at least 2 years of a PD diagnosis and at least 20% improvement on the Movement Disorders Society-United Parkinson's Disease Rating Scale motor score (MDS-UPDRS-III)[33] when on dopaminergic medications. PD patients underwent a comprehensive neurological screening examination and the MDS-UPDRS-III both off and on dopaminergic medications. As recommended by current criteria,[31] the comprehensive neuropsychological testing was performed on medications to minimize motoric interference in testing. The "practical" off state for both clinical and imaging assessments was defined as $\geq$72 hours off extended release dopamine agonists, selective monoamine oxidase inhibitors, and long-acting L-dopa, and $\geq$12 hours off short-acting dopamine agonists and L-dopa. The practical on state for both clinical and imaging assessments was defined as the patients taking their normal daily medications in the optimally medicated state, as determined by both the patient and the movement disorders neurologist. Seven PD patients were excluded from analysis: 2 due to technical failure of input device during scan acquisition, 3 due to excessive head movement (see fMRI Preprocessing below), 1 due to identification of unknown metal in the skin during scanner localization, and 1 due to subject illness precluding completion of the study. Therefore, 24 PD patients were included in the final data analysis. With regard to dopamine replacement therapy, 3 participants were taking only a dopamine agonist, 11 were taking only L-dopa, and 10 were taking a combination of an agonist and L-dopa. In addition, we recruited 23 age- and education-matched HC. Inclusion criteria for all PD and HC participants were as follows: (1) age between 45 and 90 years; (2) fluency in English; (3) no contraindications to fMRI scanning; (4) no history of significant neurological disease (other than PD), serious psychiatric illness, or substance abuse; and (5) no history of cognitive impairment during phone screening. In addition, all control participants were evaluated as healthy in a neurological screening examination, and obtained a score on the Mini-Mental State Examination (MMSE) $\geq$ 27. A subgroup of HC participants were administered the entire neuropsychological battery (see Table 1).

PD participants completed 2 fMRI sessions; 1 in the off medication state (PD_OFF) and 1 in the on medication state

TABLE 1. Demographic and Neuropsychological Data

	PD		HC		*p*
No.	24		23		—
Age, yr	65.33	(8.84)	61.17	(10.14)	0.14
Education, yr	16.88	(2.54)	15.8	(1.55)	0.22
Gender, M:F[a]	15:9		9:14		0.02[b]
LEDD	658.7	(396.7)	—	—	—
Hoehn & Yahr, off	1.92	(0.50)	—	—	—
MDS-UPDRS part III, off	32.88	(11.30)	—	—	—
MDS-UPDRS part III, on	17.54	(10.54)	—	—	—
MoCA[c]	27.58	(1.74)	28.56	(1.42)	0.15
MMSE	29.5	(0.8)	29.7	(0.5)	0.43
CVLT SD Free[c]	51.74	(8.61)	59	(8.76)	0.03[b]
CVLT LD Free[c]	51.21	(13.43)	59.0	(8.10)	0.10
BVMT-R Total Recall[c]	25.08	(7.78)	26.10	(4.79)	0.70
JLO[c]	27.71	(3.43)	29.30	(2.50)	0.23
HVOT[c]	49.21	(4.77)	48.10	(3.90)	0.52
SDMT Oral[c]	51.63	(8.94)	58.40	(11.34)	0.07
FAS[c]	53.63	(11.10)	54.80	(10.33)	0.78
WAIS-IV Digit total[c]	56.02	(11.39)	52.38	(8.08)	0.41
Trails A[c]	51.21	(8.55)	58.20	(4.02)	0.02[b]
Trails B[c]	51.13	(7.50)	56.20	(5.09)	0.06
Trails B minus Trails A[c]	−0.08	(7.21)	−2.00	(5.01)	0.45
Stroop Interference[c]	47.43	(7.21)	47.00	(5.85)	0.88
BNT[c]	57.79	(4.74)	58.10	(3.48)	0.86
Semantic Word Fluency[c]	55.38	(11.98)	57.90	(8.66)	0.55

Table depicts the mean (standard deviation) for the demographic information and neuropsychological test data, with *p*-values derived from independent sample *t* test (except where indicated).
[a]Chi-square.
[b]Statistically significant.
[c]Data from 10 HC.
BNT = Boston Naming Test, adjusted T score; BVMT-R = Brief Visuospatial Memory Test-Revised; CVLT LD Free = California Verbal Learning Test, Long Delay Free Recall (adjusted T score); CVLT SD Free = California Verbal Learning Test, Short Delay Free Recall (adjusted T score); F = female; FAS = controlled oral word fluency to the letters F-A-S, adjusted T score; HC = healthy controls; HVOT = Hooper Visual Organization Test, adjusted T score; JLO = Judgment of Line Orientation, adjusted score; LEDD = L-dopa equivalent daily dose (mg/day); M = male; MDS-UPDRS = Movement Disorders Society-United Parkinson's Disease Rating Scale motor score; MMSE = Mini-Mental State Examination; MoCA = Montreal Cognitive Assessment; PD = Parkinson disease; SDMT Oral = Symbol Digit Modalities Test, oral adjusted T score; Semantic Word Fluency = Word Fluency (animals) adjusted T score; Stroop Interference = Golden version of Stroop test, Interference score, adjusted T score; Trails A = Trail Making Test A, adjusted T score; Trails B = Trail Making Test B, adjusted T score; WAIS-IV Digit total = Wechsler Adult Intelligence Scale, digit combined total, scaled score.

(PD_ON). Sessions were counterbalanced and conducted at least 2 weeks apart. The HC participants completed 1 fMRI session. The Stanford University Institutional Review Board approved all study protocols. All study participants provided written consent.

Brain Imaging

EXPERIMENTAL PROCEDURES. Participants performed a modified Sternberg working memory task[18] during the fMRI experiment. Each trial consisted of either a high-load or a low-load

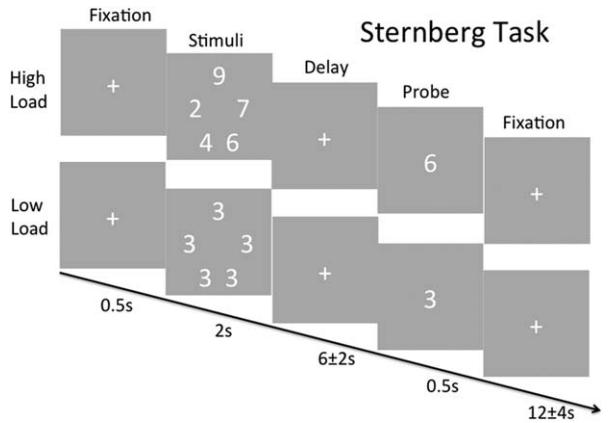

FIGURE 1: Schematic of the high-load and low-load Sternberg working memory paradigm. Following a 0.5-second fixation, participants were presented 5 numbers (0–9) simultaneously during a 2-second encoding phase. Encoding was followed by a jittered maintenance phase (6 ± 2 seconds) during which a fixation marker was displayed. Then a probe (ie, a single number) was displayed for 0.5 seconds, prompting participants to use the button box in their right hand to indicate whether the probe matched any number presented during the encoding phase. In the high-load condition the participants were presented with 5 distinct numbers; in the low-load condition the 5 numbers were identical.

working memory condition (Fig 1). Task accuracy and reaction time (RT) were recorded for each trial. Each scan included 4 task runs, which each consisted of 7 high-load and 7 low-load working memory trials randomly intermixed. Each run began with a 10-second rest interval to allow the fMRI signals to equilibrate. The stimulus presentations were implemented using E-Prime software (v2.0; Psychology Software Tools, Pittsburgh, PA; 2002) and projected at the center of the screen using a magnet-compatible projection system. Prior to each fMRI session, participants were trained with instructions and a practice session of the task.

FUNCTIONAL MRI ACQUISITION. Images were acquired on a Discovery MR750 3.0T scanner (General Electric, Milwaukee, WI) using a custom-built head coil at the Stanford University Lucas Center. Head movement was minimized during the scan by placing weighted bags over the limbs to dampen the presence of tremor and by securing the head using customized padding. A total of 29 axial slices (4.0mm thickness, 0.5mm skip), parallel to the anterior commissure–posterior commissure line and covering the whole brain, were imaged using a T2*-weighted gradient-echo spiral in–out pulse sequence[34] with the following parameters: repetition time (TR) = 2 seconds, echo time (TE) = 30 milliseconds, flip angle = 80°. The field of view was 20cm, and the matrix size was 64 × 64, providing an in-plane spatial resolution of 3.125mm. To reduce blurring and signal loss from field inhomogeneity, an automated high-order shimming method based on spiral acquisitions was used before acquiring fMRI scans.[35]

STRUCTURAL MRI ACQUISITION. For each subject, a high-resolution T1-weighted spoiled gradient recalled acquisition in steady state inversion recovery 3-dimensional (3D) MRI sequence was acquired to facilitate anatomical localization in functional scans. The following parameters were used: inversion time = 300 milliseconds; TR = 8.4 milliseconds; TE = 1.8 milliseconds; flip angle = 15°; 22cm field of view; 132 slices in coronal plane; 256 × 192 matrix; number of excitations = 2; acquired resolution = 1.5 × 0.9 × 1.1mm.

FMRI PREPROCESSING. fMRI data were analyzed using SPM8 (www.fil.ion.ucl.ac.uk/spm/). The first 5 volumes were discarded to allow for T1 equilibration. A linear shim correction was applied separately for each slice during reconstruction.[36] Images were first realigned to the first scan to correct for motion and slice acquisition timing. Translational movement (x, y, z) was calculated in millimeters based on the SPM8 parameters for motion correction of the functional images in each subject. To correct for deviant volumes resulting from spikes in movement, we used despiking procedures similar to those implemented in the Analysis of Functional NeuroImages (AFNI) toolkit maintained by the National Institute of Mental Health (Bethesda, MD). Volumes with movement exceeding 0.5 voxels (1.562mm) or spikes in global signal exceeding 5% were interpolated using the 2 adjacent volumes. In all groups, the majority of repaired volumes occurred in isolation. Three PD participants were excluded due to head movement parameters exceeding 2mm. In the remaining scans, no participant had more than a maximum scan-to-scan movement of 2mm or >2% of volumes corrected. Crucially, movement parameters did not differ between the groups in any direction of translation or rotation (Table 2). After the interpolation procedure, images were spatially transformed for registration to standard Montreal Neurological Institute (MNI) space, resampled to 2mm isotropic voxels, and smoothed with a 6mm full-width at half maximum Gaussian kernel. Coregistration quality was checked manually during the registration procedure. In addition, the Dice Similarity Coefficients between the mean functional image and the coregistered skull stripped structural image, and between fully preprocessed functional images and the MNI 152 template, were calculated. The coefficients reflect good registration quality with small variations across all subjects (Table 3).

INDIVIDUAL SUBJECT AND GROUP ANALYSIS. Task-related brain activation was identified using the general linear model implemented in SPM8. In the individual subject analyses, interpolated volumes flagged at the preprocessing stage were deweighted. The primary goal of this analysis was to examine group differences in activation related to working memory load. Brain activation related to the 2 task conditions (high-load and low-load) were first modeled at the individual subject level using boxcar functions corresponding to the block length (onset of the encoding phase to 1,000 milliseconds after the onset of the probe) and convolved with a canonical hemodynamic response function and a temporal dispersion derivative to account for voxelwise latency differences in hemodynamic response. Low-frequency noise was removed with a high-pass filter (0.5 cycle/min) applied to the fMRI time series at each

TABLE 2. Translational and Rotational Movement Parameters for HC, PD_OFF, and PD_ON Groups

	HC		PD_OFF		PD_ON		*p*, 2-Sample *t* Test	*p*, Paired-Sample *t* Test
	Average	SD	Average	SD	Average	SD		
Maximum displacement	0.92	0.58	1.03	0.62	1.12	0.79	0.53	0.64
x	0.24	0.21	0.24	0.15	0.30	0.23	1.00	0.27
y	0.20	0.10	0.30	0.29	0.28	0.22	0.16	0.79
z	0.70	0.51	0.80	0.45	0.83	0.47	0.46	0.81
RMS translational	0.45	0.31	0.53	0.30	0.55	0.32	0.38	0.84
Pitch	0.55	0.28	0.65	0.47	0.77	0.68	0.42	0.45
Roll	0.33	0.28	0.31	0.17	0.40	0.25	0.75	0.12
Yaw	0.39	0.39	0.34	0.21	0.49	0.41	0.61	0.11
RMS rotational	0.46	0.30	0.48	0.30	0.60	0.46	0.79	0.27
Maximum scan-to-scan displacement	0.46	0.31	0.52	0.40	0.63	0.57	0.57	0.39
Mean scan-to-scan displacement	0.11	0.06	0.12	0.07	0.14	0.07	0.84	0.22
Volumes repaired, %	0.68	0.00	0.71	0.11	0.74	0.25	0.19	0.54

Two-sample *t* test between HC and PD_OFF and paired-sample *t* test between PD_OFF and PD_ON are shown. Movement parameters did not differ between the groups (all $p > 0.05$).
HC = healthy controls; PD_OFF = Parkinson disease, off medication; PD_ON = Parkinson disease, on medication; RMS = root mean square; SD = standard deviation.

voxel. Voxelwise *t* statistic maps contrasting high-load and low-load were generated for each participant.

For group analysis, contrast images corresponding to the high-load and low-load tasks were analyzed using a random effects analysis. Group-level analyses were first conducted using a 1-way *t* test on pooled data from HC and PD_OFF (n = 47) to identify areas of significant load-dependent activation (high-load minus low-load). Next, 2 between-group analyses were conducted: (1) 2-sample *t* tests were used to compare load-dependent activation between HC and PD_OFF, and (2) paired-sample *t* tests were used to compare load-dependent activation between PD_OFF and PD_ON. For all analyses, significant clusters of activation were identified at the whole-brain level using a height threshold of $p < 0.001$, with familywise error (FWE) correction for multiple spatial comparisons at $p < 0.01$, determined using Monte Carlo simulations implemented in MATLAB (MathWorks, Natick, MA) using methods similar to AFNI's AlphaSim program. Specifically, 10,000 iterations of random 3D images with the same resolution and dimensions as the fMRI data were generated. The resulting images were masked for the whole brain and then smoothed with the same 6mm full-width half-maximum Gaussian kernel used to smooth the fMRI data. The maximum cluster size was computed for each iteration, and the probability distribution was estimated across the 10,000 iterations. The cluster threshold corresponding to an FWE significance level of height $p < 0.001$ and cluster extent $p < 0.01$ was determined to be 42 voxels.

TABLE 3. DSCs of Coreg and Norm for HC, PD_OFF, and PD_ON Groups

	HC		PD_OFF		PD_ON		All	
	Coreg	Norm	Coreg	Norm	Coreg	Norm	Coreg	Norm
Mean DSC (SD)	0.83 (0.09)	0.94 (0.01)	0.88 (0.05)	0.92 (0.05)	0.86 (0.06)	0.92 (0.05)	0.86 (0.07)	0.92 (0.05)
Coefficient of variation	10.9%	1.4%	6.1%	6.0%	6.6%	5.8%	8.3%	4.9%

Coreg = coregistration; DSC = Dice Similarity Coefficient; HC = healthy controls; Norm = normalization; PD_OFF = Parkinson disease, off medication; PD_ON = Parkinson disease, on medication; SD = standard deviation.

BEHAVIORAL CORRELATION ANALYSIS. The above analysis focused on PD- and dopamine-related alterations in brain recruitment associated with load-dependent working memory. We conducted additional analyses to examine the functional ramifications of altered patterns of neural activity. We identified cortical and subcortical regions within the frontostriatal and salience networks that showed peak load-dependent brain activation, and we extracted spheres around the center of activation using the MarsBaR toolbox. To investigate the possible functional role of these regions, we correlated load-dependent activation with the behavioral measure of RT (collected during the task in the scanner). In the PD group, we additionally correlated activation with working memory and executive performance during neuropsychological testing on the Symbol Digit Modalities Test (SDMT), oral administration; Trail Making Test; Wechsler Adult Intelligence Scale IV, digit span subtest; phonemic and semantic verbal fluency measures (controlled oral word fluency to the letters F-A-S [FAS] and animal naming, respectively); and Stroop.

Classification and Cross-Validation

To further validate the sensitivity of the selected regions, we examined whether activation patterns in the most contrasted regions could differentiate between PD and HC participants.[37] A linear support vector machine algorithm from an open-source library, LIBSVM (Library for Support Vector Machines [SVM]; http://www.csie.ntu.edu.tw/$cjlin/libsvm/), was used for the multivariate classification analysis. First, images from each individual were masked by a binary mask with 8 spherical regions from cortical and subcortical regions that showed load-dependent brain activation within the frontostriatal and salience networks. The centers of these regions were defined by the peak voxels detected in fMRI group analysis. We trained the SVM classifier with all the masked contrast images, so that it can predict whether an image is from an HC or PD_OFF participant. Second, the performance of classification was evaluated using a leave-1-subject-out cross-validation procedure. In this procedure, the image from 1 subject was selected as a test set. The rest of the data were used to train a classifier, which was then applied to predict the group of the test set. This procedure was repeated 46 times, with each subject's data tested once. The average prediction accuracy across all test sets was termed as the cross-validation accuracy. To justify the statistical significance of this accuracy, ×5,000 random permutation was used, where data labels of HC and PD_OFF were randomly switched in each permutation. Finally, the contribution of each region was also studied individually. Higher cross-validation accuracy indicates stronger differentiating power of the individual region. We repeated for PD_ON versus HC.

Results

Behavioral Results

PD and HC participant groups were matched for age, education, and MMSE score; however, the PD group had more male participants than the HC group (see Table 1). A mixed measures analysis of variance

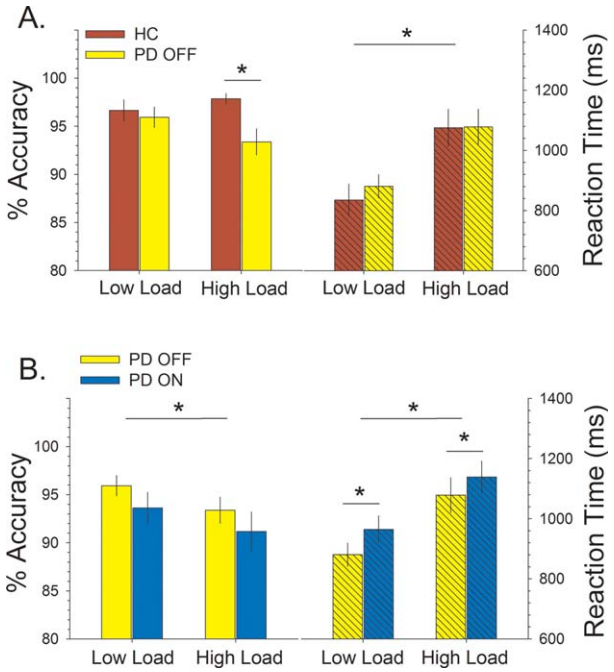

FIGURE 2: Behavioral performance in healthy controls (HC) and Parkinson disease (PD) patients. (A) HC were more accurate than PD patients off dopaminergic medications in the high-load but not the low-load condition. Reaction time was not different between groups in either condition. (B) PD patients had similar accuracy while they were off and on dopaminergic medications; however, reaction time was slower in the on state for both high-load and low-load. *$p < 0.05$. [Color figure can be viewed in the online issue, which is available at www.annalsofneurology.org.]

(ANOVA) with between-subject factor Group (HC, PD_OFF) and within-subject factor Load (high-load, low-load) was used to analyze the differences in RT (Fig 2A). The main effect of Load was significant ($F_{1,45}$ = 92.935, $p < 0.001$), with slower RT on high-load compared to low-load in both groups. The main effect of Group was not significant ($F_{1,45}$ = 0.009, p = 0.925), and the interaction between Group and Load was not significant ($F_{1,45}$ = 2.478, p = 0.123). A similar analysis was used to determine the differences in accuracy as the independent variable. The main effect of Load was not significant ($F_{1,45}$ = 0.5138, p = 0.48), but the main effect of Group was significant ($F_{1,45}$ = 6.183, p = 0.015). The interaction between Group and Load was significant ($F_{1,45}$ = 4.945, p = 0.031); post hoc t tests revealed that this was driven by PD_OFF being significantly less accurate than HC on the high-load but not the low-load condition ($p < 0.05$).

A repeated measures ANOVA with within-subject factor Group (PD_OFF, PD_ON) and within-subject factor Load (high-load, low-load) was used to analyze the differences in RT (see Fig 2B). The main effect of Group was significant ($F_{1,23}$ = 11.063, p = 0.003), with slower

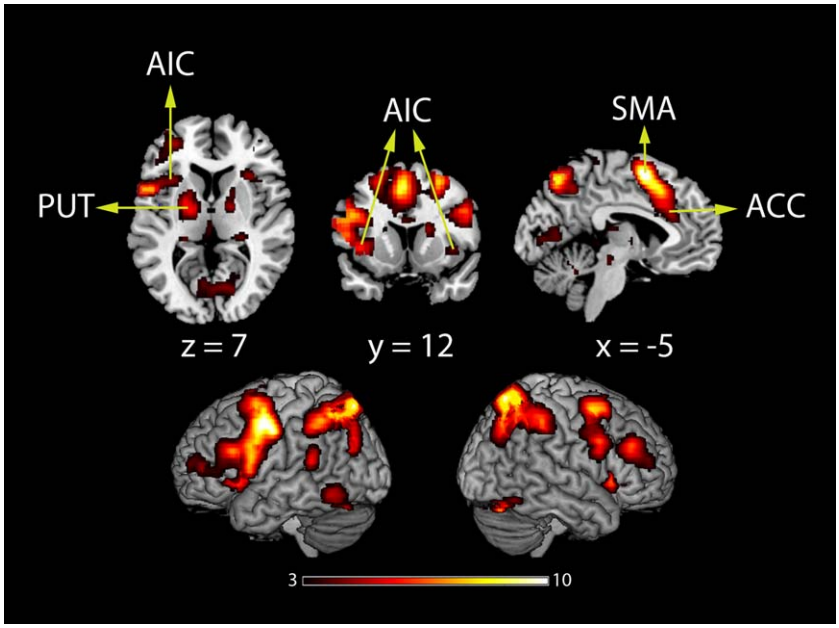

FIGURE 3: Load-dependent working memory effects on combined data from healthy controls and Parkinson disease patients off dopaminergic medications. Surface rendering and slices show significant load-dependent activation (high-load minus low-load) in hot colors ($p < 0.001$, familywise error corrected). ACC = anterior cingulate cortex; AIC = anterior–dorsal insula cortex; PUT = putamen; SMA = supplementary motor area.

RT in the PD_ON compared to PD_OFF group, and the main effect of Load was significant ($F_{1,23} = 35.060$, $p < 0.001$), with slower RT on high-load compared to low-load. The interaction between Group and Load was not significant ($F_{1,23} = 0.888$, $p = 0.356$). A similar analysis was used to determine the differences in accuracy as the independent variable. The main effect of Group was not significant ($F_{1,23} = 1.716$, $p = 0.203$), but the main effect of Load was significant ($F_{1,23} = 5.076$, $p = 0.034$), with better accuracy in the low-load compared to the high-load condition. The interaction between Group and Load was not significant ($F_{1,23} = 0.001$, $p = 0.977$).

Brain Activation during Working Memory Task

We examined the overall pattern of load-dependent (high-load greater than low-load) brain activation by pooling data from the PD_OFF and HC participants during the working memory task. We found significant load-dependent activation of the bilateral putamen, bilateral anterior–dorsal insula, bilateral supplementary motor area (SMA), pre-SMA, dorsal anterior cingulate cortex, bilateral superior parietal lobule, bilateral PFC, and bilateral cerebellum (Fig 3). See Table 4 for all peak regions of activation.

Differences in Brain Activation between PD Patients and HC

We next identified the pattern of brain activation associated with cognitively unimpaired PD by comparing load-dependent activation between the PD_OFF and HC groups. PD patients off dopaminergic medications showed greater load-dependent activation than the HC group in both subcortical and cortical brain regions, including the bilateral putamen, bilateral posterior insula, right SMA, left inferior parietal lobule, and left thalamus (Figs 4 and 5). There was no increased activation in the HC group compared to the PD_OFF group at either $p < 0.001$ or $p < 0.01$, FWE-corrected thresholds.

Differences in Brain Activation Associated with Dopaminergic Medications

We then investigated the basis of poorer (slower) RT in PD patients on dopaminergic medications by comparing fMRI brain activity in the PD patients while off versus on medications. PD_OFF showed greater load-dependent activation in the bilateral putamen, bilateral caudate, left dorsolateral PFC, left hippocampus, and left SMA than PD_ON (see Fig 5). There was no increased activation in the PD_ON than PD_OFF group at either $p < 0.001$ or $p < 0.01$, FWE-corrected thresholds.

Brain–Behavior Associations in PD

We further investigated brain–behavior associations with PD working memory by evaluating whether individual differences in activation were associated with cognitive performance in PD patients. To examine this, we created regions of interest around activation peaks identified in the contrasts: high-load minus low-load in PD_OFF relative to HC and high-load minus low-load in PD_OFF

TABLE 4. Coordinates of Peak Load-Dependent Activations in MNI Space

Region	k	Peak MNI Coordinates		
		x	y	z
PD_OFF and HC				
L supplementary motor area	16,404	−4	6	60
L precentral gyrus		−52	−2	46
L insula cortex		−32	20	0
L sup parietal lobule	7,583	−30	−56	48
R sup parietal lobule		32	−52	42
R midfrontal gyrus	1,003	42	36	28
R frontal pole		44	50	14
R intracalcarine cortex	814	14	−74	8
L lingual gyrus, cuneus		−8	−70	4
L cerebellum	754	−30	−70	−26
R cerebellum	672	36	−70	−26
R insula cortex	575	38	18	−2
L supramarginal gyrus	286	−56	−42	18
PD_OFF > HC				
R putamen	4,355	28	−10	2
R supplementary motor area		2	−18	52
R insula		42	−6	10
L putamen	1,657	−30	−10	4
L insula		−38	−4	14
L inferior parietal lobule	69	−44	−54	38
L thalamus	48	−6	−10	0
R sup frontal gyrus	47	22	−8	70
R midfrontal gyrus	42	40	−2	58
PD_OFF > PD_ON				
L putamen	404	−22	−4	12
R putamen	186	28	−16	2
L midfrontal gyrus	148	−38	50	12
L inferior frontal gyrus		−24	52	−4
L midfrontal gyrus	98	−44	24	36
R caudate	72	22	8	18
L hippocampus	67	−22	−18	−12
L precentral gyrus	53	−30	−6	66
L midfrontal gyrus		−36	−2	60

Subpeaks of interest are also included. The cluster threshold corresponds to a familywise error significance level of height $p < 0.001$ and cluster extent $p < 0.01$.
HC = healthy controls; L = left; MNI = Montreal Neurological Institute; PD_OFF = Parkinson disease, off medication; PD_ON = Parkinson disease, on medication; R = right; sup = superior.

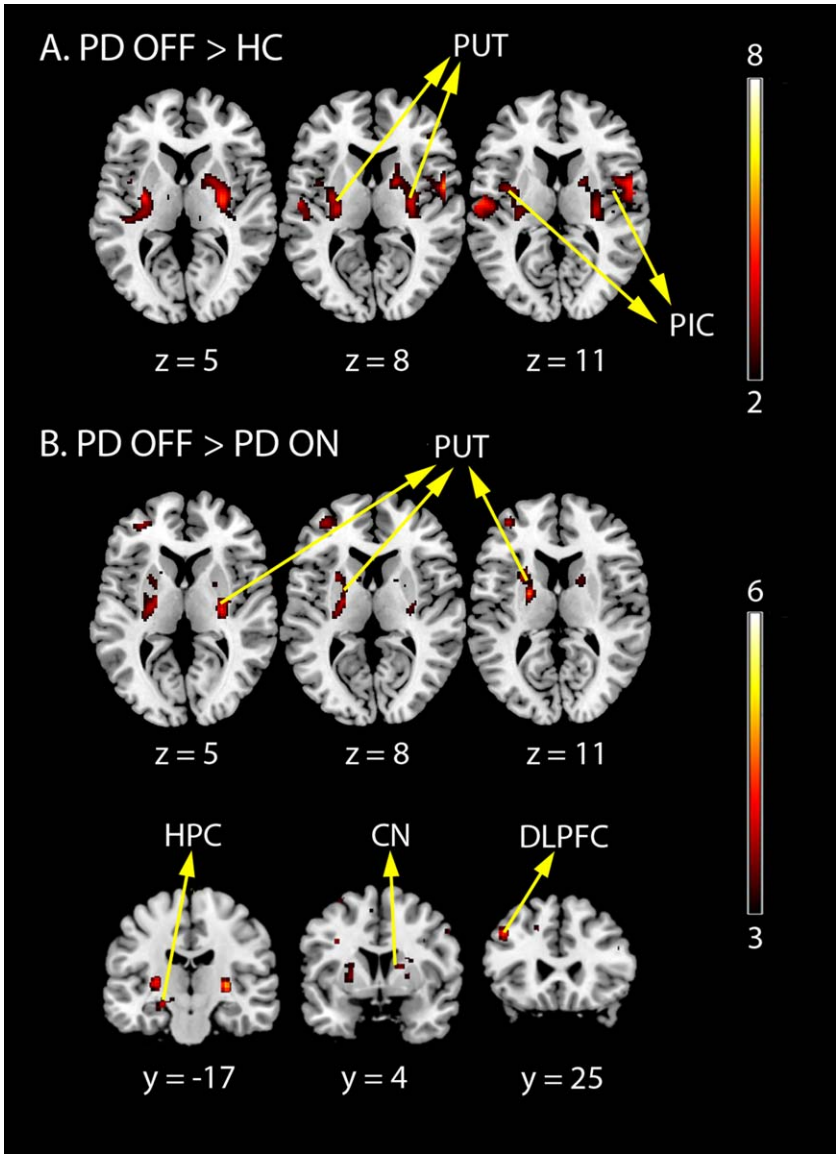

FIGURE 4: Group differences in working memory load-dependent activation. (A) Brain areas that showed greater activation in Parkinson disease (PD) patients off dopaminergic medications compared to healthy controls (HC). No brain areas showed reduced activation in PD patients off dopaminergic medications compared to HC. (B) Brain areas that showed greater activation in PD patients off compared to on dopaminergic medications. No brain areas showed reduced activation in PD patients off compared to on dopaminergic medications. Slices show significant load-dependent activation (high-load minus low-load) in hot colors ($p < 0.001$, corrected). CN = caudate nucleus; DLPFC = dorsolateral prefrontal cortex; HPC = hippocampus; PIC = posterior insula cortex; PUT = putamen.

relative to PD_ON (bilateral posterior putamen, bilateral posterior insula, left dorsolateral PFC, and left hippocampus). Finally, to examine the role of anterior–dorsal insula activation on working memory RT, we created regions around right and left insula activation peaks identified in the contrast of high-load minus low-load in the combined subject analysis, for a total of 8 regions in the analysis.

See Table 5 for RT correlations with all 8 activation peaks. In the PD_ON group, activation in the bilateral posterior putamen and the right posterior insula negatively correlated with high-load RT (ie, longer RT with less activation; Fig 6). In addition, less PD_ON activation in the bilateral posterior putamen correlated with slower responses on the SDMT (right putamen: $r = 0.398$, $p = 0.05$; left putamen, $r = 0.478$, $p = 0.02$), suggesting that dopamine suppresses recruitment of putamen activity and this suppression results in slower cognitive speed. High-load RT in HC correlated with activation in the left anterior–dorsal insula, but not the right anterior–dorsal insula. There was no relationship between anterior–dorsal insula activity and RT in either the PD_OFF or the PD_ON group. However, in PD_OFF increased left anterior–dorsal insula activity was

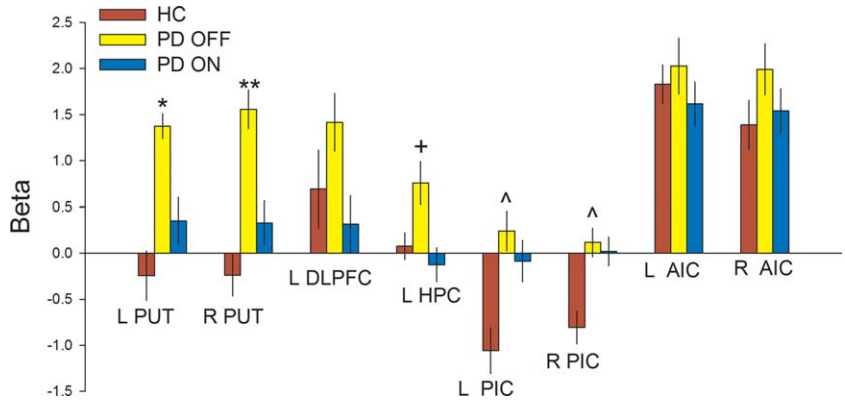

FIGURE 5: Working memory load-dependent activation levels (beta estimates) in Parkinson disease (PD) off medication (PD_OFF), PD on medication (PD_ON), and healthy controls (HC). Error bars represent standard error of the mean, with *p*-values derived from 1-way analysis of variance, Bonferroni corrected. *$p < 0.05$, HC compared with PD_OFF, and PD_OFF compared with PD_ON. **$p < 0.001$, HC compared with PD_OFF, and PD_OFF compared with PD_ON. +$p < 0.05$ PD_OFF compared with PD_ON. $\wedge p < 0.05$ HC compared with PD_OFF, and HC compared with PD_ON. AIC = anterior–dorsal insula; DLPFC = dorsolateral prefrontal cortex; HPC = hippocampus; L = left; PIC = posterior insula; PUT = putamen; R = right. [Color figure can be viewed in the online issue, which is available at www.annalsofneurology.org.]

associated with worse performance on the FAS word fluency test ($r = -0.48$, $p = 0.02$). Finally, there was no relationship between regional activation and measures of PD disease severity (MDS-UPDRS-III or disease duration).

Activation-Based Classification between PD and HC

Finally, we validated the sensitivity of load-dependent activation patterns by classification using an SVM machine learning algorithm. The 8 regions with the largest contrasts, including bilateral putamen, left dorsolateral PFC, left hippocampus, bilateral posterior insula, and bilateral anterior–dorsal insula, were combined into a mask to extract the image data for algorithm training to differentiate between PD_OFF and HC participants. A significant 78.26% cross-validation accuracy ($p = 0.019$) was achieved by the trained classifier (Fig 7). When determining the contribution of each region to the classification, training data from 3 regions achieved significant classifier accuracy: 76.1% accuracy from the right putamen ($p = 0.006$), 73.9% from the left putamen ($p = 0.04$), and 71.74% from the left anterior–dorsal insula ($p = 0.03$). This result provides robust evidence for aberrant functional organization of the putamen and insula in PD patients when off dopaminergic medications. The same mask applied to differentiate between PD_ON and HC participants achieved 68.75% accuracy, but was not significant ($p = 0.358$).

Discussion

We demonstrate that intact working memory in cognitively unimpaired PD is associated with increased activation within the bilateral putamen and bilateral posterior insula. Critically, dopaminergic medications reduced putamen hyperactivation, and individual differences in loss of compensatory hyperactivation were associated with slower cognitive speed. Our findings establish a novel framework for understanding cognitive function in PD patients, in both the dopamine depleted (off) and replenished (on) states, and identify a compensatory frontostriatal network in cognitively unimpaired PD.

Compensatory Putamen Activity in PD Working Memory

Substantia nigra dopamine neuron loss with resulting reduction in dopaminergic input to the striatum is the neurobiological basis for the cardinal motor symptoms in PD. More recently, this loss of nigrostriatal dopaminergic input has been suggested as a mechanism for PD cognitive symptoms, including executive and working memory dysfunction.[8] This is in line with studies that identify the striatum as a central node for working memory in healthy individuals, and numerous fMRI studies have demonstrated both caudate and putamen activation during various working memory tasks.[15,16,18–20] In cognitively impaired PD, striatal underrecruitment has been suggested as an etiology for executive dysfunction.[22–26] However, there have been conflicting findings regarding activation changes in cognitively unimpaired patients, in part due to variable definitions of PD cognitive impairment prior to the current operationalized definition.[32] Some studies report that cognitively unimpaired PD subjects show similar striatal activation to a healthy cohort,[23,24] whereas others suggest increases in task-related striatal activation.[21,22,28] Our findings demonstrate load-dependent putamen hyperactivation during working memory in cognitively unimpaired PD compared to well-matched healthy adults. Crucially, multivariate classification analysis using cross-

TABLE 5. Correlation between High-Load Reaction Time and Load-Dependent Percentage Signal Change in Cortical and Subcortical Regions of Interest That Show Load-Dependent Alterations in Activation

		Regions, Radius							
		L Post Putamen, 2mm	R Post Putamen, 2mm	L DLPFC, 4mm	L HPC, 4mm	L Post Insula, 4mm	R Post Insula, 4mm	L Ant Insula, 4mm	R Ant Insula, 4mm
HC	*r*	−0.210	0.139	0.124	−0.146	−0.119	−0.040	0.433[a]	0.191
	p	0.925	0.527	0.572	0.506	0.588	0.856	0.039[a]	0.383
PD_OFF	*r*	−0.105	−0.266	0.332	0.340	0.260	0.339	0.159	0.123
	p	0.625	0.208	0.113	0.104	0.219	0.106	0.459	0.568
PD_ON	*r*	−0.553[a]	−0.564[a]	0.108	−0.084	−0.049	−0.412[a]	0.248	0.394
	p	0.005[a]	0.004[a]	0.614	0.696	0.820	0.045[a]	0.244	0.056

[a]Statistically significant.
Ant = anterior; DLPFC = dorsolateral prefrontal cortex; HC = healthy controls; HPC = hippocampus; L = left; PD_OFF = Parkinson disease, off medication; PD_ON = Parkinson disease, on medication; Post = posterior; R = right.

validation procedures revealed that putamen activity alone provided >75% accuracy in distinguishing between PD_OFF and HC, providing additional evidence for the putamen as a key locus of differences between PD and HC. Although we cannot completely rule out the influence of noncognitive aspects of PD pathophysiology on these finding, it is important to note that increased putamen activation did not correlate with any measures of PD motor dysfunction (MDS-UPDRS) or general disease severity (duration). Thus, our findings identify a robust striatal mechanism in cognitively unimpaired PD that compensates for loss of nigrostriatal dopamine. We propose that the observed putamen hyperactivation is compensatory and hypothesize that in cognitively impaired patients losing this compensatory activation contributes to poor performance. Increased putamen activity during a cognitively demanding task could be an objective imaging biomarker for interventions aimed at improving cognitive performance in PD. Further studies are needed to test these hypotheses, ideally in longitudinal patients as they develop cognitive impairment.

It is interesting that the putamen was the peak activation nuclei in the basal ganglia during our working memory task, with less activation in the caudate. Animal studies initially suggested that structural subregions of the basal ganglia connect to specific cortical regions and associated cognitive functions, with the caudate and nucleus accumbens primarily involved with goal-directed learning. Human studies with fMRI, however, have revealed a more complex relationship between basal ganglia subregions and cognitive functioning. A recent meta-analysis of working memory fMRI tasks showed activation peaks in caudate, putamen, and pallidal nuclei for the main effect of task,[38] and multiple studies have identified strong putamen activation during working memory, particularly during the encoding phase,[18] with more caudate involvement during memory manipulation during the maintenance phase.[26] One study found that the putamen is engaged in preparing to filter out irrelevant information during memory encoding, and that putamen and pallidal activation correlated with working memory capacity.[39] Our study adds to this growing literature on the role of the putamen in successful working memory in PD.

Dopaminergic Modulation of Compensatory Putamen Activity

The contribution of dopamine to working memory has been extensively explored in biological,[40] computational,[41] and psychological[15] models. In clinical studies, the gold standard for investigating the contribution of dopamine to PD motor symptoms is the off–on medication testing paradigm; however, few cognitive fMRI studies have employed this rigorous approach.[42] Our structured off–on design allowed us to address an important question: how does dopaminergic medication affect brain responses in cognitively unimpaired PD and alter the observed compensatory hyperactivation? We found that dopaminergic replacement resulted in slower cognitive reaction time during the Sternberg task, and that individual differences in such slowing correlated with loss of compensatory hyperactivation in the putamen in PD. Our findings also suggest a speed–accuracy tradeoff, such that patients sacrifice speed to maintain accuracy with dopamine replacement. We argue that RT during our task was a measure of cognitive speed and not motor speed, as the PD patients on medications had faster

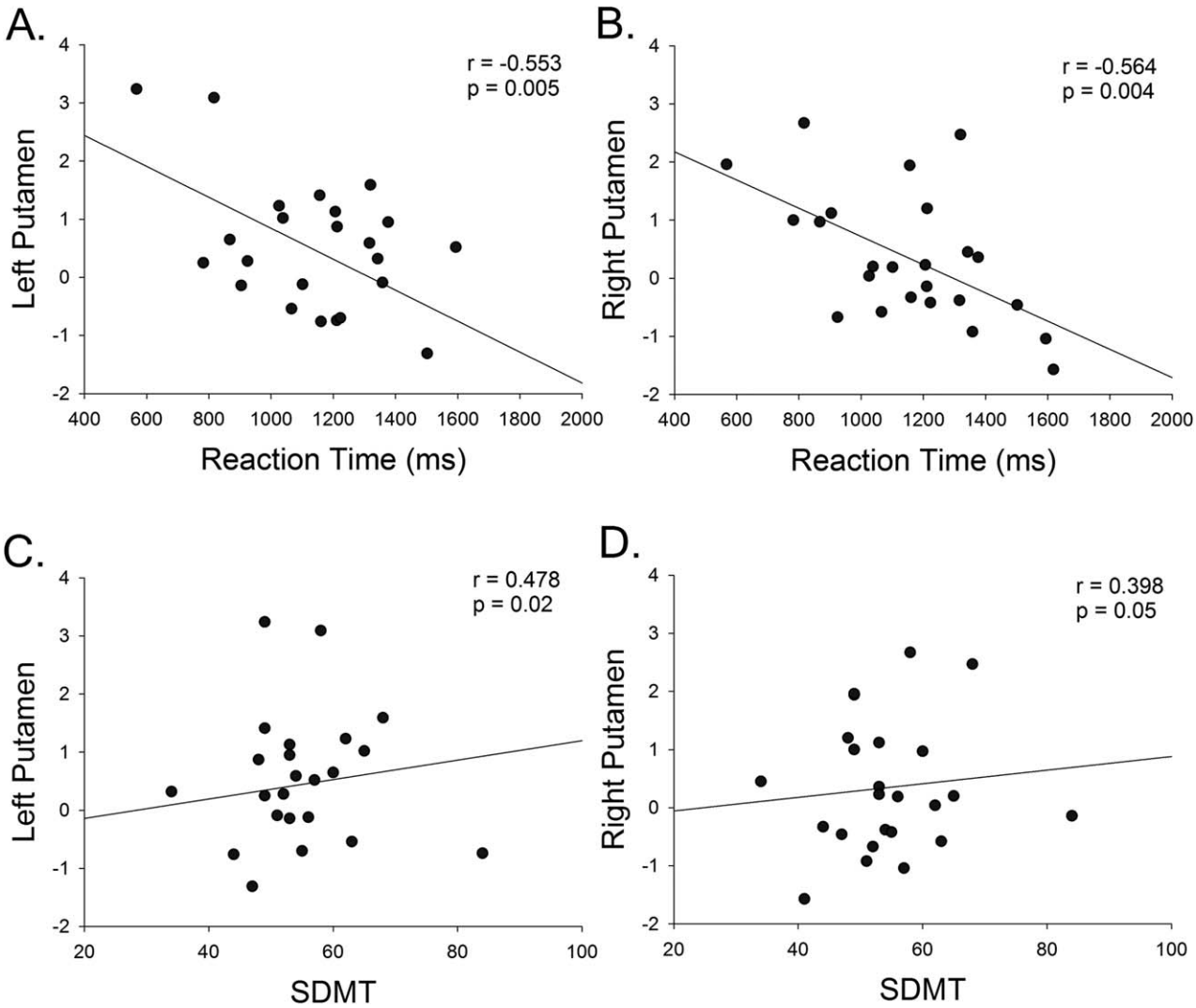

FIGURE 6: Brain–behavior relations. Bilateral putamen regions were identified from between-group peak activation differences shown in Figure 4B. Load-dependent activation levels (beta estimates) were extracted from these regions to determine the relationship between load-dependent activation and clinical cognitive measures of performance. The y-axis shows beta estimates in the Parkinson disease (PD) patients on dopaminergic medication, where lower compensatory putamen activation was associated with (A, B) slower high-load reaction time during the working memory functional magnetic resonance imaging task, and (C, D) slower performance on the Symbol Digit Modalities Test (SDMT). In PD patients on dopamine medications, there was a similar relationship between lower right posterior insula activation and slower high-load reaction time ($r = -0.412$, $p = 0.045$, not shown)

motor speed on the MDS-UPDRS-III (off = 33.4 ± 11.9, on = 18.2 ± 11.0, $p < 0.0001$), but slower RT during the task. Prior behavioral studies showing L-dopa–associated cognitive slowing during a Sternberg working memory task support our findings.[43] We also found a similar relationship between dopaminergic-associated loss of compensatory putamen hyperactivation and slower cognitive performance on the SDMT, a commonly used measure of working memory and executive functioning. Of note, the SDMT is the recommended test for identifying slowed information-processing speed in patients with multiple sclerosis.[44] Critically, we administered the oral version of the SDMT to minimize potential bias from bradykinesia. However, it is important to note that cognitive slowing in the PD patients on dopamine might not be specific to working memory and could reflect other cognitive aspects of the task, such as attention or distractibility. Further studies are needed to further understand the influences of dopamine on these complex features of executive function in PD.

This study adds valuable information to the growing literature on the cognitive and psychiatric effects of dopamine replacement therapy in PD patients.[45] In many patients, it can be difficult to find the appropriate balance between giving enough dopamine to adequately treat motor symptoms while also minimizing nonmotor side effects. The 2014 PQRS Measures Group for Parkinson's disease recommended all PD patients have an

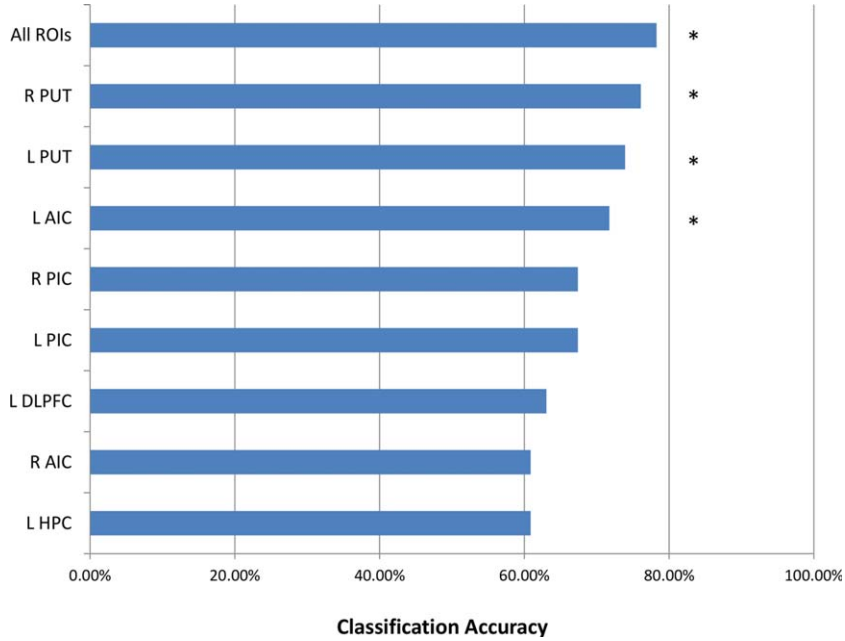

FIGURE 7: Classification accuracy for discriminating Parkinson disease patients from healthy controls. Results are based on data from 8 unbiased regions of interest (ROIs) that showed working memory load-dependent activation in a combined group of patients and controls. Separate analyses were performed for all 8 ROIs taken together, as well as each ROI individually. *$p < 0.05$ in random permutation test. AIC = anterior–dorsal insula; DLPFC = left dorsolateral prefrontal cortex; HPC = hippocampus; L = left; PIC = posterior insula; PUT = putamen; R = right. [Color figure can be viewed in the online issue, which is available at www.annalsofneurology.org.]

annual clinical assessment of cognitive function, but does not mention specific tests to administer. Our data suggest the SDMT could be a good test for physician use to regularly monitor the dopaminergic effects on PD working memory, particularly in otherwise cognitively unimpaired patients.

Cortical Activity in PD during Working Memory

In addition to the striatum, working memory is mediated by distributed cortical brain regions, and specifically regions with a large number of striatocortical dopaminergic projections such as the PFC. In 1979, Brozoski et al first demonstrated that dopamine depletion in the PFC in monkeys leads to severe deficits during a delayed response task.[40] More recent studies suggest that the relationship between PFC dopamine and working memory function is highly complex and best represented by an inverted U-shaped curve where both too little and too much dopamine impairs performance.[15,27,46] Importantly, a single U-shaped curve is insufficient to describe this relationship, and variables such as baseline cognitive performance and task difficulty influence the effect of dopamine on working memory function. A few fMRI studies have examined this relationship in PD patients specifically. Lewis et al found altered PFC activity in cognitively impaired compared to cognitively unimpaired PD patients on dopamine and concluded that impaired working memory accuracy is associated with reduced PFC activation in medicated patients.[22] Using our structured off–on design, we found similar loss of dorsolateral PFC activation in cognitively unimpaired PD patients on compared to off dopamine, which supports the inverted U-curve hypothesis and suggests that dopamine impairs PFC neuronal activity in patients with otherwise normal cognitive performance off medications. We did not, however, find a relationship between PFC activation and task accuracy, likely due to the simplicity of our task. Our task design was not optimized to investigate activation-related changes in accuracy, because all 3 groups had >92% accuracy, with a substantial ceiling effect. It is possible that dopamine-mediated loss of PFC activation would predict performance in cognitively unimpaired patients during a more challenging working memory task.[47–49]

The Insula in PD Working Memory

Although the PFC has been the cortical focus for most fMRI working memory studies, recent evidence suggests that the insula is also a critical cortical node in the modulation of cognition and working memory.[30] A recent fMRI meta-analysis showed that the anterior–dorsal, anterior–ventral, and posterior subregions of the insula are tightly linked to distinct cognitive, affective, and somatosensory functions, respectively.[50] Our data are the first to provide evidence of this functional organization in PD. The anterior–dorsal insula plays a critical role in

the detection of novel salient stimuli and facilitates bottom-up access to attentional and working memory resources.[30] In our study, all 3 groups showed load-dependent increases in anterior–dorsal insula activation, with similar activation between the PD and control participants (see Fig 5). We surprisingly found that activation of the anterior–dorsal insula correlated with PD phonemic fluency during neuropsychological testing, but not RT during the task. In PD patients, poor phonemic fluency is common and can be an early sign of general executive dysfunction. We did not have neuropsychological testing on all of our control subjects to further explore whether the relationship between insula activation and phonemic fluency was PD specific, and further studies exploring insula activation in PD patients with executive dysfunction would help clarify the role of the insula during the Sternberg task.

By contrast, we found working memory load-dependent hyperactivation of the posterior insular cortex in PD_OFF relative to controls. Similar to the striatum, loss of compensatory hyperactivation predicted slower RT in PD patients on dopaminergic medications. The posterior insula is thought to modulate planning movements and somatosensory execution of movements through projections to the posterior putamen.[50] There is an anatomic gradient between the insula and the basal ganglia, and the posterior insula specifically projects to the posterior putamen, which is the region of the putamen most affected in early PD.[51] One recent study found reduced dopamine receptor availability in the bilateral posterior insula, which was associated with poor executive task performance, suggesting that PD-associated denervation from the putamen to the posterior insula modulates cognition impairment.[29] Further studies are needed to better delineate the complex role of the posterior insula in PD cognitive processes.

Methodology and Limitations

We hypothesized that intact working memory in PD is associated with compensatory changes in brain activity, thus we recruited subjects based on cognitive performance alone rather than motor-based categorizations, such as duration or Hoehn and Yahr stage. To increase the specificity for unimpaired cognition in our cohort, we employed a stricter cutoff of 1.5 SD on neuropsychological testing,[52] and we showed that our PD patients did not differ substantially from a representative subgroup of HC. Despite these strict criteria, our PD group had slightly worse performance during the more demanding high-load working memory task. However, we only included accurate trials in the analysis; therefore, it is unlikely that these slight differences in accuracy account for our findings. One possible confound is that the PD patients were on a mixture of dopamine agonists and L-dopa, which can differently modulate working memory and executive function in PD.[28,53] In our sample, 21 of 24 PD participants were on L-dopa; therefore, our dopaminergic-associated findings most likely represent the specific effect of L-dopa on working memory. Finally, although we cannot completely discount coregistration errors in small subcortical structures, such as the putamen and neighboring white matter tracks, our quality assurance analysis showed good registration performance.

Our study has several strengths, including comprehensive cognitive testing, a large sample size, and a structured off–on testing paradigm. Furthermore, we were careful to minimize head motion during scans, and no differences in head motion were identified between groups.

Conclusion

In summary, our study provides novel evidence that PD patients maintain intact cognitive performance through compensatory hyperactivation of the putamen. Furthermore, we found that dopamine-mediated downregulation of putamen hyperactivation predicts behavior. Prospective, longitudinal studies are needed to determine whether these identified changes can predict future conversion from normal cognition to PD cognitive impairment.

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Author Contributions

Concept and design of the study: K.L.P., F.M.T., S.L., V.M.; data acquisition and analysis: K.L.P., S.Y., K.Z., W.C., D.E., F.M.T., S.L., V.M.; drafting of the manuscript and figures: K.L.P., K.Z., W.C., V.M.

Potential Conflicts of Interest

Nothing to report.

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