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Levodopa improves response inhibition and enhances striatal activation in early-stage Parkinson's disease

Peter Manza[a,*], **Guy Schwartz**[b], **Mala Masson**[a], **Sarah Kann**[a], **Nora D. Volkow**[c,d], **Chiang-shan R. Li**[e,f,g,h], and **Hoi-Chung Leung**[a,**]

[a]Department of Psychology, Integrative Neuroscience Program, Stony Brook University, Stony Brook, NY, USA

[b]Department of Neurology, Stony Brook University, Stony Brook, NY, USA

[c]National Institute on Alcoholism and Alcohol Abuse, National Institutes of Health, Bethesda, MD, USA

[d]National Institute on Drug Abuse, National Institutes of Health, Bethesda, MD, USA

[e]Department of Psychiatry, Yale University, New Haven, CT, USA

[f]Department of Neuroscience, Yale University, New Haven, CT, USA

[g]Interdepartmental Neuroscience Program, Yale University, New Haven, CT, USA

[h]Beijing Huilongguan Hospital, Beijing, China

Abstract

Dopaminergic medications improve the motor symptoms of Parkinson's disease (PD), but their effect on response inhibition, a critical executive function, remains unclear. Previous studies primarily enrolled patients in more advanced stages of PD, when dopaminergic medication loses efficacy, and patients were typically on multiple medications. Here, we recruited 21 patients in early-stage PD on levodopa monotherapy and 37 age-matched controls to perform the stop-signal task during functional magnetic resonance imaging. In contrast to previous studies reporting null effects in more advanced PD, levodopa significantly improved response inhibition performance in our sample. No significant group differences were found in brain activations to pure motor inhibition or error processing (stop success vs. error trials). However, relative to controls, the PD group showed weaker striatal activations to salient events (infrequent vs. frequent events: stop vs. go trials) and fronto-striatal task-residual functional connectivity; both were restored with levodopa. Thus, levodopa appears to improve an important executive function in early-stage PD

[*]Corresponding author at: Laboratory of Neuroimaging, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health 10 Center Drive, Bethesda, MD 20892-1013, USA. Tel.: +1 301 402 9724; fax: +1 301 496 5568. peter.manza@nih.gov (P. Manza). [**]Corresponding author at: Department of Psychology, Stony Brook University, Stony Brook, NY 11794-2500. Tel.: +1 631 632 7820; fax: +1 631 632 7876. hoi-chung.leung@stonybrook.edu (H.-C. Leung).

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.neurobiolaging.2018.02.003.

via enhanced salient signal processing, shedding new light on the role of dopaminergic signaling in response inhibition.

Keywords

Cognitive control; Executive function; Dopamine; Stop-signal task; Movement disorders; Basal ganglia

1. Introduction

Parkinson's disease (PD), a neurodegenerative disorder characterized by severe loss of dopamine in midbrain-striato-thalamocortical circuits, presents with a host of motor and cognitive deficits. Dopamine-replacement therapies improve parkinsonian motor symptoms, but their effects on cognition vary. The variable findings cast doubt on what specific cognitive deficits arise primarily from dopamine loss or instead from other forms of neuropathology (Robbins and Cools, 2014). In particular, the dopaminergic basis of one key cognitive deficit has been repeatedly questioned: response inhibition, the ability to suppress unwanted, habitual behavioral responses (Rae et al., 2016; Ye et al., 2014b). Response inhibition represents a critical therapeutic target in PD, as deficits are thought to be a key factor in freezing of gait (e.g., Shine et al., 2013), and potentially a stronger predictor of future development of dementia than semantic fluency or visual perception (Pedersen et al., 2013).

Although it is well established that individuals with PD consistently display behavioral response inhibition deficits (Gauggel et al., 2004; Kehagia et al., 2014; Ye et al., 2014b), the few studies that directly examined individuals both "on" and "off" dopamine-replacement therapies implied a lack of medication-related improvement (Alegre et al., 2013; Campbell et al., 2008; George et al., 2013; Obeso et al., 2011). Yet a wealth of data in healthy adults implicates a key role of dopamine in response inhibition. For instance, cortical dopamine release (Albrecht et al., 2014), striatal dopamine D1- and D2-receptor availability (Ghahremani et al., 2012; Robertson et al., 2015), and genetic polymorphisms of the dopamine system are strongly associated with individual differences in response inhibition performance and corresponding brain activation during go/no-go and stop-signal tasks (SSTs) (Congdon et al., 2008, 2009; Kasparbauer et al., 2015a,b).

Because the substantial evidence supporting a role of dopamine in response inhibition contradicts the mixed findings in PD, the effects of dopaminergic medication in PD require a closer examination. We recently conducted a meta-analysis on response inhibition studies of PD (Manza et al., 2017) and found that although dopaminergic drugs appear to benefit response inhibition performance in early-stage PD, this effect is missing in advanced PD, ostensibly because there are few remaining dopaminergic cells for the drugs to operate on (Bravi et al., 1994). Furthermore, individuals in previous studies often were taking a mix of medications including dopaminergic agonists, which have different mechanisms of action on the fronto-striatal circuitry and are associated with the development of impulse control disorders (Weintraub et al., 2010). Therefore, we sought to address these concerns by

studying individuals in the early stages of PD (Hoehn & Yahr stages I & II) on levodopa monotherapy, using the SSTs during functional magnetic resonance imaging (fMRI).

Previous studies have demonstrated that successful response inhibition performance is dependent on a network of brain regions including right inferior frontal gyrus (IFG), preesupplementary motor area (preSMA), and striatum (Duann et al., 2009). Dopaminergic drugs alter activation in these regions during response inhibition in healthy populations (Kasparbauer et al., 2015b; Nandam et al., 2014), and individuals with PD show deficient stop-related activation and connectivity between these regions (Vriend et al., 2014; Ye et al., 2014a). Although other medications, including atomoxetine and citalopram (noradrenaline and serotonin reuptake inhibitors), have shown some promise in improving response inhibition performance and brain activation/connectivity in mid-stage PD (Ye et al., 2014a,b, 2016), to date, it remains unclear if dopaminergic medications would have similar effects in early-stage PD. We hypothesized that levodopa would influence response inhibition performance and brain activation/connectivity during the SSTs in early-stage PD.

2. Materials and methods

2.1. Participants

Twenty-one individuals (6 females, mean age of 61.9 ± 11.2 years) diagnosed with PD participated in the study. This cohort participated in the experiment after a minimum 12-hour washout of PD medications (“off” medication). Thirty-seven healthy age-matched controls (16 females, mean age of 62.5 ± 8.2 years) participated for 1 session. All patients were free from major medical illnesses other than PD and were diagnosed by a practicing neurologist. They were on a stable dosage of oral carbidopa-levodopa, with no other PD drugs or drugs for cognitive impairment, except 11 participants who were also taking 1 mg/d of the mild monoamine oxidase B inhibitor Azilect. Based on self-report, none had impulse control disorder or hallucinations. One patient demonstrated accuracy on go trials, which was less than 3 SDs from the mean, and another self-reported symptoms of depression (Geriatric Depression Score = 21). These 2 patients were included and indicated by different colors in the plots (individual with self-reported depression shown in brown and individual with low accuracy shown in black in Figs. 1C and 3A, right panel), and additional analyses were conducted without these participants to confirm that the main findings were not changed. Written informed consent was obtained from all participants, and the study was performed under protocols approved by the Stony Brook Human Investigation Review Board.

For fMRI data, 4 of the 21 patients and 19 of the 37 controls completed the experiment on a different scanner with a different MR protocol. Thus, the final sample for fMRI analysis included 17 individuals with PD (6 females, mean age of 61.0 ± 11.9 years) “on” and “off” medications (order of “on” and “off” sessions was counterbalanced), and 18 healthy controls (9 females, mean age of 65.3 ± 7.7 years). Table 1 shows the PD fMRI cohort demographics and clinical characteristics, including PD medication status. The most common non-PD medications were for cholesterol/blood pressure (3 controls and 5 patients) and for thyroid conditions (3 controls and 2 patients). In addition, 1 control and 2 patients were taking an antidepressant.

2.2. Behavioral task

During fMRI, participants performed the SSTs (Fig. 1A; Logan et al., 1984; Manza et al., 2016a), after a meta-analysis indicated this may be the most sensitive measure for identifying response inhibition deficits in PD, relative to antisaccades, go/no-go, and Stroop tasks (Manza et al., 2017). There were 2 randomly intermixed trial types: go and stop. On "go" trials, a small dot first appeared on the screen signaling the beginning of a trial. After a variable time interval (foreperiod, with a random uniform distribution of 1−5 seconds), the dot turned into a circle (the go signal), prompting the participant to press a button. The circle vanished with the button press or after 1 second had elapsed, whichever came first, and the trial terminated. A premature button press before the appearance of the circle also terminated the trial. On "stop" trials, an X appeared shortly after the circle and replaced the go signal. The participants were told to withhold their button press on seeing the X, the stop signal. The stop-signal delay (SSD)—the time interval between the go and stop signal—started at 200 ms and varied according to a staircase procedure, increasing or decreasing by 67 ms, respectively, after a successful or failed stop trial (De Jong et al., 1990; Levitt, 1971). The intertrial interval was 2 seconds. Approximately, three-quarters of all trials were go trials and one-quarter were stop trials. Participants were instructed to respond to the go signal quickly while keeping in mind that a stop signal could come up occasionally. Participants were not explicitly informed about the ratio of go/stop trials or the SSD staircase procedure. Each participant completed four 10-minute runs of the task during fMRI. Depending on the foreperiod duration and speed of response, the total number of trials varied slightly across participants (mean 283 = 16 ± go trials and 95 ± 10 stop trials). Despite the slight variation in the number of stop trials between participants, our average of 95 stop trials is well above the suggestion of 50 stop trials needed for a stable stop-signal reaction time (SSRT) estimation (Band et al., 2003; Verbruggen and Logan, 2009). With the staircase procedure, participants successfully withhold their response in approximately half of the stop trials. The SSRT of each participant was computed by subtracting the critical SSD (i.e., the estimated SSD required to get half of stop trials correct) from the median go reaction time (GoRT) (Li et al., 2008a; Logan et al., 1984). We used this "maximum likelihood method" so that results were comparable to our previous studies. However, to confirm that the primary findings were not due to inflation of the SSRT using the maximum likelihood method, we also computed SSRT using the integration method (see Verbruggen et al., 2013 for details).

2.3. Imaging protocol and preprocessing of image data

Brain images were acquired using a 3-T Siemens Prisma (64-channel coil). Whole-brain high-resolution T1 anatomical scan was conducted (176 sagittal slices, repetition time = 2400 ms, echo time = 2.24 ms, flip angle = 8°, field of view = 256 × 256 mm, Matrix = 320 × 320, and 0.8 mm^3 isotropic voxels). Functional MRI scans were obtained using an echo-planar imaging (EPI) sequence (52 axial-oblique slices, multiband factor = 4, repetition time = 1000 ms, echo time = 33 ms, flip angle = 52°, field of view = 210 × 210 mm, matrix = 84 × 84, and 2.5 mm^3 isotropic voxels with no gap; 600 image volumes in each session and 4 task sessions). An additional 10-minute resting-state session was collected a minimum of 10 minutes after completion of the SSTs (identical parameters to the task fMRI sequence), to reduce carryover effects.

Data were analyzed with Statistical Parametric Mapping (SPM12; Wellcome Department of Imaging Neuroscience, University College London, UK). There were no significant group differences in head motion in any of the 4 task scans or in the resting state scan, as assessed by framewise displacement and root mean square variance of % signal intensity (data available upon request; for details of motion calculation, see Section 2.5). Nevertheless, we further minimized sources of motion and physiological noise in the functional images by regressing out signals from the white matter using aCompCor, a principle component analysis−based cleaning method (Behzadi et al., 2007). The first 10 images of each session were discarded for signal steady-state equilibrium. Functional images were corrected for slice timing and realigned (motion-corrected) to the mean EPI image. Images were then distortion-corrected with FMRIB Software Library v5.0's "topup" program (Andersson et al., 2003; Smith et al., 2004) by unwarping a pair of spin-echo field maps with reversed phase-encode blips and applying the transformation to all EPI images. A mean functional image volume was constructed for each participant for each run from the distortion-corrected, realigned image volumes and coregistered with the high-resolution structural image, which was segmented. The resulting structural segments were matched to the PD25 EPI Montreal Neurological Institute atlas (Xiao et al., 2015) with affine registration followed by nonlinear transformation. Finally, images were smoothed with 6 mm at full width at half maximum.

2.4. Generalized linear models

Our goal was to identify the effects of Parkinson's disease and the effects of dopaminergic medications on brain activation, as measured using SST contrasts for response inhibition. There were 4 basic types of SST trial outcomes: go success, go error, stop success, and stop error. A statistical analytical design was constructed for each individual participant, using the general linear model with the onsets of go signal in each of the 4 main trial types (go success, go error, stop success, stop error) convolved with a canonical hemo-dynamic response function (HRF) and with the temporal derivative of the canonical HRF and entered as regressors in the model (Friston et al., 1995). Realignment parameters in all 6 dimensions were also entered in the model. Serial autocorrelation of the time series was corrected by the fast model for highetemporal resolution images (Todd et al., 2016). The general linear model estimated the component of variance that could be explained by each of the regressors.

In the first-level analysis, we constructed 2 separate contrasts that probed distinct aspects of SST performance: "saliency" processing (i.e., stop > go trials, or infrequent [~25%] versus frequently presented [~75%] stimuli) and "successful stopping" (i.e., stop success > stop error trials). The contrast (difference in β) images of the first-level analyses were then used for the second-level group statistics (random effect analysis; Penny and Holmes, 2003). The data were high-pass filtered (1/128 Hz cutoff) to remove low-frequency signal drifts.

2.5. Task-residual and resting-state functional connectivity analysis

We sought to understand whether group differences in regional task activation were related to changes in functional networks during task and resting state. Therefore, we conducted functional connectivity analysis using similar methods as our previous work (Manza et al., 2015, 2016b). We used seed regions that showed significant and overlapping disease and

medication-related effects in the task contrasts. We first "scrubbed" the data (Power et al., 2012) to remove time points affected by head motions. Briefly, for every time point t, we computed the *framewise displacement* given by $FD(t) = |\Delta d_x(t)| + |\Delta d_y(t)| + |\Delta d_z(t)| + r|\alpha(t)| + r|\beta(t)| + r|\gamma(t)|$, where ($d_x$, d_y, d_z) and (α, β, γ) are the translational and rotational movements, respectively, and r (= 50 mm) is a constant that approximates the mean distance between center of MNI space and the cortex and transform rotations into displacements. The second head movement metric was the root mean square variance of the differences (DVARS) in % signal intensity $I(t)$ between consecutive time points across all voxels, computed as follows: $DVARS(t) = \sqrt{|I(t) - I(t-1)|^2}$, where the brackets indicate the mean across brain voxels. We removed every time point that exceeded the head motion limit $FD(t) > 0.5$ mm or DVARS(t) > 0.5% via regression. In addition, during the task state, HRF-convolved task events and their derivatives were regressed out to remove the influence of transient events on functional connectivity estimates (Fair et al., 2007). Regressing out task events is a critical step, as external stimuli can induce inflated correlations between brain regions (McIntosh and Korostil, 2008). Task-residual signals make a major contribution to task performance, and this approach has been successfully applied in recent work (Alavash et al., 2015; Cole et al., 2014; Rudolph et al., 2017; Zhang and Li, 2010, 2012); furthermore, it is especially useful in sample sizes like the current one that may be underpowered for task event-driven connectivity methods, for example, dynamic causal modeling (Goulden et al., 2012). Thus, after regressing out task events and their derivatives, the fMRI signal time courses were averaged across all voxels for the seed region. We computed the correlation coefficient between the averaged time course of each seed region and the time course of each voxel in the whole brain for each individual. To assess and compare the resting-state correlation maps, we converted the r values, which were not normally distributed, to z scores by Fisher's z transform (Jenkins and Watts, 1968): $z = 0.5\log_e[(1 + r)/(1 - r)]$.

2.6. Group-level statistical analysis

In the second-level analysis, images were thresholded at a cluster-forming threshold of $p < 0.005$ and $p < 0.05$ family-wise error (FWE) cluster-corrected. To ensure cluster-level type I error rates were controlled for, in line with current reporting guidelines (Eklund et al., 2016), we calculated cluster corrections with the Statistical nonparametric mapping toolbox (SnPM13: http://warwick.ac.uk/snpm; 5000 permutations). One-sample t-tests were performed to estimate the group-level effects for each group: the PD "on", PD "off", and control groups. Disease effects were determined using 2-sample t-tests between the control and PD "off" groups. Levodopa effects were determined using paired t-tests between the "on" and "off" states in PD.

3. Results

3.1. Behavioral performance

GoRT did not differ significantly between the 3 groups, whereas SSRT was significantly slower in the PD "off" group relative to the other 2 groups [control vs. PD off: $t(56) = -2.43$, $p = 0.018$; PD on vs. PD off: $t(16) = -2.86$, $p = 0.008$; see Table 2, Fig. 1B], indicating that a

response inhibition deficit in the "off" medication state is improved with levodopa in early-stage PD. SSRT results were highly similar between the "maximum likelihood" and "integration" methods ($R^2 = 0.87$), and group differences were significant using either approach (Table 2). Results were also similar when excluding the participant with self-reported depression and the participant who was an outlier by go accuracy [control vs. PD off: $t(54) = -2.34$, $p = 0.023$; PD on vs. PD off: $t(14) = -2.90$, $p = 0.012$]. Across participants, greater benefits in response inhibition (i.e., reduction in SSRT from "off" to "on" status) was positively correlated with their SSRT "off" medication ($R^2 = 0.48$, $p = 0.002$, Fig. 1C), indicating that patients with worse response inhibition deficit benefited more from levodopa. A Pitman test (Kelly and Price, 2005) suggested that this was not simply an effect of regression to the mean, as the variance in SSRT was significantly different between the "on" and "off" state [$t(16) = 2.49$, $p = 0.012$] (van Wouwe et al., 2016). These differences also did not appear to be due to differences in performance that would violate the assumptions of the race model (i.e., as the SSD increased, stop-error rates increased in all 3 groups, Fig. 1D, and stop-error RT was faster than GoRT in all 3 groups, Table 2). To confirm that medication-based changes in SSRT were not simply due to alleviation of motor symptoms, we conducted an across-participant correlation between change in SSRT ("on" minus "off") and between change in Unified Parkinson's disease rating scale III motor ratings ("on" minus "off"). Indeed, SSRT changes between "on" versus "off" state were not significantly associated with changes in UPDRS rating ($r = 0.09$; $p = 0.74$), suggesting that medication-based improvement in response inhibition performance was not directly linked to alleviation of motor symptoms as measured by UPDRS. Furthermore, medication-based differences in SSRT were not significantly associated with other clinical features of PD (age, levodopa-dose equivalency, or years from diagnosis; all p's > 0.35).

3.2. Task-fMRI results

We examined regional activations in each group that were specific to the "saliency" and "successful stopping" SST contrasts. In 1-sample t-tests, each group showed significant activations in the saliency, stop > go, contrast, including bilateral insula/IFG, bilateral primary and association visual cortices, superior temporal gyrus, dorsal anterior cingulate cortex, and preSMA (Fig. 2A). In the reverse contrast (go > stop), all 3 groups showed significant activation in the sensorimotor cortex. For the "successful stopping", stop success > stop error, contrast, each group showed significant activations in the lateral occipital cortex, and for the reverse contrast (stop error > stop success), there were widespread activations in medial occipital, superior frontal, sensorimotor, and insular cortices, as well as striatum and thalamus (Fig. 2B).

The whole-brain 2-sample t-test between the PD "off" group and controls (i.e., disease effects) revealed significantly lower saliency-related activations in the PD "off" group in the right striatum ($p_{FWE} = 0.039$; Table 3; Fig. 3A), though the left striatum and regions typically considered part of the "salience" network, such as the cingulate cortex (Seeley et al., 2007), are also evident at a reduced threshold of $p < 0.005$ uncorrected (Supplementary Fig. 1). There were no significant disease effects for the successful stopping contrast at the corrected threshold or at a reduced threshold of $p < 0.005$ uncorrected.

The whole-brain paired *t*-tests for PD "on" versus "off" (i.e., medication effects) revealed significantly greater saliency-related activations in the "on" group in the right striatum, thalamus, IFG, and insular cortices ($p_{FWE} = 0.044$; Table 3; Fig. 3A). When examining the overlap between disease- and medication-related activations, 1 cluster emerged in the right striatum that encompassed the ventral and anterior-dorsal putamen as well as anterior pallidum. Thus, patients "off" medication showed significantly lower saliency-related activation in this striatal cluster that was increased with medication. There were no significant medication effects for the successful stopping contrast (or the reverse contrast, stop error > stop success) at the corrected threshold or at a reduced threshold of $p < 0.005$ uncorrected. Results were virtually identical when excluding the participant with self-reported depression and the participant who was a go-accuracy outlier. Post hoc analysis of the striatal cluster confirmed that effects were significantly stronger in the stop > go contrast than the stop success > stop error contrast (disease effect: Cohen's $D = 1.62$ vs. -0.44; $z = 3.97$, $p < 1 \times 10^{-4}$; medication effect: Cohen's $D = 1.36$ vs. -0.13; $z = 2.92$, $p = 0.004$; for analysis of individual trial types contributing to these effects, see Supplementary Fig. 2). Medication-based differences in striatal activations were not significantly associated with clinical features of PD (age, levodopa-dose equivalency, years from diagnosis, or symptom side onset; all p's > 0.39). The observed disease and medication effects appeared to originate from altered neural processing of a salient stimulus (stop signal) when compared to processing nonsalient, frequent stimuli (go signal), rather than outright stopping compared to impulsive errors. This region was extracted and used for functional connectivity analysis.

3.3. Task-residual functional connectivity results

In task-residual functional connectivity analysis of the right-striatum cluster, no significant disease- or medication-related effects emerged in whole-brain analysis at the more stringent a priori FWE-corrected threshold. At an exploratory, reduced threshold (conjunction $p < 0.0025$, with a minimum cluster size $k > 20$), we found an overlap between disease- and medication-related effects in task-residual functional connectivity between right striatum and left inferior frontal junction (IFG), SMA, left primary motor cortex (M1), and bilateral premotor cortices (Table 4; Fig. 3B), regions associated with response inhibition processes in previous studies (Cai et al., 2014; Li et al., 2006). However, these functional connectivity effects were not observed during the resting state (Fig. 3B). Owing to an increased risk for false positives at this lower threshold, we do not interpret the individual disease- and medication-related effects separately, but only the conjunction.

4. Discussion

We find that levodopa significantly improved SST performance in the early stages of PD. Functional MRI results suggest that levodopa also enhanced the saliency-related activation during SST performance and the functional connectivity of a fronto-striatal network that is critical for goal-directed movement. We discuss these findings in further detail below.

4.1. Impact of levodopa on response inhibition performance

Dopaminergic medication benefited the commonly observed response inhibition deficit in PD, improving SSRT roughly to the level of healthy controls. To our knowledge, this is the

first study to show that dopamine-boosting medications improve SSRT in early-stage PD using a within-participant design. We speculate that previous studies did not observe significant dopaminergic effects on SSRT because they typically included participants using mixed medications and in the later stages of PD, when dopaminergic medications are less effective (Bravi et al., 1994). Importantly, the improvements in SSRT observed here were not associated with medication-based recovery of motor symptoms. This supports the intriguing possibility that levodopa benefits cognitive control of motor output independently of its effects on primary motor symptoms in PD, probably through a different dopamine-modulated fronto-striatal mechanism (Rowe et al., 2008).

These data provide further evidence that the specific task and population of interest can have a major impact on how dopamine-boosting medications affect response inhibition. Among healthy young adults, levodopa impaired interference-effect RT on a modified Stroop/Simon task (Onur et al., 2011), and methylphenidate and pramipexole did not significantly improve go/no-go performance (Hester et al., 2012; Kasparbauer et al., 2015b; Nandam et al., 2014; Yang et al., 2016). SST performance may be more amenable to the influence of dopaminergic medications (Manza et al., 2017), as SSRT has improved with methylphenidate (Nandam et al., 2011; but see; Farr et al., 2014), tyrosine (Colzato et al., 2014), and the dopamine agonist cabergoline (Nandam et al., 2013) in healthy adults. The effects of dopamine agonists on SSRT may be strongest in individuals with genetic profiles conferring low basal dopamine transmission (MacDonald et al., 2016). Although levodopa did not significantly improve SST performance in moderate-to-advanced PD (George et al., 2013; Obeso et al., 2011), it did improve Stroop performance in early-stage PD (Fera et al., 2007), particularly among those with poor baseline performance (Costa et al., 2014). The latter finding is in line with our observation that the individuals with the slowest SSRT benefited the most from levodopa. Together, these considerations highlight the need for careful selection and evaluation of study populations when making inferences about the role of dopamine in response inhibition.

4.2. Levodopa boosts deficient striatal activations to salient stimuli in PD

By examining the overlap between disease- and medication-related effects during SST performance, we isolated a striatal region that showed deficient “salience” (i.e., stop > go) activity in the “off” state that was improved with levodopa. This is another demonstration of the critical role that the striatum plays in SST performance (Zandbelt and Vink, 2010). Levodopa also significantly increased salience-related activations in the right thalamus, insula, and IFG. A previous study demonstrated reduced stop-related activation in the right IFG in de novo PD (Vriend et al., 2014), although that was an analysis of stop success > go trials only, and it is unclear if it actually was a direct response suppression effect or it extends to the same stop > go contrast presented here.

Interestingly, the effect here was present for both stop success and stop error trials. This suggests that task-related striatal deficits are not only related to pure motor inhibition but also a deficit in the processing and response to salient, infrequent stimuli. Our work suggests that the striatum may be part of the “ventral attention system” for the detection of infrequent events, in addition to the inferior prefrontal and parietal regions that have been previously

identified (Corbetta and Shulman, 2002). These findings build on a body of work demonstrating the strong role of dopamine in processing salient events, regardless of valence or reward (Bromberg-Martin et al., 2010; Horvitz, 2000), and is another example of how striatal dopamine loss impairs executive functions dependent on saliency processing. Individuals with mid-stage PD showed blunted responses to surprising stimuli on an oddball task (Gurvich et al., 2007), which were improved with dopaminergic medication in early-stage PD (Georgiev et al., 2015). Furthermore, PD patients "off" medication showed selective deficits in cognitive control of movement when they had to respond to highly salient, surprising stimuli, and this impairment was ameliorated with levodopa (Galea et al., 2012). This deficit was replicated in healthy adults who were given the D2 receptor blocker haloperidol, confirming a role for dopamine in this behavior (Bestmann et al., 2015). Thus, response inhibition deficits and blunted striatal activations in PD may be a result of impaired salient signal processing, which is improved with levodopa administration.

It is important to clarify what is meant by "salient" processing in the context of this study. In their seminal paper on the "salience network"—which includes the right striatal region identified here—Seeley et al. (2007) note that the salience network performs 2 distinct physiological functions: conflict/infrequency response and also interoception/motivational drive. Our definition of "salience" in this context maps onto the former and should not be confused with the latter function, which may operate in parallel in this system. This type of striatal infrequency response has indeed been observed in the SST previously. Sharp et al. (2010) used a modified SST with a majority of go trials, 20% stop trials, and 20% "continue" trials. The continue trials had identical frequency and timing to stop signals, but the go response was allowed to continue as normal. The contrast "continue (20%) > go (50%)" trials significantly activated the right striatum, whereas the contrast "stop (20%) > continue (20%)" did not. Therefore, this striatal region appears to be critical for the infrequency (saliency) response during the SST, and not necessarily the final motor output of stopping or going. Still, another explanation for stop > go effects (in the absence of stop success > stop error effects) has been posited in previous work. This striatal region could be important for early processing during response inhibition—that is, the initiation of the stop process, which may or may not result in successful stopping on any given trial (Cai et al., 2014; Cai and Leung, 2011; Wessel and Aron, 2013, 2017). The temporal profile of this activation could be dissected with combined electroencephalography (EEG)-fMRI to test this hypothesis in future research. In addition, future studies could examine the nature of the right-lateralized findings here (although the left striatum also emerged at a lower threshold), since a right-lateralized fronto-striatal inhibitory control circuit has been implicated in the literature previously (e.g., Zandbelt et al., 2013).

4.3. Levodopa may increase task functional connectivity between the striatum and a motor planning network

We found that task-residual functional connectivity between the right striatum region (identified from task analysis) and left IFJ was reduced in PD and increased with levodopa. The IFJ is thought to play a critical role in detecting unexpected or salient stimuli, in contrast to a more pure role in response inhibition attributed to the IFG (Corbetta and Shulman, 2002; Leung and Cai, 2007; Verbruggen and Aron, 2010). Although the right IFJ

has received relatively more attention than the left IFJ in the response inhibition literature (Cai and Leung, 2011; Levy and Wagner, 2011; Swann et al., 2012), the left IFJ appears to play an important role in maintaining rule sets during tasks that require flexible switching of behavior (Bunge, 2003; Ueltzhöffer et al., 2015). Interestingly, A1 allele carriers of the DRD2-Taq1A polymorphism, who tend to have higher striatal dopamine D2 receptor density, show greater activation of the left IFJ during task switching relative to non-carriers (Stelzel et al., 2010). These findings correspond well with our observations that individuals with PD show reduced brain activation on salient stop trials generally, and not only during successful stopping, which is improved with levodopa administration. Thus, striatal-left IFJ functional connectivity during the task state may be an indicator of rule maintenance and vigilance for salient stimulus detection, which is sensitive to dopaminergic transmission.

We also observed an overlap of disease- and medication-related effects in task-residual functional connectivity between striatum and SMA, left M1, and bilateral premotor cortices. These regions have all been associated with the preparation and execution of goal-directed movement and, critically, are all modulated by dopamine. Prominent theories suggest that dopamine cells support the anticipation of salient stimuli by sending cascading signals through an insula-basal ganglia-SMA network to generate goal-directed motor output during cognitive control (e.g., Uddin, 2015). Recent positron emission tomography and fMRI studies in healthy adults have demonstrated support for these theories. For instance, striatal activations are linked to M1 and SMA output during SST performance (Zandbelt and Vink, 2010). More generally, increased dopamine release in the SMA was associated with faster learning of motor sequence output (Garraux et al., 2007), and depleting dopamine precursors (phenylalanine/tyrosine) decreased brain activation in striatum/SMA along with impaired timing of motor output on a perceptual task (Coull et al., 2012). The premotor cortex is also a critical region for motor planning, as it purportedly generates the “go” signal to basal ganglia to disinhibit the thalamus and excite motor cortex (Li et al., 2008b). While there is little direct evidence for how dopamine modulates premotor function to support response inhibition, some studies have shown hyperactive premotor responses in PD during movements that are associated with Stroop inhibitory control performance (Huang et al., 2007) and normalized with levodopa (Haslinger et al., 2001; Toxopeus et al., 2012). Thus, synchrony between regions critical for the planning and execution of goal-directed movements is disrupted in early-stage PD and responsive to levodopa.

4.4. Limitations

A common limitation of studies that manipulate dopaminergic drug intake in PD, including the present study, is a lack of a true double-blind placebo experimental design. More work is also needed to clarify whether levodopa’s impact on response inhibition is purely due to changes in dopaminergic signaling because levodopa is also a precursor for norepinephrine, which plays a role in response inhibition (Bari et al., 2009; Rae et al., 2016). In addition, while previous studies have concluded that carbidopa-levodopa does not significantly alter cerebral blood flow (Henriksen and Boas, 1985; Hershey et al., 2000, 2003), future studies could include arterial spin labeling sequences to control for any subtle blood flow differences based on medication use. Another potential issue relates to the sample size of the fMRI cohort, which limited our ability to examine PD subgroups, for example, rigid versus

tremor dominant, or left- versus right-lateralized symptom groups. However, recent studies suggest that there are no substantial differences in SSRT between these subgroups (Mirabella et al., 2017; Tolleson et al., 2017). Finally, the task-residual functional connectivity results were exploratory and observed at a reduced statistical threshold; replication in a larger cohort with a more stringent thresholding procedure is necessary.

In summary, response inhibition deficits in Parkinson's disease are associated with reduced striatal activation and connectivity during task performance that appears to be related to deficient salient signal processing. Crucially, these behavioral and neural markers were improved with levodopa in early-stage PD, a finding that was not observed in prior investigations in more advanced PD with more heterogeneous medication profiles. These results highlight the importance of carefully examining cohort characteristics when interpreting dopaminergic medication effects and shed new light on the role of dopamine in response inhibition.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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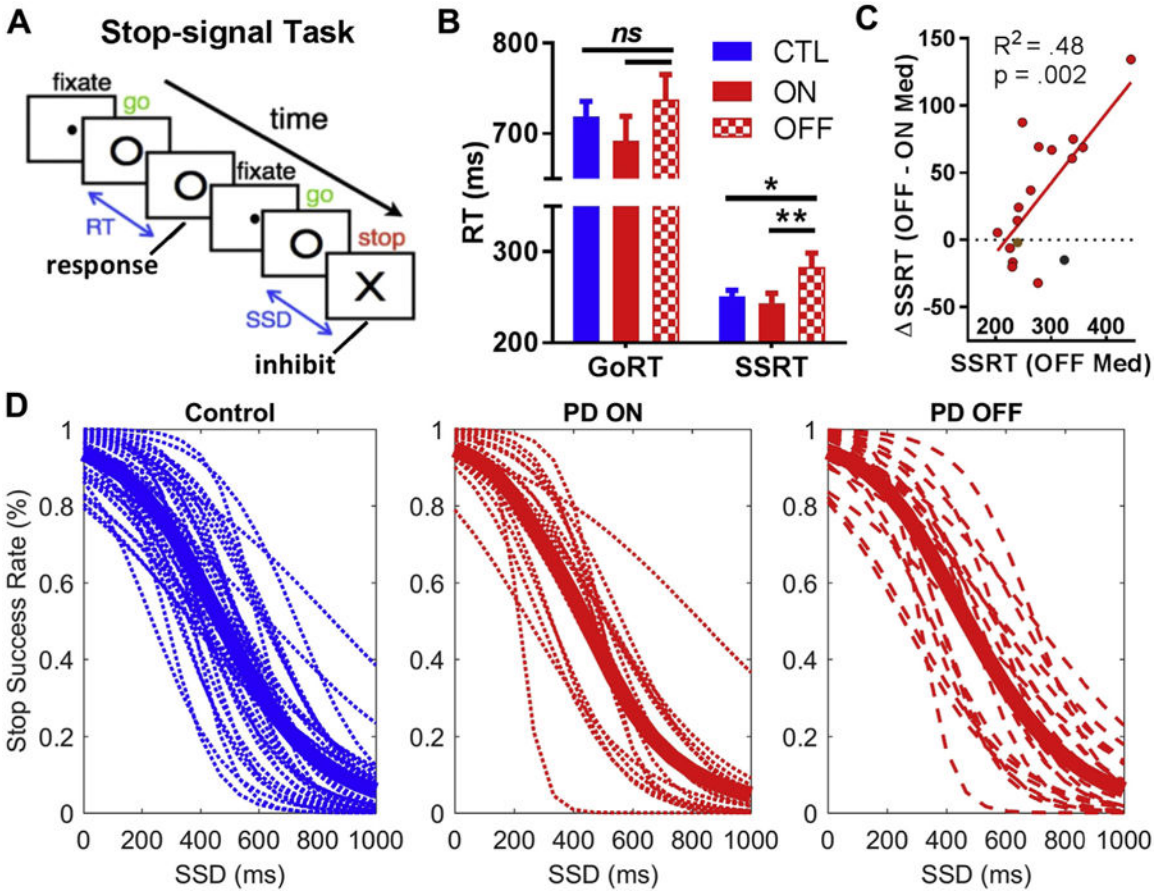

Fig. 1.

Stop-signal task and behavioral results. (A) A go stimulus "O" appears on each trial, and on 25% of the trials, a stop signal "X" appears shortly after the go signal to instruct participants to withhold the planned response. The SSD, or the time between the go stimulus and the stop signal on a stop trial, is varied based on a staircase procedure. (B) Response time measures on the stop-signal task for all participants. Participants with PD showed significantly longer SSRT in their "off" state (red hatch) compared to their "on" state (red) and the control group (blue), indicating a response inhibition deficit, whereas differences in GoRT were not significant. (C) Greater benefits in response inhibition (i.e., reduction in SSRT from "off" to "on" status) were positively correlated with SSRT "off" medication. The individual with self-reported depression (brown dot) and the individual with low go accuracy (black dot) are shown. (D) Inhibition function for each group, demonstrating that all 3 groups did not violate the basic assumption of the "race model": as the SSD increases, stop success rate decreases or error rate increases. The thick line in each plot represents the group mean. Note: *, $p < 0.05$; **, $p < 0.01$; ns, not significant. Error bars indicate standard error of the mean. Abbreviations: GoRT, go reaction time; PD, Parkinson's disease; SSD, stop-signal delay; SSRT, stop-signal reaction time. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

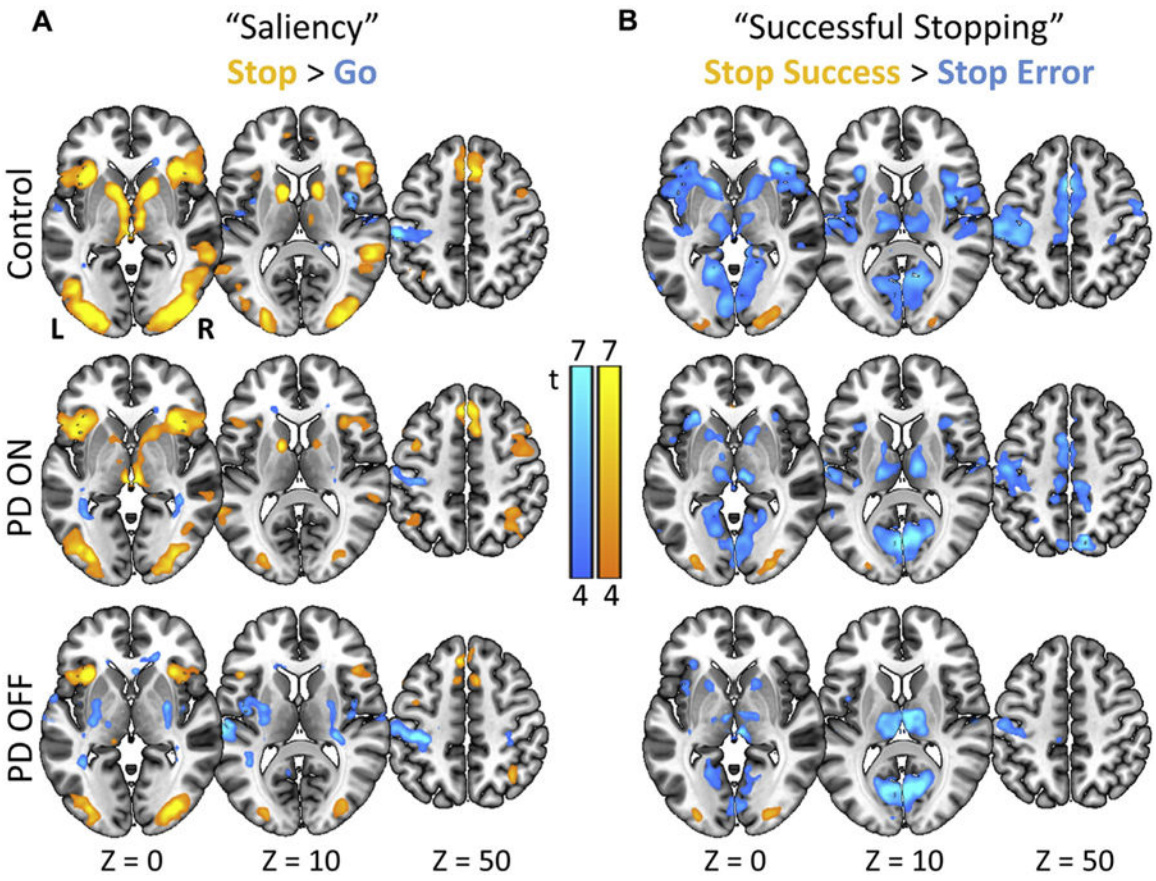

Fig. 2.

Functional magnetic resonance imaging results: 1-sample *t*-tests showing SST activations for each group. (A) Activations to "saliency" or all stop > go trials (i.e., infrequent stimuli compared to frequent stimuli). (B) Activations to "successful stopping" or stop success > stop error trials. Maps are thresholded at $4 > t > 7$ (where brighter colors indicate higher values), for visualization. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

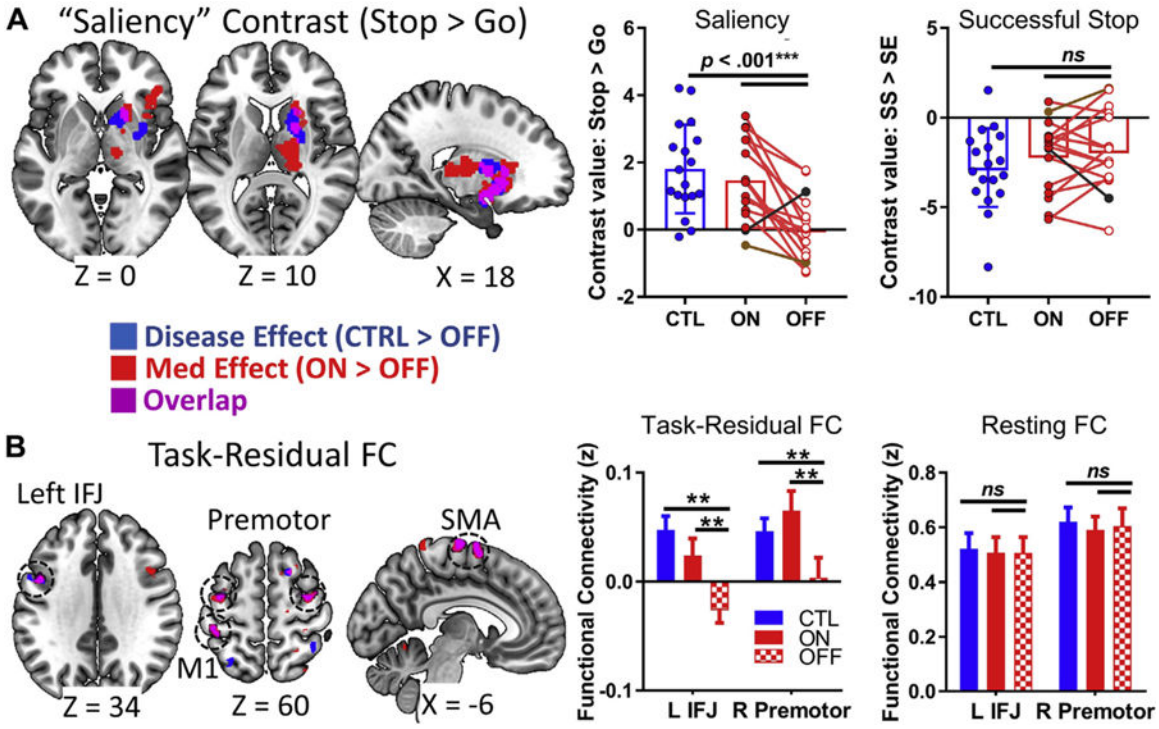

Fig. 3.

Functional magnetic resonance imaging results: Group differences for SST contrasts and functional connectivity (FC), showing disease effects (controls > PD "off", shown in blue), medication effects (PD "on" > PD "off", shown in red), and their overlap (shown in purple). (A) Left: Significant disease and medication effects are shown in the thalamus, striatum, and right insula/inferior frontal gyrus for the saliency contrast, including an overlapping region in the right striatum (purple). Right: Post hoc analysis showing that the PD group had lower right striatum saliency-related activations than when on levodopa or compared to controls; however, there were no consistent group differences in this region between successful versus failed stopping. The individual with self-reported depression (brown dot) and the individual with low go accuracy (black dot) are indicated. (B) Left: In exploratory task-residual functional connectivity analysis using the right striatum region from part (A) as a seed region, there were overlapping disease and medication effects in L IFJ, M1, SMA, and bilateral premotor cortices. Right: Post hoc analysis for 2 example regions (L IFJ and R premotor) showing group differences in task-residual functional connectivity, but not resting-state functional connectivity. Task contrast results have a cluster-forming threshold of $p < 0.005$, with a nonparametric $p < 0.05$ FWE cluster correction, using SnPM13. Functional connectivity results were not significant at this nonparametric cluster-level threshold, and so only the conjunction is analyzed at an exploratory threshold of $p < 0.0025$ uncorrected, with a minimum cluster size $k > 20$. $^{**}p < 0.01$; $^{***}p < 0.001$. Abbreviations: CTL, control; FWE, family-wise error; IFG, inferior frontal junction; L, left; M1, primary motor cortex; PD, Parkinson's disease; R, right; SMA, supplementary motor area. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Table 1

Demographics and clinical characteristics for the PD cohort included in the fMRI analysis (n = 17)

Participant number	Age	Sex	Years of Education	Hand	Years since diagnosis	H&Y	Med	LEDD	GDS	STAI	BIS-11	MoCA	TMT A (on)	TMT A (off)	TMT B (on)	TMT B (off)	UPDRS III (on)	UPDR SIII (off)	Last dose (on)	Last dose (off)
1	64	F	16	R	2	2	Lev	338.4	21	47	75	29	29	30	48	80	24	25	2.5	13
2	68	M	18	R	1	1.5	Lev+A	325.6	2	55	63	30	20	28	36	27	15	17	2	16
3	67	F	21	R	0.2	1.5	Lev	451.1	9	52	63	29	23	31	44	64	14	20	1	17
4	58	M	13	R	5	2	Lev+A	889.5	4	52	68	28	33	47	87	99	21	29	0.5	17
5	79	M	16	R	2	1.5	Lev	563.9	12	51	73	24	40	52	100	115	16	25	4	12
6	51	M	14	L	1	1	Lev+A	663.9	4	53	57	29	20	26	32	36	10	15	3	15
7	45	M	16	R	0.3	1	Lev+A	212.8	0	48	63	28	25	26	68	77	10	16	4	18
8	69	M	12	L	1	1	Lev+A	325.6	4	53	63	25	22	24	39	45	7	13	2	16
9	68	M	20	L	2	1	Lev+A	438.4	1	52	61	28	39	51	56	85	7	13	1	26
10	49	M	14	R	8	2	Lev+A	325.6	8	49	81	28	18	25	31	32	22	29	3	26
11	49	F	13	R	0.25	1	Lev	225.6	6	54	56	28	16	19	40	39	15	18	2	15
12	80	F	21	R	6	1.5	Lev	771.4	5	52	64	29	36	49	80	87	14	26	1	14
13	73	F	18	R	5	2	Lev+A	401.4	5	52	67	25	35	48	63	63	14	27	1	16
14	65	M	18	R	6	1	Lev+A	425.6	5	52	60	26	29	32	73	134	9	14	2	14
15	48	M	16	R	4	2	Lev+A	551.1	0	47	43	27	22	23	74	47	15	22	1.5	15
16	52	M	14	R	4	2	Lev	789.5	5	50	62	25	50	31	49	47	21	25	4	16
17	54	F	18	R	1	1	Lev+A	400.8	1	52	40	30	23	27	51	41	9	16	0.5	15
PD mean (SD)	61.1 (11.2)	11 M,6 F	16.4 (2.8)	14 R,3 L	2.9 (2.4)	1.5 (0.4)		476.5 (200.0)	5.4 (5.1)	51.2 (2.3)	62.3 (10.1)	27.5 (1.9)	28.2 (9.3)	33.5 (11.1)	57.1 (20.4)	65.8 (31.0)	14.3 (5.3)	20.6(5.7)	2.1 (1.2)	16.5 (3.9)
CTRLmean(SD)	65.3 (7.7)	9 M, 9 F	15.1 (3.0)	17 R,1 L					3.6 (3.9)	51.4 (3.1)	57.1 (8.2)	27.9 (1.3)		28.9 (10.1)		64.2 (21.1)				

The last 2 rows show average (mean) and standard deviation (SD) in parentheses for this PD group and the matched control group (n = 18).

Key: BIS-11, Behavioral Inhibition Scale-11; CTRL, control; F, female; fMRI, functional magnetic resonance imaging; GDS, Geriatric Depression Scale; Hand, handedness; H&Y, Hoehn & Yahr; L, left; Last dose, time (in hours) since the last dose of medication; LEDD, levodopa-dose equivalency; Lev, carbidopa-levodopa monotherapy; Lev+A = carbidopa-levodopa and Azilect; M, male; Med, medication profile; MoCA, Montreal Cognitive Assessment; PD, Parkinson's disease; R, right; STAI, State-Trait Anxiety Inventory (trait score only used here); TMT, Trail Making Test.

Table 2

Behavioral results for the stop-signal task, presented as mean (standard deviation)

Group	SSRT (maximum likelihood method)	SSRT (integration method)	GoRT	GoRT-SERT	GoRT CoV	Mean SSD	Go Acc	Stop Acc
CTL	251.2 (40.7)	247.1 (37.2)	718.6 (106.3)	94.3 (38.3)	0.22 (0.05)	455.16 (98.37)	0.98 (0.02)	0.53 (0.03)
PD ON	249.0 (45.1)	242.4 (47.6)	686.3 (112.8)	85.8 (35.3)	0.22 (0.05)	432.69 (107.32)	0.97 (0.05)	0.53 (0.03)
PD OFF	283.3 (60.0)	273.9 (63.9)	734.8 (113.5)	115.5 (70.1)	0.24 (0.06)	444.41 (105.18)	0.96 (0.03)	0.54 (0.04)
CTL vs. ON	0.17 (0.864)	0.40 (0.692)	1.02 (0.314)	0.78 (0.442)	−0.02 (0.985)	0.76 (0.452)	0.62 (0.539)	0.88 (0.380)
CTL vs. OFF	−2.43 (0.018)[a]	−2.03 (0.047)[a]	−0.54 (0.588)	−1.50 (0.140)	−1.70 (0.112)	−0.10 (0.704)	1.95 (0.093)	−0.10 (0.925)
ON vs. OFF	−2.86 (0.008)[a]	−2.42 (0.016)[a]	−2.16 (0.064)	−1.64 (0.112)	−1.13 (0.241)	−0.96 (0.443)	1.20 (0.355)	−1.98 (0.122)

CTL versus ON and CTL versus OFF are t (p) values for 2-sample t-tests; ON versus OFF is t (p) values for paired t-tests of patients “on” and “off” their medications.

Key: Acc, accuracy; CoV, coefficient of variation; CTL, control; GoRT, go reaction time; SERT, stop-error reaction time; SSD, stop-signal delay; SSRT, stop-signal reaction time.

[a] $p < 0.05$.

Table 3

Brain activation differences for SST "saliency" contrast analysis (i.e., stop > go trials) between groups, including paired *t*-test comparison of participants with PD in their "ON" versus "OFF" medication state (Medication effects) and 2-sample *t*-test comparison of participants with Parkinson's disease in their "OFF" medication state versus controls (disease effects)

Contrast	Cluster size (mm^3)	*p*-value (FWE corrected)	*t*-score	MNI coordinates (mm)			Identified regions
				X	Y	Z	
ON > OFF (medication effect)							
Stop > Go	5828	0.044	6.47	20	0	−12	R striatum, R thalamus, R insula, R IFG
			6.08	16	−12	10	
			5.19	16	−27	8	
CTL > OFF (disease effect)							
Stop > Go	6764	0.039	5.07	23	3	−18	R striatum
			4.69	23	8	−22	
			4.55	13	10	0	

Task contrast results have a cluster-forming threshold of $p < 0.005$, with a nonparametric $p < 0.05$ FWE cluster correction, using SnPM13.

Key: CTL, control; FWE, family-wise error; IFG, inferior frontal junction; MNI, Montreal Neurological Institute; R, right.

Table 4

Task-residual functional connectivity differences between groups

Contrast	Cluster size (mm^3)	*p*-value (FWE corrected)	*t*-score	MNI coordinates (mm)			Identified regions
				X	Y	Z	
Conjunction							
Striatal functional connectivity	406	<0.001	5.25	−37	−4	62	L premotor
	313	<0.001	4.62	−47	8	32	L IFJ
	906	<0.001	4.55	−24	−14	70	L M1
			4.43	−24	−2	68	
	1328	<0.001	4.46	−7	0	68	L SMA
	703	0.001	3.99	30	−7	65	R premotor
			3.37	26	−10	75	
	500	0.001	3.91	−44	−32	68	L M1

The overlapping right striatum region is shown in Fig. 3A, left was used as the seed region in the analysis. Conjunction of disease (CTL vs. PD “OFF”) and medication (“ON” vs. “OFF”) striatal connectivity revealed a set of prefrontal and frontal motor areas at an exploratory threshold of $p < 0.0025$, with a minimum cluster size $k > 20$.

Key: CTL, control; IFG, inferior frontal junction; L, left; M1, primary motor cortex; MNI, Montreal Neurological Institute; PD, Parkinson’s disease; R, right; SMA, supplementary motor area.