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Dopamine-related dissociation of cortical and subcortical brain activations in cognitively unimpaired Parkinson's disease patients OFF and ON medications

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Abstract

Background: Despite dopaminergic depletion that is severe enough to cause the motor symptoms of Parkinson's disease (PD), m any patients remain cognitively unimpaired. Little is known about brain mechanism s underlying such preserved cognitive abilities and their alteration by dopaminergic medications.

Objectives: We investigated brain activations underlying dopamine-related differences in cognitive function using a unique experimental design with PD patients off and on dopaminergic medications. We tested the dopamine overdose hypothesis, which posits that the excess of exogenous dopamine in the frontal cortical regions can impair cognition.

Methods: We used a two-choice forced response Choice Reaction Time (CRT) task to probe cognitive processes underlying response selection and execution. Functional magnetic resonance imaging data Were acquired from 16 cognitively unimpaired (Level-II) PD participants and 15 Well-matched healthy controls (HC). We compared task performance (i.e. reaction time and accuracy) and brain activation of PD participants off dopaminergic medications (PD_OFF) in comparison with HC, and PD_OFF participants with those on dopaminergic medications (PD_ON).

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Disclosure statements

None.

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neuropsychologia.2018.07.024.

Results: PD_OFF and PD_ON groups did not differ from each other, or from the HC group, in reaction time or accuracy. Compared to HC, PD_OFF activated the bilateral putamen less, and this w as compensated by higher activation of the anterior insula. No such differences Were observed in the PD_ON group, Compared to HC. Compared to both HC and PD_OFF, PD_ON participants showed dopamine-related hyperactivation in the frontal cortical regions and hypoactivation in the amygdala.

Conclusion: Our data provide further evidence that PD_OFF and PD_ON participants engage different cortical and subcortical systems to achieve similar levels of cognitive performance as HC. Crucially, our findings demonstrate dopamine-related dissociation in brain activation between cortical and subcortical regions, and provide novel support for the dopamine overdose hypothesis.

Keywords

Parkinson’s disease; Dopamine; fMRI; Choice Reaction Time

1. Introduction

Parkinson’s disease (PD) is the second most common neurodegenerative disorder in the aging population, and the prevalence of PD is estimated to grow substantially over the next few decades (Kowal et al., 2013). Lewy-body neuronal inclusions in the substantia nigra with subsequent nigrostriatal dopamine neuron losses are pathognomonic for the disease. These substantia nigra dopaminergic neurons project to the basal ganglia as part of several parallel basal ganglia-thalamocortical circuits (Alexander et al., 1986). Dopamine loss in the motor circuitry, with corticostriate inputs to the motor cortex, is responsible for the cardinal motor symptoms in PD (bradykinesia, rigidity, and rest tremor). Thus, oral dopamine replacement is the most widely used pharmacotherapy in individuals with PD and can provide substantial clinical benefit for these impaired motor symptoms.

The relationship between dopamine and PD cognitive symptoms, however, is more complex. PD-related dopamine loss in the fronto-striatal circuitry, with corticostriate inputs to the dorsolateral pre-frontal cortex, is thought to contribute to impaired cognition in PD (Boot et al., 2017). Dopamine is critical for normal cognitive functioning (Cools and D’Esposito, 2011), and past studies have shown that in primates and humans, dopamine dependent cognitive processes rely on intact functioning of this fronto-striatal circuitry (Chudasama and Robbins, 2006). One consequence of dopamine loss is deficits in executive function and cognitive control, which many PD patients experience (Cools et al., 2001a; Goldman et al., 2014; Halliday et al., 2014). Previous functional magnetic resonance imaging (fMRI) studies have found that PD patients exhibit executive cognitive deficits that localize to the prefrontal cortex (Gerrits et al., 2015; Rowe et al., 2008; Trujillo et al., 2015b), and ^{18}F-fluorodeoxyglucose positron emission tomography (PET) studies have shown metabolic reductions in the dorsolateral prefrontal cortex associated with PD cognitive impairment (Bruck et al., 2005; Huang et al., 2007). Thus, the executive dysfunction experienced by most PD patients could be attributable to the loss of dopaminergic input to the prefrontal cortex.

However, 60–85% of newly diagnosed PD patients continue to perform normally on executive cognitive tasks (Aarsland et al., 2009; Foltynie et al., 2004; Poletti et al., 2012; Yarnall et al., 2014) despite over 50% of the substantia nigra dopamine neurons lost at the time of motor diagnosis. Brain processes underlying this preserved executive function are poorly understood, but several studies have shown that PD patients can engage cognitive brain systems that compensate for this dopaminergic loss, presumably resulting in normal executive cognitive functioning (Bohnen et al., 2012; Poston et al., 2016). Whether these compensatory mechanisms are task-specific or generalized is not known. For instance, fMRI studies have demonstrated activation changes in either cortical or subcortical regions during different cognitive tasks of working memory and executive function in cognitively unimpaired PD (Lewis et al., 2003; Poston et al., 2016; Trujillo et al., 2015a). Such findings suggest that in the dopamine depleted state, there are uniquely altered cortical and subcortical recruitment patterns that are engaged during different cognitive tasks.

Finally, some PD patients experience worsening of cognitive symptoms because of oral dopamine replacement. Studies have shown slower cognitive reaction time (Dirnberger and Jahanshahi, 2013; Poston et al., 2016; Ruitenberg et al., 2016; Warden et al., 2016; Wylie et al., 2017) when PD patients are taking typical therapeutic doses of dopamine. This has been explained by the ‘dopamine overdose hypothesis’, which posits that in early stages of PD, while dopaminergic medications can improve cognitive performance on tasks associated with the depleted dorsolateral fronto-striatal circuitry (e.g., putamen), such as task-switching, such medications can interfere with cognitive performance on tasks associated with the relatively intact ventral fronto-striatal circuitry (e.g., prefrontal cortex, caudate), such as reversal learning, by overdosing such regions (Cools, 2006; Kwak et al., 2010). Therefore, especially in the early stages of PD, the effect of dopaminergic medications on cognitive performance is suggested to be task-specific and dependent on the underlying neural substrates of the task (Cools, 2006).

Here, we studied PD patients in the clinically defined ‘off’ medication state and in the optimally treated ‘on’ medication state as a model to investigate the different brain mechanisms underlying these cognitive responses to dopamine depletion and dopamine replacement. We used this off-on study design during a two-choice forced response Choice Reaction Time (CRT) fMRI task to probe executive cognitive processes underlying the selection and execution of voluntary actions. The CRT task is known to engage both the cortical and subcortical regions of the brain (Jahanshahi et al., 1992; Schluter et al., 2001). For instance, the basal ganglia play an active role in decision-making under time pressure (Forstmann et al., 2008), which is crucial for normal CRT task performance. Prior fMRI studies in non-Parkinson’s participants have shown that the basal ganglia (together with fronto-parietal regions) are the key regions involved in different versions of CRT task (Hughes et al., 2013; Keuken et al., 2014; Naismithet al., 2010). While these regions are also known to be affected by the nigrostriatal neuronal loss in PD, no prior fMRI studies have used this task to probe cortical and subcortical activation in PD.

Taken together, our experimental design and analysis allowed us, for the first time, to (1) determine whether PD patients engage cortical and subcortical regions that are typically activated during the CRT task, (2) identify brain regions that may compensate for

dopaminergic loss, and (3) determine whether activation in these brain regions is normalized or altered by dopaminergic medications. Our study contributes to improved understanding of not only the effect of dopaminergic medications on the brains of individuals with PD, but also dopamine's general role in human cognition and behavioral control processes.

2. Materials and methods

2.1. Participants

We recruited 29 PD participants and 21 healthy controls (HC) from the Stanford Movement Disorders Clinic and the surrounding community. Inclusion criteria for both PD and HC were as follows: (1) age between 45 and 90 years; (2) fluency in English; (3) no contra-indications to MRI; (4) no history of significant neurological disease (other than PD), serious psychiatric illness, substance abuse, or head trauma; (5) right-handed; and (6) normal or corrected-to-normal vision.

PD diagnosis was determined by a board-certified neurologist with specialty training in movement disorders (K.L.P.) based on UK Parkinson's Disease Society Brain Bank criteria (Litvan et al., 2003). Further, we required at least two years of PD diagnosis and at least 20% improvement on the Movement Disorders Society-Unified Parkinson's Disease Rating Scale motor score (MDS-UPDRS-III) when on dopaminergic medications (Goetz et al., 2008) to improve diagnostic accuracy. In addition to a complete neurological screening examination and MDSUPDRS-III off and on dopaminergic medications, all participants underwent comprehensive neuropsychological testing and met level-II criteria for no cognitive impairment (Litvan et al., 2012). According to published guidelines, we assessed the neuropsychological testing only on medications to minimize motor-related interferences during testing (Litvan et al., 2012).

PD participants completed two fMRI sessions; one off and one on dopaminergic medications (off-on study design), counterbalanced on separate days, which were at least two weeks apart to prevent residual learning effect from the initial task completion. We defined the off medications state according to published protocols, with ≥ 72 h off extended release dopamine agonists, selective monoamine oxidase inhibitors, and long-acting levodopa, and ≥ 12 h off short-acting dopamine agonists and levodopa (Ng et al., 2017). We defined the on medications state as participants taking their normal daily medications, thus in the optimally medicated state, as determined by both the participant and the movement disorders neurologist. PD medication details are listed in Table 1. Of the 29 cognitively unimpaired PD participants who attempted the task during their fMRI session, we excluded 13 from the analysis due to button box failure during the task (n = 7), excessive head movement (n = 2), poor task performance (i.e. average of two runs of task is < 90%) on both visits (n = 2), and incomplete OFF-ON pair due to scheduling or personal reasons (n = 2). Therefore, we included 16 PD participants in the final data analysis.

HC were determined by a neurological screening examination and having no more than one test 1.5 standard deviations below age- and education-normative data on comprehensive neuropsychological testing. Of the 21 HC participants who completed one fMRI session, we excluded six from the analysis due to button box failure during the task (n = 3),

incomplete task data (n = 1), prior chemotherapy exposure (n = 1), and severe brain atrophy in subcortical regions (n = 1). Therefore, we included 15 HC in the final data analysis.

Altogether, we included a cohort of 16 PD and 15 HC participants in the final analysis (Table 2). The Stanford University Institutional Review Board approved all study protocols. All study participants provided written consent.

2.2. Data acquisition and preprocessing

2.2.1. Experimental procedure (two-choice forced response Choice Reaction Time Task)—For each fMRI session, participants performed two runs of CRT task using E-Prime software (v2.0; Psychology Software Tools, Pittsburgh, PA; 2002). Each trial consisted of an arrow stimulus (Go signal) pointing to either the left or right (Fig. 1). We recorded task accuracy (Go accuracy) and reaction time (Go reaction time) for each trial and averaged over the two runs. Each task run began with a 10-s rest interval to allow the fMRI signals to equilibrate. A magnet-compatible projection system projected the task at the center of the screen attached to the head-coil. Prior to each fMRI session, participants received oral instructions and completed practice runs outside of scanner until they reached at least 90% accuracy.

2.2.2. fMRI acquisition—We acquired fMRI data using a Discovery MR750 3.0T scanner (General Electric, Milwaukee, WI) with a custom-built 8-channel head-coil at the Stanford University Lucas Center according to previously published protocols (Poston et al., 2016). We acquired each scan using a T2*-weighted gradient echo spiral in-out pulse sequence (Glover and Law, 2001) with the following parameters: Repetition Time = 2 s, Echo Time = 30 ms, 31 axial slices (4.0 mm thickness, 0.5 mm skip) parallel to the anterior commissure-posterior commissure line and covering the whole brain, flip angle = 80°, field of view = 220 mm, matrix size = 64 × 64, voxel size = 3.44 × 3.44 × 4.5 mm. We minimized head movement during the scan by securing the centralized head position with customized ear and neck pads, and by placing weighted cushions on limbs to dampen any tremor. To reduce signal loss from field inhomogeneity, we used an automated high-order shimming based on spiral acquisitions before acquiring fMRI data (Kim et al., 2002).

2.2.3. Structural MRI acquisition—We acquired a high-resolution structural T1-weighted spoiled gradient recalled acquisition in steady state inversion recovery 3-dimensional MRI sequence for each participant to spatially register functional scans with the following parameters: Inversion Time = 400 ms, Repetition Time = 6.0 ms, Echo Time = 1.9 ms, flip angle = 15°, field of view = 220 mm, 158 slices in axial plane, 256 × 256 matrix, number of excitations = 2, acquired resolution = 0.859 × 0.859 × 1 mm.

2.2.4. fMRI preprocessing—We preprocessed fMRI scans using SPM12 software package (Wellcome Department of Cognitive Neurology; www.fil.ion.ucl.ac.uk/spm/). To allow for T1 equilibration, we discarded the first five volumes, and during reconstruction, we separately applied a linear shim correction to each slice (Lai and Glover, 1998). We first realigned the images to the first scan to correct for motion and slice acquisition timing. Translational movement (x, y, z) was calculated in millimeters based on the

SPM12 parameters for motion correction of the functional images in each participant. We used ArtRepair software suite (http://cibsr.stanford.edu/tools/human-brain-project/artrepair-software.html) to correct for deviant volumes resulting from sudden head motion and transient artifacts (Mazaika et al., 2009). In all groups, the majority of repaired volumes occurred in isolation. All included participants had less than 2 mm maximum scan-to-scan movement and less than 2% of volumes corrected. Further, movement parameters did not differ between the groups in any translational or rotational directions (Supplementary Table S1). After the artifacts repair procedure, we estimated the deformation fields from the mean functional images to standard Montreal Neurological Institute (MNI) 152 template, with the exception of four scans (two HC, one PD_OFF, and one PD_ON), which were instead coregistered to the corresponding participant's high-resolution T1 structural image for improved quality. We chose the former as a default procedure, as it showed superior overall coregistration and normalization quality in the majority of our aged cohort. We then normalized all images to standard MNI space for group-level analysis. Images were resampled to 2 mm isotropic voxels and smoothed with a 4 mm full-width at half-maximum Gaussian kernel.

2.3. Data analyses

2.3.1. Brain imaging analysis—We determined Go signal-associated activation (i.e. brain activation associated with correct response to Go signal) using the general linear model implemented in SPM12. Because there were few incorrect responses during the CRT task, we only studied brain activation during correct responses to Go signal.

2.3.2. Individual-level analysis—We modeled Go signal-associated activation at the individual subject level using a boxcar function corresponding to the duration of Go signal display (1400 ms) convolved with the canonical hemodynamic response function and a temporal dispersion derivative to account for voxel-wise latency differences in hemodynamic response. We included six movement parameters as nuisance regressors in the individual-level design matrix. We compared the Go beta map trials to a zero baseline for all three groups (i.e. HC, PD_OFF, and PD_ON). We then removed low-frequency noise with a high-pass filter (0.5 cycle/min) applied to the fMRI time series at each voxel. This generated a voxel-wise contrast map of Go signal-associated activation for each participant.

2.3.3. Group-level analysis—First, we generated a general Go signal-associated mask to be used for all further within- and between-group analyses. To do this, we performed three within-group analyses of Go signal-associated activation, one for each group (HC, PD_OFF, PD_ON), with one-way *t*−tests. This generated three group-specific Go signal-associated activation masks at the height threshold of $p < 0.03$, uncorrected, which were then concatenated as a single general Go signal-associated mask. We used this looser threshold to ensure that the mask likely included most Go signal-associated regions while excluding many residual non-task related regions. We then consistently used this single mask across all analyses (i.e. within- and between-group analyses).

Second, we determined the common regions of Go signal-associated activation in HC and PD, regardless of medication status. To do this, we performed a single within-group analysis

of Go signal-associated activation with pooled data from all three groups. We limited further analyses to regions included in the above generated Go signal-associated mask.

Third, we determined the differences in Go signal-associated activation between each of the three groups, again using the generated Go signal-associated mask above. To do this, we generated three between-group Go signal-associated activation maps: (1) a two-sample *t*–test between HC and PD_OFF (i.e. HC > PD_OFF, PD_OFF > HC) to study the effect of disease on Go signal-associated activation; (2) a paired sample *t*–test between PD_OFF and PD_ON (i.e. PD_OFF > PD_ON, PD_ON > PD_OFF) to study the effect of dopaminergic medications directly; and (3) a two-sample *t*–test between HC and PD_ON (i.e. HC > PD_ON, PD_ON > HC) to study whether Go signal-associated activation is altered when PD participants are on their regular medication. Therefore, we had a total of six group-based contrasts.

2.3.4. Statistical thresholds—For all between-group analyses, we selected significant clusters of activation at the whole-brain level using a height threshold of $p < 0.01$, with family wise error (FWE) correction for multiple comparisons at $p < 0.01$, determined using Monte Carlo simulations according to previously published protocols (Forman et al., 1995; Poston et al., 2016; Rosenberg-Lee et al., 2011). We determined a cluster threshold of 30 voxels corresponding to an FWE-corrected height threshold of $p < 0.01$ and cluster extent threshold of $p < 0.01$. If our default threshold did not reveal significant clusters of activation, we then reran the group-level analysis at a slightly looser height threshold of $p < 0.01$ with FWE correction for multiple spatial comparisons at $p < 0.05$, which corresponded to a cluster threshold of 23 voxels. This looser threshold, which is still considered a statistically appropriate threshold to control for false positives (Huang et al., 2017; Japardi et al., 2018; Rosenberg-Lee et al., 2011; Zhuo et al., 2017), was only used for PD_OFF > HC, and HC contrast. For the within-group analysis of all three groups combined, we determined significant clusters of activation using a height threshold of $p < 0.001$, with FWE correction for multiple spatial comparisons at $p < 0.01$, corresponding to a cluster size of 10 voxels. We used this even stricter threshold for within-group analysis because the default threshold yielded large areas of activation, hindering data interpretation.

2.3.5. Activation pattern and region selection—We identified three distinct activation patterns from the between-group contrasts: normalization, hyperactivation, and hypoactivation. Dopamine normalization is defined as instances when PD_OFF activation is altered from HC in either direction, but then PD_ON is similar to HC. Dopamine hyperactivation is defined as when PD_OFF shows increased activation compared to HC, but then the activation increases further, rather than normalizes, in PD_ON. Dopamine hypoactivation is defined as when PD_OFF shows decreased activation compared to HC, but then the activation decreases further, rather than normalization, in PD_ON. We defined the pattern by averaging the percent signal change of the regions within each contrast. We then selected representative cortical and subcortical regions from each activation pattern based on their connection to fronto-striatal circuitry in order to study how activation patterns of those select regions change in accordance with dopaminergic medications in PD. Using MarsBaR (http://marsbar.sourceforge.net/) (Brett et al., 2002), we created spherical regions of interest

(ROIs) with the radii of 6 mm and 4 mm for cortical and sub-cortical regions, respectively (Supplementary Table S3). We determined percent signal change of brain activation within each ROI based on all scans, which we then used for between-group and brain-behavior analyses.

To examine the behavioral and activation differences (Go reaction time, Go accuracy, ROI activation) across all three groups, we performed several analysis of variance (ANOVA) models. In this analysis, we sought to determine the pattern of activation changes within each ROI comparing HC to the PD dopamine depleted state (i.e. PD_OFF) and then the PD dopamine replenished state (i.e. PD_ON). To compare HC group with either of the PD groups, we performed one-way multivariate ANOVAs with a between-subject factor, Participant-Group (HC and PD_OFF; HC and PD_ON). To compare the two PD groups with each other, we performed repeated-measures ANOVA with two-level within-subject factor, Medication-Group (PD_OFF and PD_ON). For all analyses, two-tailed p values were used; those values of $p \leq 0.05$ were defined as significant, and a trend was defined as $p \leq 0.1$. All statistical analyses were conducted using Statistical Package for the Social Sciences software (IBM SPSS Statistics for Windows, Version 23.0).

2.3.6. Brain-behavior relations—To explore the functional role of the significant task-related brain regions, we correlated percent signal change in each of the select brain regions from each activation pattern with Go reaction time. Since accuracy had a substantial ceiling effect, we only used reaction time for analysis. We additionally correlated regional percent signal change with clinical metrics. Successful CRT performance requires sufficient executive functioning to make the appropriate choice of response; therefore, we focused this analysis on executive tests included in our neuropsychological battery, namely: Trail Making Test (i.e. Trail B time minus Trail A time, Trail B-A), Stroop (i.e. Stroop color and word switching, Stroop C_W; and Stroop interference), and phonemic verbal fluency (i.e. controlled oral word fluency to the letters F-A-S, FAS). To determine which brain activations are best associated with reaction time or neuropsychological performance, we performed five regression analyses. Each analysis included a behavior variable (Go reaction time, Trail B-A, Stroop C_W, Stroop interference, and FAS) as the dependent variable with age, education, and percent signal change of each region as independent variables. We used stepwise regression so that the final model only includes the independent variable(s) that are significantly associated with behavior. The results of this section are in Supplementary materials.

3. Results

3.1. Demographics and behavioral results

The HC and PD participants were matched for age, education, and MoCA (Table 2). There were no between-group differences in Go reaction time or Go accuracy (Table 3). The individual PD participants' OFF and ON behavioral performances are listed in Supplementary Table S2. Furthermore, we confirmed that the direction of the arrow stimulus (i.e. left and right) did not show any differences in Go reaction time or Go accuracy (Go

reaction time (all groups combined): $p = 0.87$; Go accuracy (all groups combined): $p = 0.51$).

3.2. Brain imaging results

3.2.1. Combined group go signal-associated activation—We generated a within-group activation by pooling data from all three groups to study the general pattern of Go signal-associated activation. We noticed activation in the bilateral striatum (putamen and caudate), anterior insula, middle frontal gyri, supplementary motor area, postcentral gyri, superior parietal lobes, occipital pole, and the cerebellum (Fig. 2; Supplementary Table S3). Supplementary Fig. S1 shows within-group activation of all three groups combined on a Go signal-associated mask to demonstrate that all activations are specific to the regions bound by the mask.

3.2.2. Brain activation associated with Parkinson's disease—We studied the effect of disease on Go signal-associated activation by comparing PD_OFF with HC. HC showed higher Go signal-associated activation than PD_OFF (i.e. HC > PD_OFF) in the bilateral putamen and left superior temporal gyrus. In contrast, PD_OFF showed higher activation (i.e. PD_OFF > HC) in the left insula and left parahippocampal gyrus. Supplementary Table S3 lists the coordinates of the regions.

3.2.3. Brain activation associated with dopaminergic medications—We then examined the direct effect of dopaminergic medications on Go signal-associated activation in PD. PD_ON showed higher Go-signal associated activation than PD_OFF (i.e. PD_ON > PD_OFF) in the left putamen, bilateral middle cingulate gyri, left inferior frontal gyrus, and the bilateral cerebellum. There were no significant activations in the reverse contrast (i.e. PD_OFF > PD_ON) at $p < 0.05$, FWE-corrected thresholds. Supplementary Table S3 lists the coordinates of the regions.

3.2.4. Dopaminergic medication-related alterations in brain activation in PD_ON—We then determined whether Go signal-associated activation is altered when PD participants are on their regular medications. HC showed higher Go signal-associated activation than PD_ON (i.e. HC > PD_ON) in the bilateral amygdala. However, PD_ON showed higher activation (i.e. PD_ON > HC) in many frontal cortical regions, including the bilateral anterior cingulate cortex, right medial frontal gyrus, bilateral middle frontal gyri, left pre-supplementary motor area, and the right supplementary motor area. Supplementary Table S3 lists the coordinates of the regions. The results from the three between-group analyses using whole-brain mask are in Supplementary materials (Supplementary Fig. S2).

3.2.5. Activation patterns associated with dopaminergic medications: normalization, hyperactivation, and hypoactivation—In Go signal-associated between-group contrasts, we observed and examined three activation patterns associated with dopaminergic medications: normalization, hyperactivation, and hypoactivation. From each activation pattern, we further selected the cortical and subcortical regions based on their relevance to fronto-striatal circuitry in order to study how activation patterns of those select regions change without and with dopaminergic medications in PD.

In HC > PD_OFF we identified medication normalization of the PD_OFF under-activation (Fig. 3A), and from this contrast we selected the bilateral putamen (Fig. 4). In PD_OFF > HC we identified medication normalization of the PD_OFF over-activation (Fig. 3B), and from this contrast we selected the left insula (Fig. 4). In PD_ON > HC we identified medication hyperactivation (Fig. 3C), and from this contrast we selected several frontal cortical regions (Fig. 5). In HC > PD_ON we identified medication hypoactivation (Fig. 3D), and from this contrast we selected the bilateral amygdala. The insula, though not directly involved in the fronto-striatal circuitry, was selected because prior studies (http://www.neurosynth.org/) (Yarkoni et al., 2011) suggest insula plays a meaningful role in response selection. Likewise, though not directly involved in the fronto-striatal circuitry, the amygdala was selected due to the novel activation pattern (i.e. medication-associated hypoactivation).

3.3. Brain-behavior relations

The results of this section are in Supplementary materials.

4. Discussion

We used an off-on medication design in cognitively unimpaired PD participants to investigate the effects of disease vs. the effects of dopaminergic medications. In the off phase, PD participants highly activated the insula to compensate for the weak putamen activation during successful CRT task performance. In the on phase, we found a dissociation between the effects of dopamine on subcortical and frontal cortical regions. Specifically, we found that dopamine has a normalizing effect on the putamen, whereas in the frontal cortical regions, dopamine results in hyperactivation during successful task performance. Together, findings from this simple task paradigm strongly support the dopamine overdose hypothesis in cognitively unimpaired PD patients.

4.1. Putamen-to-insula switch in PD off dopaminergic medications

We found that in the dopamine depleted or ‘off’ state, PD participants activate the insula when they perform the CRT task with similar reaction time and accuracy as HCs. Prior CRT studies using different task paradigms on non-Parkinson’s participants have found the basal ganglia, especially the putamen, important for normal choice response (Keuken et al., 2014; Naismithet al., 2010). In addition, Forstmann et al observed increased striatal activation when making decisions under time pressure (Forstmann et al., 2008). The putamen is also known to be critical for motor planning during decision-making. For instance, putamen response can predict response selection during a stop-change task (Stock et al., 2015) and motor preparation in a moving dots task (Forstmann et al., 2010). Our PD participants, however, were not able to activate the putamen as much as the HC cohort during the CRT task. This is likely due to the decreased dopamine input from the substantia nigra to the putamen. Indeed, by the time PD motor symptoms develop, over 50% of the substantia nigra dopamine neurons have been lost (Braak et al., 2006), which can be seen on dopamine PET imaging of newly diagnosed PD patients (Conrado et al., 2018).

In contrast, our PD participants engaged the anterior insula more than HCs. We suggest that this insula activation may be a compensatory prefrontal control mechanism that allows PD participants to achieve the same level of accuracy as HCs. While Lewy-body pathology can involve the insula, this typically occurs at later stages of disease (Braak stage 5) (Braak et al., 2006). Given the relatively short disease duration and normal neuropsychological performance in our cohort, it is unlikely that they had yet progressed to this stage of neuropathology. Therefore, it is possible that the presumed neural compensation from the insula would diminish or be lost once the disease progresses and Lewy-bodies reach the insula. This could be one explanation for how PD patients remain cognitively normal early in disease, but then 80% progress to cognitive impairment and dementia after disease duration of 10 years. Longitudinal studies in PD patients as they develop cognitive impairments could test this hypothesis. Alternatively, the observed insula activation by our PD cohort could be due to a more general role the insula plays in detecting novel salient stimuli and orienting attention to them. The anterior insula, along with the dorsal anterior cingulate cortex, is among the most commonly activated regions in human neuroimaging studies; it is involved in a wide range of complex cognitive functions by presumably serving as an integral hub in mediating dynamic interactions between brain networks of different cognitive processes (Cai et al., 2014; Kurthet al., 2010; Menon and Uddin, 2010). Thus, the relative increase in insula activation by our PD compared to the HC cohort suggests that this is a task-specific compensatory mechanism.

4.2. Dopamine normalization in putamen and insula

We found that in the optimally treated or ‘on’ state, dopamine restores the normal brain engagement back in the putamen and insula (i.e. engagement of the putamen and disengagement of the insula) during the CRT task. We hypothesize that PD patients do not need to engage the insula as much for successful CRT task performance after sufficient dopamine replacement in the striatum, thus when taking dopaminergic medications, the PD cohort showed an activation pattern similar to HC. Previous studies have shown that when treated with dopaminergic medications, impaired executive functions, such as flexible switching between perspectives, were largely rescued (Boot et al., 2017). Our data support this idea and provide new evidence that in early, cognitively normal PD, dopamine can restore normal subcortical activation patterns associated with normal task performance.

However, the direction of this dopamine-related normalization appears to be task-specific. Our prior studies have shown that PD participants off dopaminergic medications *increase* putamen activation during successful working memory, with dopamine-associated loss of activation (Poston et al., 2016), which is opposite from the CRT findings. Further, during our CRT task, only HCs showed a relationship between reaction time and putamen activation, while in our prior working memory study, only PD participants on dopaminergic medications showed a relationship between reaction time and putamen activation. Importantly, our prior studies found that dopaminergic medications slowed reaction time during working memory tasks (Poston et al., 2016; Warden et al., 2016), whereas in this study, dopaminergic medications did not alter reaction time during CRT task. This suggests that dopamine replacement and putamen activation do not have a simple relationship with reaction time, but rather this relationship is task dependent and

performance dependent, which reflects a rather complex role of the putamen during the execution of different executive tasks.

4.3. Dopamine hyperactivation in frontal cortical regions

Compared to HCs, PD participants off dopaminergic medications engaged the frontal cortical regions more to generate a successful CRT response. From macaque electrophysiological data to human brain imaging studies, the frontal cortical regions have long been known to play an important role in executive functioning, especially task preparation and response selection (Brass and von Cramon, 2002; Deiber et al., 2012; Hoffstaedter et al., 2013; Taylor et al., 2007), which are required for normal CRT task performance. Past findings from the CRT task using PET also report the importance of frontal cortical regions to successfully complete the task (Schluter et al., 2001). Our HC cohort, however, did not heavily engage the frontal cortical regions, presumably due to the simplicity of our task paradigm. Our data suggests that unlike HC, PD participants off dopaminergic medications additionally require these regions for normal task performance presumably to compensate for the relative loss of putamen activation (Cools et al., 2010). Furthermore, instead of normalizing these regions, as was found in the insula, dopaminergic medications hyperactivated the frontal cortical regions. We propose that while dopaminergic medications would replenish dopamine in dopamine-depleted sub-cortical nigrostriatal circuits, it enhances relatively spared regions, such as the frontal cortex (Arnsten, 1998; Beigi et al., 2016; Cools et al., 2001a; Schrag et al., 2000). Though some studies suggest that dopamine overdose in the frontal cortex generates detrimental effects on cognition (Arnsten, 1998; Cools et al., 2001b; Cools and D'Esposito, 2011), our study did not find a cognitive consequence of frontal hyperactivation. This could be due to the nature and simplicity of our task paradigm or due to successful activation of the putamen when on dopaminergic medications. Further studies are needed to understand the relationship between dopamine-induced frontal cortical hyperactivation and potential dopamine-induced cognitive dysfunction in PD.

4.4. Dopamine hypoactivation in amygdala

Though amygdala is not part of the fronto-striatal circuitry, we found it interesting to see PD participants off dopaminergic medications engage the amygdala less than HCs to generate a successful CRT response. Amygdala is known to be involved in the generation and modulation of normal fear responses (Bowers et al., 2006). Past findings using emotional task-based functional imaging techniques reported in vivo alterations of amygdala activation in early stages of PD that seems directly linked to dopaminergic status (Bowers et al., 2006). For instance, several facial emotion recognition studies showed decreased activation in the amygdala in PD participants, compared to HCs (Argaud et al., 2018). Such reduced activation of amygdala was explained to show emotional deficiencies in PD, as the amygdala circuitry is involved in emotional arousal and emotion-saliency appraisal (Diederich et al., 2016). However, with the given choice response stimulus in our study, which is not intended to study emotional response, it is unclear why amygdala activation was reduced in PD. Further, dopaminergic influence on the amygdala activation has been shown to vary. For instance, Tessitore et al reported reduced amygdala activation during a facial emotion recognition task in PD participants, which then partially normalized with dopaminergic

medications (Tessitore et al., 2002). However, similar to our study, Delaveau et al reported a medication hypoactivation pattern in the amygdala during emotional recognition in PD participants (Delaveau et al., 2009). Such variances could depend on the disease duration. For instance, in early stages of PD, mesocorticolimbic pathways would be relatively spared compared with the motor pathway. Thus, dopamine replacement needed to improve motor symptoms may simultaneously overdose mesolimbic projects to the amygdala and consequently contribute to the reduced task-related activation (Argaud et al., 2018).

4.5. Methodology and Limitations

Our study has several strengths, including comprehensive cognitive testing, clearly defined and matched cognitive status of our cohort, and a counterbalanced off-on study design. However, because we only included PD participants with normal task accuracy on either visits (i.e. > 90% average accuracy of two runs), our cohort represents patients with very high cognitive performance. Therefore, our findings may not be generalizable to all PD patients, and those with cognitive impairments in particular. With respect to dopaminergic medications, our PD participants were on a mixture of dopamine agonists and levodopa, which could have impacted reaction time and cognitive performance differently. However, in our study, 15 out of 16 PD participants were on levodopa; therefore, our findings associated with dopaminergic medications may likely represent a specific effect of levodopa. Although we cannot completely discount MRI coregistration errors in small subcortical regions, such as the putamen, our quality assurance steps confirmed good registration. In addition, while the cluster extent threshold of 0.05 is a statistically appropriate threshold (Huang et al., 2017; Japardi et al., 2018; Rosenberg-Lee et al., 2011; Zhuo et al., 2017), we feel more confident in our primary results (normalization, hyperactivation, and hypoactivation) that meet the stricter threshold of 0.01. Thus, we recommend that the proposed putamen-to-insula switch we report in Section 4.1 of the discussion be replicated to confirm. Finally, we were careful to minimize head motion during scans and discovered no between-group differences in head motion (Supplementary Table S1).

5. Conclusion

In summary, our study provides novel evidence that PD patients off dopaminergic medications can successfully perform a CRT task, and that they do so by engaging the anterior insula to compensate for weak activation of the putamen. A novel finding of our study is that dopaminergic medications not only normalize putamen and insula activation, but also hyperactivate frontal cortical regions and hypoactivate amygdala. Thus, dopamine can have differential effects on cortical and subcortical regions in PD. Our study has important implications for not only improving management in PD patients, but also enriching our understanding of the effect of dopamine on cognitive functioning. Longitudinal studies will allow us to test the predictive value of the observed brain activation patterns as an imaging marker for PD cognitive changes. Further, studying CRT task-specific brain activation and functional connectivity in both cognitively impaired and unimpaired PD patients will allow us to better understand the behavioral implications of the dissociation between the cortical and subcortical task-associated brain activations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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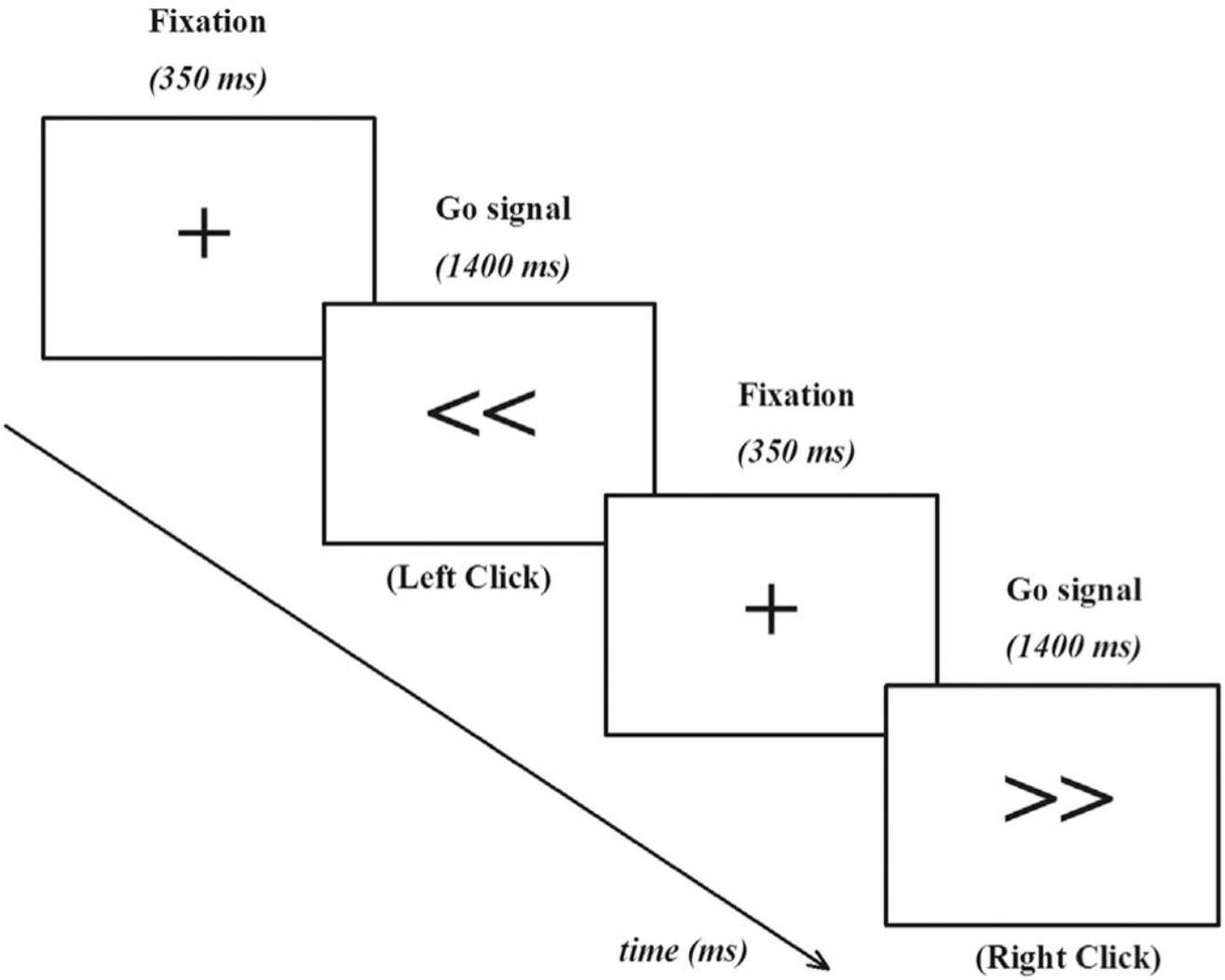

Fig. 1.

Choice Reaction Time Task paradigm. After a 350 ms fixation, the task displays an arrow stimulus, representing a Go signal, pointing to either the left or right for 1400 ms, followed by a jittered inter-stimulus interval of 1750 ± 500 ms. Participants promptly give a left or right mouse click with their index or middle finger, respectively, in response to the direction of Go signal within the 1400 ms timeframe. All participants used their right hand to complete two runs of the task. Each run included 50 Go signals with left and right randomly intermixed. (Single Column).

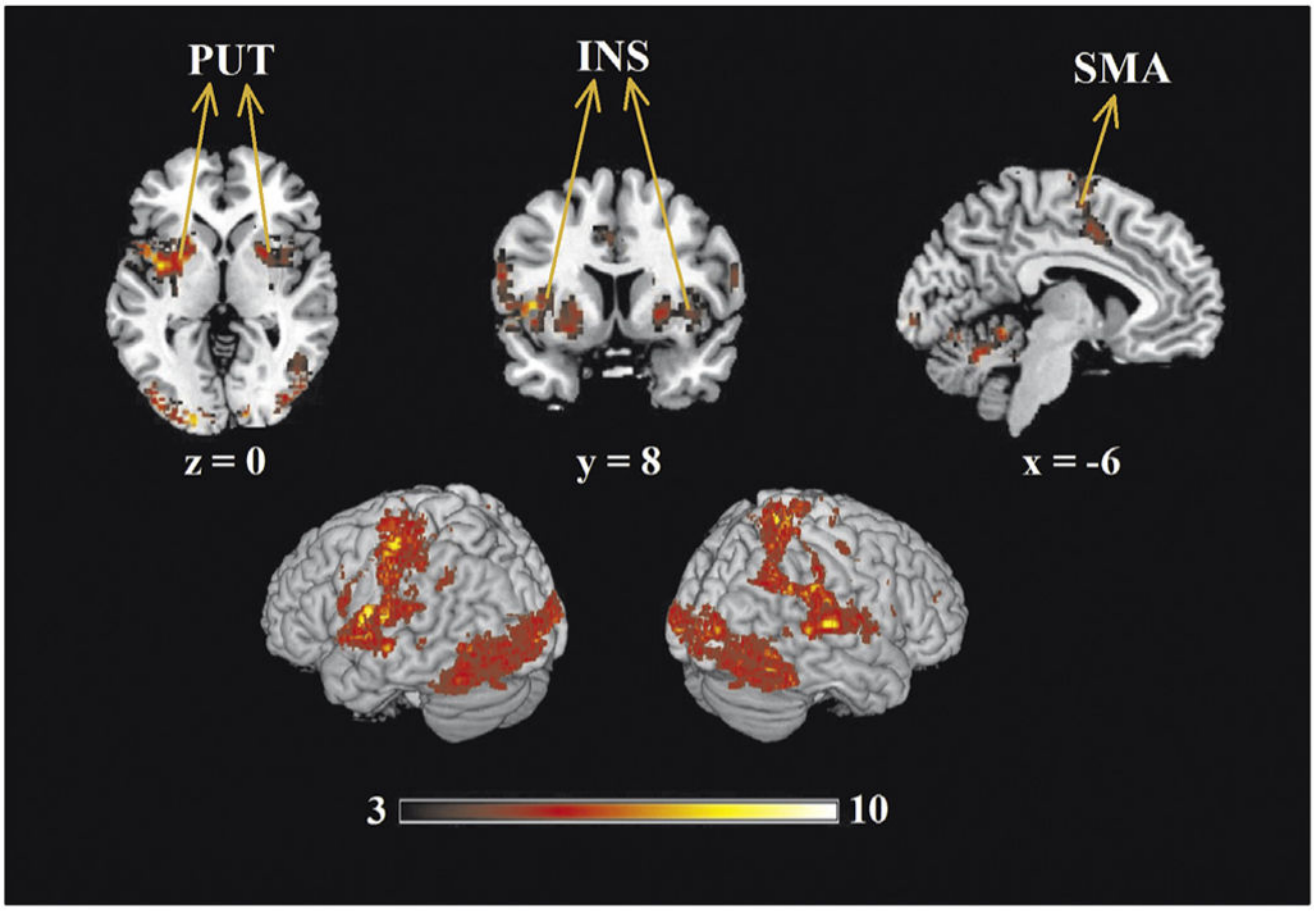

Fig. 2.

Go signal-associated activation on combined data from HC, PD_OFF, and PD_ON groups. Surface rendering and slices show significant Go signal-associated activation (successful Go trials) in ho t colors ($p < 0.001$, family wise error corrected). INS = insula; PUT = putamen; SMA = supplementary motor area. (Single Column; color print).

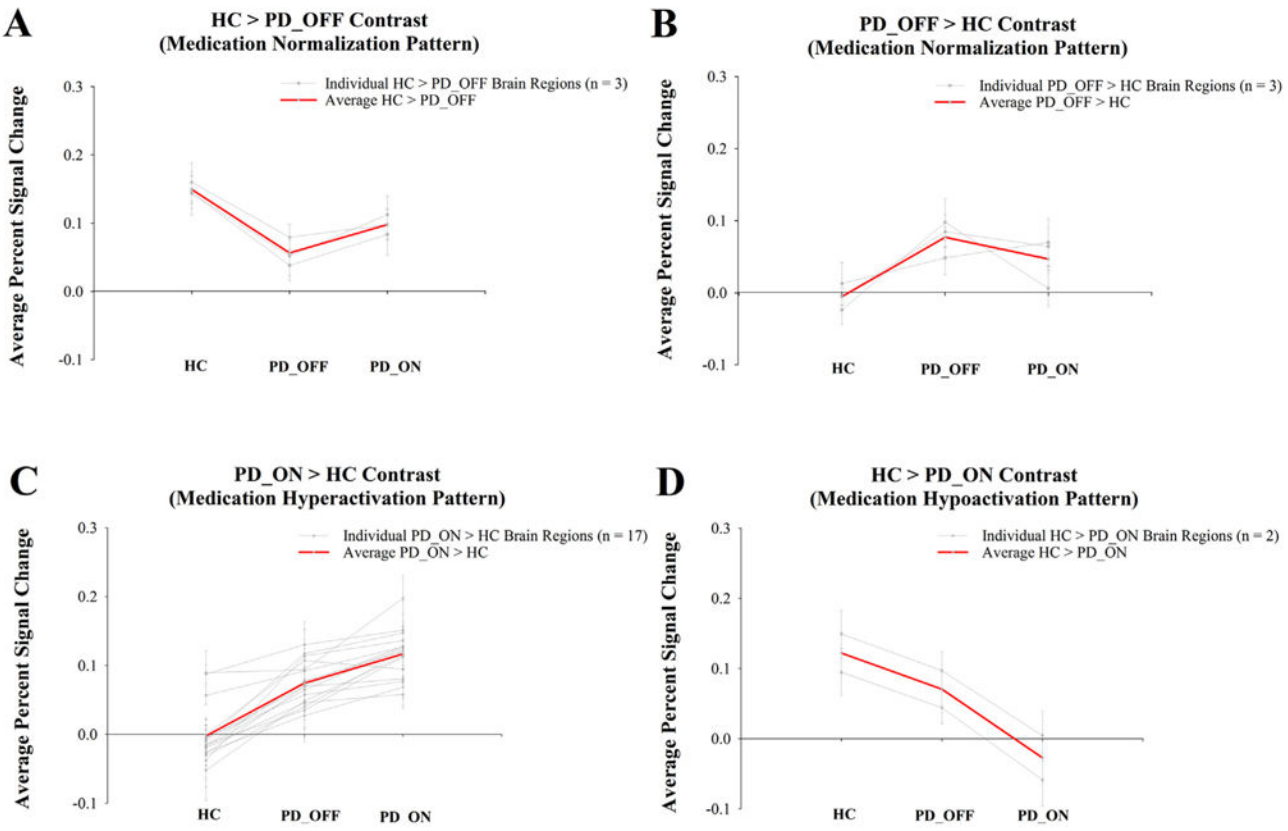

Fig. 3.

Activation patterns associated with dopaminergic medications. The grey lines show the individual activation pattern change (among HC, PD_OFF, and PD_ON) of the specific regions activated in each between-group contrast. The red line shows the averaged activation pattern change for each between-group contrast. Error bars represent standard error of the mean of each region. (A) Medication normalization of PD_OFF's under-activation in the regions of HC > PD_OFF contrast. (B) Medication normalization of PD_OFF's over-activation in the regions of PD_OFF > HC contrast. (C) Medication hyperactivation in the regions of PD_ON > HC contrast. (D) Medication hypoactivation in the regions of HC > PD_ON contrast. HC = healthy controls; PD_OFF = Parkinson's disease, off dopaminergic medications; PD_ON = Parkinson's disease, on dopaminergic medications. (1.5 or Double Column; color print).

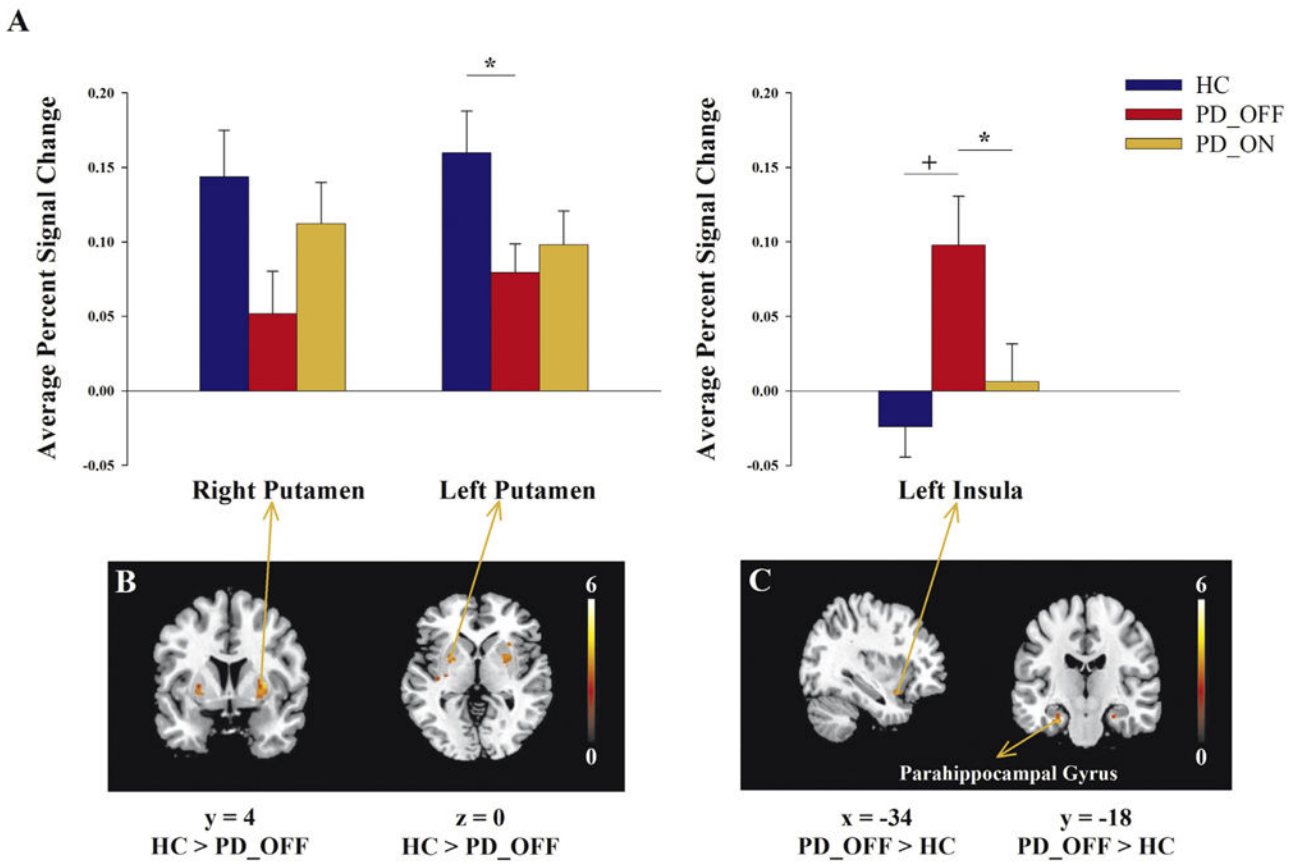

Fig. 4.

HC vs. PD_OFF go signal-associated activation and dopamine normalization effect. (**A**) Error bars represent standard error of the mean, with *p* values derived from one-w ay analysis of variance (ANOVA), post-hoc Tukey corrected for multiple comparisons. Bar graphs show the putamen-to-insula switch in PD_OFF Compared to HC as Well as the dopamine normalization effect. Normalization effect is w here PD_OFF activation is altered from HC, but PD_ON is similar to HC. (**B**) Brain slices show reduced activation in PD_OFF Compared to HC. The bilateral putamen Were selected as two of the regions of interest from this contrast. (**C**) Brain slices show greater activation in PD_OFF Compared to HC. The left insula was selected as one of the regions of interest from this contrast. Slices show significant Go signal-associated activation (successful Go trials) in ho t colors ($p < 0.01$, family wise error corrected). HC = healthy controls; PD_OFF = Parkinson's disease, off dopaminergic medications; PD_ON = Parkinson's disease, on dopaminergic medications. *$p < 0.05$, + $p < 0.01$. (1.5 or Double Column; color print).

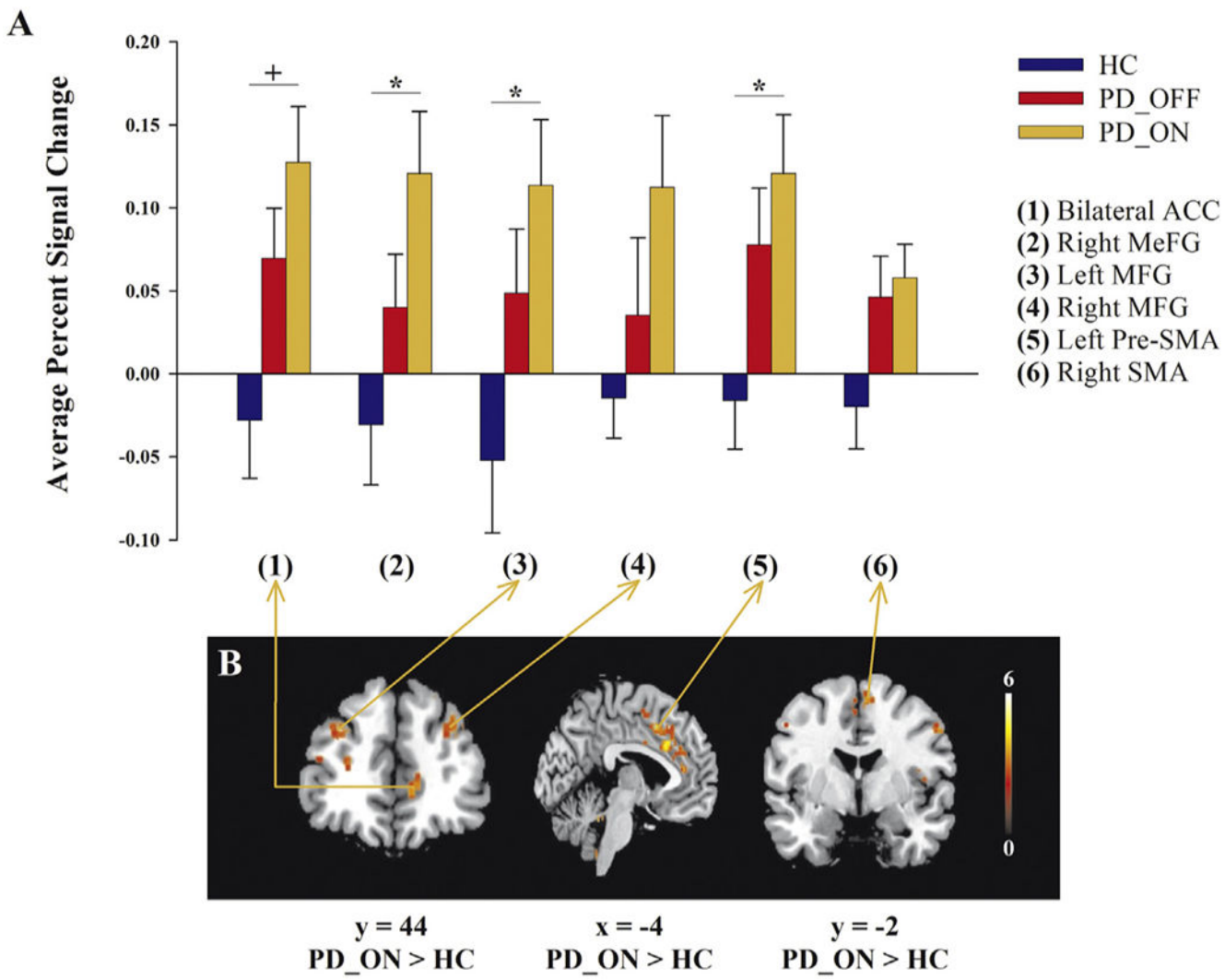

Fig. 5.

HC vs. PD_ON go signal-associated activation and dopamine hyperactivation effect. (**A**) Error bars represent standard error of the mean, with *p* values derived from one-way analysis of variance (ANOVA), post-hoc Tukey corrected for multiple comparisons. Bar graph shows dopaminergic medication hyperactivation effect. Hyperactivation effect is w here PD_OFF showed increased activation from HC, but the activation goes even higher in PD_ON. (**B**) All three brain slices show greater activation in PD_ON Compared to HC. The bilateral ACC, right MeFG (not shown), bilateral MFG, left Pre-SMA, and the right SMA Were selected as the regions of interest from this contrast. Slices show significant Go signal-associated activation (successful Go trials) in ho t colors ($p < 0.01$, family wise error corrected). ACC = anterior cingulate cortex; HC = healthy controls; MeFG = medial frontal gyrus; MFG = middle frontal gyrus; PD_OFF = Parkinson's disease, off dopaminergic medications; PD_ON = Parkinson's disease, on dopaminergic medications; Pre-SMA = pre-supplementary motor area; SMA = supplementary motor area. * $p < 0.05$, + $p < 0.01$. (1.5 or Double Column; color print).

Table 1

Parkinson's disease dopaminergic medications. Table lists the daily dopaminergic medications of each PD participant. 15 out of 16 PD participants are on levodopa. CR = extended release; ER or XL = extended release; LEDD = levodopa equivalent daily dose (m g/day); PD = Parkinson's disease. (Single Column).

LEDD	Names of dopaminergic medications
1560	Amantadine, Carbidopa-Levodopa, Ropinirole
1150	Carbidopa-Levodopa, Carbidopa-Levodopa CR, Pramipexole
1050	Carbidopa-Levodopa, Carbidopa-Levodopa CR, Pramipexole ER
898	Carbidopa-Levodopa, Entacapone, Rasagiline
870	Carbidopa-Levodopa, Rasagiline, Ropinirole XL
750	Carbidopa-Levodopa, Carbidopa-Levodopa CR, Rasagiline
625	Amantadine, Carbidopa-Levodopa, Pramipexole
550	Carbidopa-Levodopa CR, Rasagiline
450	Carbidopa-Levodopa, Rasagiline
450	Amantadine, Pramipexole ER, Rasagiline
410	Carbidopa-Levodopa, Ropinirole
400	Carbidopa-Levodopa, Rasagiline
400	Carbidopa-Levodopa, Rasagiline
360	Carbidopa-Levodopa, Ropinirole
300	Carbidopa-Levodopa
225	Carbidopa, Carbidopa-Levodopa CR

Table 2

Demographic information, clinical features, and neuropsychological data. Table shows the mean ± standard deviation of the demographic information and clinical features, with *p* values derived from two-sample *t*–test between HC and PD_OFF (except where indicated) and significance set a t $p \leq 0.05$. F = female; FAS = controlled oral word fluency to the letters F-A-S, raw score; LEDD = levodopa equivalent daily dose (m g/day); M = male; MoCA = Montreal Cognitive Assessment; MDS-UPDRS-III = Movement Disorders Society-Unified Parkinson's Disease Rating Scale motor score; Stroop C_W = Golden version of Stroop test, color and word switching, raw score; Trails B-A = Trail Making Test B time minus Test A time, raw score.

	Healthy controls	Parkinson's disease	*p*
No.	15	16	-
Age (yr)	64.1 ± 6.4	63.1 ± 7.3	0.69
Education (yr)	16.9 ± 2.2	16.5 ± 2.4	0.60
Gender (M:F) [a]	5:10	8:8	0.35
MDS-UPDRS-IIP' OFF	-	36.0 ± 11.5	-
Hoehn & Yahr, OFF	-	2.0 ± 0.0	-
LEDD	-	653.0 ± 366.8	-
MoCA	28.1 ± 1.8	28.3 ± 1.5	0.76
FAS	44.3 ± 11.5	51.7 ± 13.8	0.12
Trails B-A	39.1 ± 16.1	36.5 ± 19.0	0.68
Stroop C_W	40.4 ± 8.4	42.7 ± 12.0	0.54

[a] Pearson Chi-Square Test (value: 0.883; asymptotic significance (2-sided): 0.347). (Single Column).

Table 3

Choice Reaction Time Task behavioral results. Table shows the mean ± standard deviation of the performance on the Choice Reaction Time Task. *p* values of HC vs. either of the PD groups (i.e. OFF or ON) are derived from one-way multivariate ANOVAs with a between-subject factor, Participant-Group (HC and PD_OFF; HC and PD_ON). *p* values of the two PD groups (i.e. OFF vs. ON) are derived from repeated-measures ANOVA with two-level within-subject factor, Medication-Group (PD_OFF and PD_ON). For all analyses, two-tailed *p* values Were used, with significance set a t $p \leq 0.05$. HC = healthy controls; PD = Parkinson's disease; PD_OFF = Parkinson's disease, off dopaminergic medications; PD_ON = Parkinson's disease, on dopaminergic medications. (1.5 Column).

	HC	**PD_OFF**	**PD_ON**	***p value***		
				HC vs. PD_OFF	**PD_OFF vs. PD_ON**	**HC vs. PD_ON**
Go Reaction Time (ms)	628.6 ± 125.9	610.9 ± 104.7	637.7 ± 105.3	0.67	0.27	0.83
Go Accuracy (%)	99.0 ± 1.3	98.3 ± 2.5	97.1 ± 3.8	0.30	0.25	0.08