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Neurocomputation, dopaminergic treatment, and cognitive control in early-stage Parkinson's Disease

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Peter Manza

We, the dissertation committee for the above candidate for the

Doctor of Philosophy degree, hereby recommend

acceptance of this dissertation.

Dr. Hoi-Chung Leung
Professor of Integrative Neuroscience, Department of Psychology
(Advisor)

Dr. Turhan Canli
Professor of Integrative Neuroscience, Department of Psychology
(Defense Chairperson)

Dr. Christian Luhmann
Professor of Cognitive Science, Department of Psychology

Dr. Chiang-shan Ray Li
Professor of Psychiatry, Yale University School of Medicine

This dissertation is accepted by the Graduate School

Charles Taber

Dean of the Graduate School

Abstract of the Dissertation

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Parkinson's disease (PD) is a neurodegenerative disorder involving the basal ganglia that results in a host of motor and cognitive deficits. The hallmark motor symptoms of the disease, such as tremor and rigidity, are generally well-treated with medications that boost the neurotransmitter dopamine. However, whether dopamine-replacement therapy restores cognitive function is under intense debate. While some studies have shown cognitive benefits for individuals taking dopaminergic medications, others have reported null findings or even exacerbated cognitive impairment for individuals in the medicated state. Current theories generally attribute the variety of findings to task differences and the uneven pattern of PD neuropathology across the basal ganglia. However, few studies consider how disease duration may interact with medication status to produce changes in cognitive function. This is an important consideration, as profound loss of dopamine-containing cells in the advanced stages of PD renders dopaminergic medication relatively ineffective. Here, in a meta-analysis it is evident that disease duration modulates cognitive function for individuals on dopaminergic medication. In a functional magnetic

resonance imaging study of the stop-signal task (SST), we find that early-stage individuals have a restoration of response inhibition behavior with dopaminergic medication, in contrast to previous studies reporting null effects in more advanced individuals with PD. Bayesian computational modeling of SST performance identified a possible mechanism by which dopaminergic medication improves response inhibition in early-stage PD. Specifically, compared to a 12-hour washout "off" medication state, individuals in the "on" state showed improvements in their ability to make behavioral adjustments across trials of the task. This manifested itself in increased brain activations to the anticipation of salient events, and decreased activations to surprise in lateral and medial frontoparietal regions. Together, these findings highlight the importance of disease duration when considering medication effects on cognitive function in PD. They also identify a potential novel mechanism by which dopamine supports frontoparietal cognitive control, centered on trial-to-trial learning, behavioral adjustment and increased neural signatures of anticipation.

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CHAPTER I. GENERAL INTRODUCTION

Parkinson's disease: Introduction and Background

Parkinson's disease (PD) is a neurological disorder with a prevalence of about 1% in the population over the age of 60 (Tanner and Goldman, 1996; Pringsheim et al., 2014). The primary pathological feature of Parkinson's disease is a severe loss of dopamine (DA) cells in the caudal lateral substantia nigra pars compacta (Damier et al., 1999). This results in a host of motor, cognitive, and motivational deficits; however, the clinical presentation of two of the four cardinal motor symptoms (tremor, rigidity, akinesia, and bradykinesia) is all that is required to merit diagnosis of PD. Along with DA degeneration, other neurotransmitter systems including cholinergic, serotonergic, and noradrenergic processes are also disrupted. This has profound consequences for myriad behaviors dependent upon function in cortico-cortical and cortico-striatal-midbrain circuits. In the most advanced stages of the disease, individuals with PD become wheelchair bound and, just as debilitating, develop dementia.

Indeed, the symptom that caregivers of individuals with PD rated the most difficult to manage was not motor dysfunction but cognitive impairment (Leroi et al., 2012). Numerous reports have found that up to 50% of individuals with PD display clinically significant levels of cognitive impairment even at first diagnosis (Muslimovic et al., 2005; Dujardin et al., 2013). These deficits, including working memory, response inhibition, and attention, are associated with increased levels of apathy and depression (Santangelo et al., 2009; Lueken et al., 2014), and this contributes to reduced quality of life (Schrag et al., 2000; Muntean and Perju-Dumbrava, 2012; Lawson et al., 2016). Perhaps most challenging for patients is that, while current therapies vastly improve motor symptoms, the only drugs approved for cognitive impairment in PD (acetylcholinesterase inhibitors) show very limited efficacy and have adverse side effects (Emre

et al., 2004). Thus, a substantial effort has been put forth in the past two decades to understand the basic neuropathological mechanisms behind this troubling non-motor symptom.

Investigations into the neural basis of cognitive dysfunction in PD generally fall under at least one of the following four domains: postmortem pathology, genetics, pharmacological manipulation, and neuroimaging studies. The following paragraphs briefly summarize some influential findings from each of these domains. There is also an extensive literature on rat and nonhuman primate models of PD that is outside the scope of this work; for reviews see (Tieu, 2011; Bové and Perier, 2012).

Review of studies of cognitive dysfunction in PD

Postmortem Pathology

Several forms of neuropathology seem to be intimately linked to cognitive decline in PD. A primary candidate associated with PD dementia is Lewy body pathology: spherical aggregates of the protein alpha-synclein that develop inside the cytoplasm of nerve cells. These neurotoxic clusters appears in the substantia nigra of PD cases but in some individuals can also be observed throughout the cortex (Gibb et al., 1991; Hurtig et al., 2000). The majority of PD cases with cognitive impairment or dementia show substantial cortical Lewy body pathology, and the amount of Lewy bodies observed in frontal and temporal cortex correlates with severity of cognitive deficit. Importantly, while many advanced cases also have comorbid Alzheimer's disease pathology (i.e., amyloid-beta plaques and neurofibrillary tangles of tau protein), several studies have concluded that Lewy body pathology is the postmortem marker most closely associated with dementia in PD (Mattila et al., 2000; Aarsland et al., 2005; Irwin et al., 2012). Nevertheless, Alzheimer's pathology often correlates with Lewy body deposition, and the

combination of the two appears to confer particularly severe cognitive outcomes (Compta et al., 2011). While Lewy bodies and amyloid-beta are the most heavily studied pathological markers associated with cognition in the PD literature, markers of neurovascular and white matter disease also show some relation to dementia in PD (Choi et al., 2010; Schwartz et al., 2012). An important limitation of these studies relates to their inherent inability to measure longitudinal effects. Postmortem studies, by nature, have a biased subject pool towards the eldest individuals with the most advanced cases of PD, making it difficult to disentangle factors contributing to PD-related cognitive decline with comorbid pathologies occurring with normal aging. Recent advances in positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) offer some hope for understanding longitudinal progression of these pathological markers *in vivo* (Gomperts et al., 2008; Shimada et al., 2009).

Genetics

Although there are cases of autosomal dominant inheritance of PD (e.g., Polymeropoulos et al., 1997) these represent a small fraction of the overall PD population; therefore this discussion will focus on the "sporadic", or non-familial, genetic contributions to cognitive decline in PD. Mutations in two genes, the glucocerebrosidase (GBA) and microtubule-associated protein tau (MAPT) confer higher risk of PD in the general population (Nichols et al., 2009; Simón-Sánchez et al., 2009) and also higher risk of cognitive decline among individuals with PD (Setó-Salvia et al., 2011; Alcalay et al., 2012). These findings suggest that improper lysosomal function, and hence impaired ability of enzymes to break down Lewy body and tau protein aggregates, may play a role in the etiology of cognitive decline in PD (Lwin et al., 2004).

Polymorphisms of the catechol-O-methyl transferase (COMT) gene are also implicated in cognitive function in PD. The COMT variants are associated with differences in DA uptake in frontal cortex as well as differences in neuropsychiatric performance among PD patients (Ziegler et al., 2014; Gallagher et al., 2015). Interestingly, variants of MAPT but not COMT are associated with PD dementia (Goris et al., 2007; Williams-Gray et al., 2009). These observations have been part of the foundation for the *dual-syndrome hypothesis*, a prominent theory proposing two distinct (but possibly overlapping) disorders underlying PD-related cognitive dysfunction (Kehagia et al., 2013). The first is fronto-striatal, DA-dependent impairment in executive function that varies with COMT polymorphisms. The second is posterior cortical, cholinergic impairment related to visuospatial deficits that is associated with development of dementia (for a more thorough review, see Robbins and Cools, 2014). This framework has been very useful in describing the heterogeneous pattern of cognitive impairment across individuals with PD, and will be revisited in Chapter III.

Pharmacological Manipulations

The vast majority of studies in this domain manipulate drugs that boost DA, as degeneration of dopamine cells is considered the primary pathological feature contributing to PD symptomatology. A great variety of findings has been reported, ranging from complete amelioration of cognitive deficit, to null results or even exacerbation of cognitive impairment with medications that boost dopamine (Rowe et al., 2008; Cools and D'Esposito, 2011; Robbins and Cools, 2014). Perhaps the most widely-cited theory that attempts to reconcile these findings suggests a Yerkes-Dodson inverted U-shaped function for DA: too much or too little DA

transmission leads to behavioral impairment (e.g., Arnsten, 1997). This theory has been refined in recent years to describe how striatal DA computes the cost of cognitive effort and prefrontal DA maintains a balance between flexibility and stability (Cools, 2015). And because DA loss is uneven across the striatum, following a posterior-to-anterior gradient (Kish et al., 1988; Braak et al., 2003; Kordower et al., 2013)**,** DA drugs may differentially affect the various cortico-striatal circuits that subserve different cognitive behaviors. Anterior/ventral portions of the striatum that are relatively spared of DA loss may become "overdosed" with DA medication, and subsequently lead to impaired behavior on tasks probing ventral striatal function (e.g., reversal learning) (Cools et al., 2001, 2006; Rowe et al., 2008). Meanwhile, the same medications restore the DA-depleted dorsal striatum back towards optimal levels, and behaviors dependent upon dorsal striatum (e.g., task-switching, spatial working memory) are improved (Lange et al., 1992; Lewis et al., 2003; Williams-Gray et al., 2009; Ekman et al., 2012).

While hypotheses of DA function have received support from a large number of studies, it has been insufficient to describe the all of the complex patterns of PD-related cognitive deficits, prompting researchers to examine the role of other neurotransmitters in these behaviors. For instance, recent attempts to boost noradrenaline and serotonin with atomoxetine and citalopram have shown promise in improving response inhibition in individuals with moderate-to-advanced PD (Kehagia et al., 2014; Ye et al., 2014b; Rae et al., 2016). In PD dementia, anticholinesterase inhibitors have shown some mild efficacy in improving memory deficits (Emre et al., 2004). However, it is clear that compared to DA, little is known about how other neurotransmitters contribute to cognitive decline in PD, and this is a burgeoning area of investigation.

Neuroimaging Studies

A large literature of magnetic resonance imaging (MRI) studies describes large-scale structural changes in PD patients that are associated with cognitive deficits. Systematic reviews currently exist on voxel-based morphometry (VBM) and diffusion tensor imaging (DTI) correlates of cognitive dysfunction in PD (Ibarretxe-Bilbao et al., 2011; Monchi and Stoessl, 2012; Duncan et al., 2013), and so this review will briefly summarize the main findings from this literature. In particular, one consistent finding is that PD individuals with cognitive deficits or with dementia show reduced gray matter volume in the caudate, hippocampus, and prefrontal cortex, whereas in cognitively unimpaired PD individuals, volume in these regions is not significantly different from controls (Burton et al., 2004; Camicioli et al., 2004; Nagano-Saito et al., 2005; Apostolova et al., 2010; Melzer et al., 2012). Surprisingly, DTI studies have failed to show differences in fractional anisotropy or mean diffusivity of the striatal nuclei between PD individuals and controls (Chan et al., 2007; Gattellaro et al., 2009) or between PD individuals with versus without cognitive impairment (Theilmann et al., 2013; Zheng et al., 2014). Instead, executive function deficits in PD are correlated with reduced fractional anisotropy and increased mean diffusivity in white matter tracts of the frontal cortex like the cingulum (Theilmann et al., 2013; Zheng et al., 2014). This may be due to a limitation of the DTI technique in estimating tractography patterns of subcortical structures. However, diffusion imaging studies of cognitive function in PD are only beginning to be published; much more work is needed to determine if microstructural abnormalities of the basal ganglia are associated with executive function in PD.

Even in the absence of macroscopic structural differences, functional changes might be associated with cognitive decline in PD. Functional MRI (fMRI) and PET studies have attempted to localize the effects of neuropathology, genetic variation, and therapeutic medications on

cognition in PD. Early region-of-interest studies found that early-stage PD patients without cognitive deficit show increased lateral prefrontal activity relative to controls on working memory and set-shifting tasks that was normalized with dopaminergic medication (Cools et al., 2002; Monchi et al., 2004; Marié et al., 2007). However, patients with cognitive deficits show decreased activity in caudate, lateral prefrontal, and anterior cingulate regions on a number of tasks including Tower of London planning (Dagher et al., 2001), spatial working memory (Lewis et al., 2003; Ekman et al., 2012), and set-shifting (Nagano-Saito et al., 2014). Reduced metabolic activity in dorsal prefrontal regions has also been found to correlate with cognitive dysfunction in PD during the "rest" state (this activity is part of the "PD-related cognitive pattern"; Huang et al., 2007; Niethammer et al., 2013; Mattis et al., 2016). Taken together, these findings suggest that PD patients with cognitive deficits underrecruit key fronto-striatal regions associated with executive function, whereas in the cognitively intact, putative compensatory activity may ramp up in PFC to levels higher than healthy controls.

A few recent studies using resting state functional connectivity analysis have lent insight to broader, network-level contributions to cognitive decline in PD. Graph theory analysis has revealed stronger resting state connectivity between fronto-parietal regions and weaker connectivity between anterior medial frontal cortex and anterior striatum in association with more positive cognitive outcomes in PD (Lebedev et al., 2014). These results are in line with a recent seed-based analysis showing that lower connectivity between rostral anterior cingulate and dorsal anterior caudate was associated with better memory and visuospatial function in early-stage PD (Manza et al., 2016c). However, changes in fronto-striatal networks that are heavily modulated by DA are not the only network-level correlates of cognitive deficit in PD. An emerging literature suggests that diminished negative correlations between typically-opposing

networks may play a role in cognition in aging and neurological illness (Bai et al., 2008; Wu et al., 2011; Zhang and Li, 2012; Manza et al., 2015). Accordingly, Baggio et al., (2015) found that a reduction in negative connectivity (i.e., increased connectivity) between the default mode network and the dorsal attention network differentiated PD patients with cognitive impairment compared to cognitively intact patients. A challenge for future research is to track these network changes longitudinally and determine which networks contribute to the various forms of cognitive impairment observed in PD.

All of the aforementioned studies, while certainly not comprehensive, highlight the many complexities that need to be considered when trying to understand the neurobiological basis of cognitive dysfunction in PD. Keeping this larger framework in mind, this thesis will focus on a narrow portion of the PD literature, attempting to shed light on how dopaminergic medications affect one domain of cognition in early-stage PD.

CHAPTER II. REVIEW AND META-ANALYSIS OF COGNITIVE CONTROL IN PD: INTERACTION BETWEEN DISEASE DURATION AND MEDICATION STATUS

Introduction

Cognitive control, the ability to flexibly switch between actions to support daily needs, is a critical executive function and impaired in PD. Here, we focus on one vital component of cognitive control: response inhibition, the ability to suppress a pre-potent or habitual behavioral response. Of the various cognitive deficits that PD patients experience, (e.g., working memory, planning, and visuospatial attention) response inhibition is of particular importance for the recognition of its negative impact on patient quality of life (Schrag et al., 2000; Gauggel et al., 2004; Muntean and Perju-Dumbrava, 2012; Lawson et al., 2016) and its relevance for clinical outcomes in PD. Loss of response inhibition is associated with motor symptom severity (e.g.; Dujardin et al., 2013) and is suggested to be the critical factor in freezing of gait, a particularly debilitating feature of the disease (Lewis and Barker, 2009; Vandenbossche et al., 2012; Shine et al., 2013; Walton et al., 2015). In addition, a recent longitudinal study of PD patients with mild cognitive impairment found that Stroop performance at baseline showed the strongest predictive value in who would convert to dementia three years later, relative to semantic fluency, verbal learning, and visual perception (Pedersen, 2013). The tight link between response inhibition and broader clinical deficits has prompted discussion about using response inhibition performance as a sensitive outcome measure for cognitive impairment for PD (MacDonald and Byblow, 2015). Thus, great emphasis has been placed on understanding the neurochemical basis of this deficit, and in particular, the role of dopaminergic medication in response inhibition.

Early investigations probed the role of dopaminergic medications, particularly levodopa during response inhibition paradigms. However, unlike previous findings that dopaminergic medication improved task switching and working memory (Cools et al., 2002; Monchi et al., 2007; Ekman et al., 2012) several studies concluded that the medications did not provide significant response inhibition benefits to individuals with PD (Obeso et al., 2011; Alegre et al., 2013; George et al., 2013). Some studies in particular suggested that DA deficiency is not the critical factor in poor response inhibition, and other neurotransmitters, such as noradrenaline and serotonin, were postulated to play a more central role (Robbins and Roberts, 2007; Robbins and Cools, 2014).

Several studies in humans and animals have provided evidence that response inhibition is supported by neurotransmitters other than DA (Bari et al., 2009; Mayse et al., 2015). A number of studies have found that the noradrenaline uptake inhibitor atomoxetine provides benefit for response inhibition in healthy adults (Chamberlain et al., 2006, 2009), adults with attention-deficit hyperactivity disorder (ADHD; Chamberlain et al., 2007), and individuals with PD (Kehagia et al., 2014; Ye et al., 2014b; Rae et al., 2016). In PD, atomoxetine may exert its effects by increasing connectivity of prefrontal circuits critical for response inhibition (Borchert et al., 2016). The serotonin-boosting drug citalopram has also shown some beneficial effects on response inhibition in these populations (Ye et al., 2014b, 2016). Studies in rats have come to similar conclusions; while DA transporter blockade had minor effects on SST performance, atomoxetine improved SSRT (Bari et al., 2009). In addition, a recent study using optogentics found that non-DA cell bodies in the basal forebrain of rats were critical for implementing stopping behavior on the SST (Mayse et al., 2015). Thus, the role of DA in response inhibition

has been questioned and emphasis has been placed on other neurotransmitter systems in recent years.

However, some evidence from studies of other specific populations and healthy adults suggests that DA deserves reconsideration in response inhibition. Several studies found that a single dose of methylphenidate (which boosts DA as well as noradrenaline) improved response inhibition behavior in individuals with ADHD (Aron et al., 2003), cocaine dependence (Li et al., 2010) and in healthy adults (Nandam et al., 2011; Ivanov et al., 2014; but see Farr et al., 2014). More convincingly, PET studies have found that higher levels of striatal D_1 and D_2/D_3 receptors predict better performance on the SST (Ghahremani et al., 2012; Robertson et al., 2015) and that SST performance evokes DA release in prefrontal, parietal, and temporal cortex in healthy adults (Albrecht et al., 2014).

How then, can we reconcile these divergent findings? An important starting place is to consider the characteristics of the PD populations that did not show significant response inhibition improvement with dopaminergic medication (Obeso et al., 2011; Alegre et al., 2013; George et al., 2013). These studies typically include patients in the moderate-to-advanced stages of PD (i.e., Hoehn & Yahr stage III or later). This is problematic because of the well-known finding that DA loss is profound in the later stages of PD, and that dopaminergic drugs lose their efficacy when there are few remaining dopaminergic cells for the drugs to operate on (e.g.; Bravi et al., 1994). Thus, studies of moderate-to-advanced patients with PD may not be the best model for examining the role of DA medication effects.

To re-examine the effects of dopaminergic medications on response inhibition in PD with disease duration in consideration, we performed a meta-analysis of studies in PD populations that

used relatively common response inhibition paradigms (the SST, Go/No-Go, Simon, Flanker, Stroop, and anti-saccade tasks) and looked for an interaction between disease duration and medication status on response inhibition performance while controlling for effects of age. We hypothesized that studies enrolling patients in the earlier stages (H & Y I and II) of PD would show the largest benefit of dopaminergic medication, and hence show performance that was less severely affected relative to healthy controls.

Materials and Methods

We performed a literature search using PubMed (www.ncbi.nlm.nih.gov/pubmed) to identify studies that compared a PD cohort with an age-matched healthy adult group on one of six relatively common response inhibition tasks (Stop-Signal, Go-NoGo, Simon, Flanker, Stroop, and Antisaccade tasks). In September 2016 a systematic search was conducted using the terms [("Stop-Signal Task" OR "Stop Signal Task" OR "Go-NoGo" OR "Go NoGo" OR "GoNoGo" OR "Go/NoGo" OR "Go No-Go" OR "Antisaccade" OR "Anti-saccade" OR "Simon Task" OR "Flanker" OR "Stroop") AND (Parkinson OR Parkinson's)]. We only included articles that were from peer-reviewed journals and written in English. This initial search yielded 305 results. An additional 5 studies were identified from previous knowledge and recursive reference searching.

We then searched through the text of the initial 310 studies to screen for: 1) Review papers, case studies, book chapters or other non-original research papers; 2) evidence of dementia or surgical intervention (although some studies with a surgical intervention group had an additional PD cohort without surgery, and that data was included); 3) no adequate age-matched control group; 4) atypical versions of the response inhibition tasks that mixed response

inhibition with other complex behaviors (e.g., Go-NoGo tasks that had a reward component); 5) No information reported on medication status or disease duration for the PD group.

Forty-five comparisons from 38 studies remained after applying the exclusion criteria. Corresponding authors were contacted for studies that satisfied all other criteria but did not report sufficient statistics for response inhibition performance, and/or medication status and disease duration. This resulted in the addition of three studies. Thus, for the final analysis, data were was extracted from 48 comparisons from 41 articles and entered into a spreadsheet (for the full flow-chart, see **Figure 1**). No studies of the Flanker Task or the Simon Task remained after screening for exclusion criteria; thus, we only report on studies of the SST (k=9), Go-NoGo (k=6), Anti-Saccade (k=13), and Stroop tasks (k=20). For analysis, we chose the primary outcome measure of each response inhibition task that was most often reported across studies: for the SST, this was the stop-signal reaction time (SSRT), for the Go-NoGo/anti-saccade tasks, the commission error (false alarm) rate, and for the Stroop/Flanker/Simon tasks, the interference effect on response time (i.e., Incongruent RT minus Congruent RT). We coded studies based on whether patients were taking their normal dopaminergic medications ("on" medication) or if they underwent a medication washout of at least 12 hours ("off" medication) prior to study participation. We also included the average disease duration (years since diagnosis) and mean age of the PD group.

We used *Comprehensive Meta-Analysis* software version 3 to perform the meta-analysis (Borenstein et al., 2005). As in previous studies in this field (Kudlicka et al., 2011) we used a random-effects model. We calculated the effect size (Hedges' g) of mean between-group (PD versus control) differences in response inhibition performance for each study, which corrects for within-study variance that, among other causes, can be a consequence of small sample size. We

also assessed the heterogeneity (Q) and inconsistency (I^2) across studies. Heterogeneity is the ratio of between-study to within-study variance, and inconsistency refers to the ratio of heterogeneity to total variance across studies, i.e. the percentage of heterogeneity that results from differences between studies (Borenstein et al., 2009).

Lastly, we performed meta-regression (Houwelingen et al., 2002) to assess the relationship between PD duration and response inhibition performance in the medicated and unmedicated state. Meta-regression carries the same assumptions of a standard regression analysis, except that in the meta-regression here, each data point refers to the effect size of performance difference between the PD group and control group for an entire study, rather than, e.g., one individual's performance on a response inhibition task. Because effect sizes in this analysis are weighted by within-study variation, studies with the highest variability contribute the least to the regression model. In the final analysis, we performed two regressions: one that included the studies with PD patients "on" medication, and another regression with "off" medication studies. Both regressed average disease duration (years) on the effect size of response inhibition deficit (Hedges' g). We also ran additional multiple regression analyses that were identical except we included the average age of the PD group in each study as a covariate, to account for any potential effects of aging on response inhibition performance that may be independent of medication status and disease duration. Finally, to account for a possible diminution effect (the finding that effect sizes tend to be larger in older studies and diminish with replication in more recent studies; Ioannidis, 2005) we ran multiple regression analyses while including publication year is a covariate.

Results

The final sample included 48 comparisons from 41 studies which are described in **Table 1**.

To assess differences in response inhibition performance for PD on and off medication in comparison to healthy control, we extracted means and standard deviations from the PD and control groups from the critical outcome measure of each task: SSRT for the SST, false alarm rate for Go-NoGo and Anti-saccade tasks, and the Stoop interference effect (i.e., Incongruent RT minus Congruent RT); all outcome measures were continuous variables. If standard deviations were not reported (five studies), we extracted means for each group, or the mean difference between groups, and the *t*- or *p*-value of the PD vs. control comparison to calculate effect sizes. **Table 1** describes the samples included from each study, including average age and disease duration of the PD group. Effect sizes for each comparison are shown in the Forest plot in **Figure 2**. The average effect size across all comparisons was moderate and significant, suggesting that across all studies, patients with PD showed response inhibition deficits relative to their matched controls ("off" med: Hedges' g = -.86; "on" med Hedges' g = -.68; all studies; Hedges' g = -.73, all *p*'s < .001). The vast majority of studies find poorer performance among the PD group (47 out of 48 comparisons), but effect sizes were variable across studies, with 34 out of 48 studies showing a significant PD vs control group effect size in response inhibition performance. There was significant heterogeneity in the "off" and "on" samples ("off" med sample: Q = 36.97, $p < .001$, $I^2 = 67.54$; "on" med sample: Q = 52.93, $p = .02$, $I^2 = 35.76$), but heterogeneity did not significantly differ between medication status (Q = .11, $p = .74$). There was significant heterogeneity in the Anti-saccade (Q = 28.48, $p < .01$, $I^2 = 57.80$), Go-NoGo (Q = 11.61, $p < .05$, $I^2 = 56.94$) and Stroop tasks (Q = 34.90, $p < .02$, $I^2 = 45.53$), but not the SST (Q =

9.50, $p = .30$, $I^2 = 15.71$). However, heterogeneity did not significantly differ across the four tasks ($Q = 5.57$; $p = .13$).

To analyze how the effect size of PD vs. control group differences in response inhibition varied across studies with relation to disease duration and medication status, we performed a meta-regression with years of disease duration as the factor for both the "off" and "on" medication groups. For "on" versus control comparisons, the effect of disease duration was significant ($z = -2.81$, $r^2 = .47$, $p = .005$), however for "off" versus control comparisons, disease duration was not significantly associated with response inhibition deficits across studies, ($z = -0.87$, $r^2 = .00$, $p = .38$; **Figure 3**). In other words, in the "on" medication state, studies of patients with longer average disease duration showed more severe response inhibition deficits, whereas "off" dopaminergic medication, deficits were relatively unaffected by disease duration. Disease duration explained more variance in response inhibition deficits across studies with participants "on" medication compared to the "off" medication studies, and the test for differences in slopes is significant ($z = 2.34$, $p = .02$). The same pattern of disease duration effects remained even when age was controlled for in the regression analysis. Specifically, for both the "on" and "off" med samples, effect of age was not significant (z's < 0.9, p's $> .38$), and disease duration remained significant in the "on" med sample ($z = -2.67$, $p = .008$); but not the "off" med sample ($z = -.85$, $p = .39$). There was a significant effect of publication date for both the "on" and "off" med samples, such that earlier studies showed larger effect sizes between PD and controls (i.e., the diminution effect; z's > 2.2, p's $> .05$). However, including publication year as a covariate did not change the primary findings: the effect of disease duration remained significant in the "on" med sample ($z = -2.87$, $p = .004$) and not the "off" med sample ($z = .53$, $p = .53$).

Discussion

The primary results from the meta-analysis demonstrate that individuals with PD show deficits in response inhibition performance, specifically on tasks that test cognitive control of behavioral responses, including SST, Go-NoGo, Anti-saccade, and Stroop tasks. These deficits were of moderate effect size and significant for both the "on" and "off" medication samples, comparable to those in a previous meta-analysis examining a broader range of cognitive tasks in PD (Kudlicka et al., 2011). However, our meta analysis revealed an interactive effect of dopaminergic medication status and disease duration on response inhibition performance across studies. Specifically, "off" medication, patient groups tended to show moderate deficits relative to controls regardless of disease duration, but "on" medication, disease duration predicted the severity of response inhibition deficit. Thus, in the earlier stages of PD, patients on dopaminergic medication tend to show performance that is more comparable to healthy control levels.

These results suggest that disease duration is a very important factor when considering medication effects on response inhibition performance in PD. Previous work has compared dopaminergic effects on response inhibition directly within subjects "on" and "off" medication and emphasized null findings (Obeso et al., 2011; Alegre et al., 2013; George et al., 2013), but these studies tended to include patients with moderate to advanced PD (e.g., individuals with Hoehn & Yahr rating > 2 or with disease duration > 10 years). We suggest that these studies observed no significant effects of DA-replacement therapy because of severe loss of dopaminergic midbrain cells in the later stages of PD (Kish et al., 1988; Damier et al., 1999). It is routinely observed that dopaminergic drugs lose their efficacy in advanced PD (e.g., Bravi et al., 1994), putatively because diminishing numbers of DA cells render few targets for the drugs to exert their effects. Although the evidence is indirect, this study provides a starting point to

suggest that the role of DA in response inhibition deserves reconsideration, particularly in early-stage PD. Thus, a critical next step is to directly test dopaminergic medication effects on response inhibition in a within-study experiment with patients in the early stages of PD (see **Chapter III**).

It is important to consider the alternative possibility that impulse control disorders may play a role in these findings. One might hypothesize that advanced PD patients "on" medication show poor response inhibition due to increased likelihood of having impulse control disorders. It is estimated that 15-20% of individuals using dopaminergic medications long-term, especially DA agonists, are susceptible to developing impulse control problems over time (Weintraub et al., 2010). However, several lines of evidence suggest that impulse control problems would not be the most likely contributor to response inhibition deficits in PD. Recent studies have delineated separable neural and behavioral substrates of motivational vs. cognitive/motor impulsivity (e.g., gambling addiction vs. stop-signal inhibition; Bari and Robbins, 2013). While PD patients with impulse control disorders are prone to compulsive motivational behaviors including gambling, shopping, sex, and binge-eating (Weintraub et al., 2010), they do not demonstrate increased cognitive/motor impulsivity on the Stroop and SST compared to matched PD patients without impulse control disorder (Djamshidian et al., 2011; Claassen et al., 2015). Further, acute withdrawal of dopaminergic medication did not help improve impulsive error rates relative to the "on" medication state in the Simon task (Wylie et al., 2012b; van Wouwe et al., 2016). Thus, the type of impulsivity described with long-term medication use in PD does not map on well to the type of impulsivity implied in the response inhibition literature. There is some limited evidence that other clinical factors in PD such as motor subtype (tremor vs. postural instability) may play

a role in response inhibition capability (Wylie et al., 2012a); more work is needed to tease apart how these factors relate to medication use and response inhibition over the course of the disease.

Our findings correspond with several recent studies that found an association between dopaminergic function and response inhibition performance in both healthy adults and clinical populations (Aron et al., 2003; Li et al., 2010; Nandam et al., 2011; Ghahremani et al., 2012; Albrecht et al., 2014; Ivanov et al., 2014; Robertson et al., 2015). There are some notable exceptions: some studies in healthy adult humans (Hershey et al., 2004) and rats (Eagle et al., 2007; Bari et al., 2009) have used the SST and found that pharmacologically manipulating DA transmission had minor effects on response inhibition performance. There are several possible explanations for these seemingly discrepant findings. First, animal neurophysiology and behavioral performance may not translate directly to humans. Second, it is possible that there are subtle differences in how DA supports performance on different response inhibition tasks. Indeed, average response inhibition deficits in PD varied somewhat across the tasks reported in this meta-analysis (average Hedges' g: Antisaccade: -.85; Go-NoGo: -.35; SST: -.82; Stroop task: -.72), perhaps due to differences in task difficulty. For instance, no significant group differences were observed when accuracy was > 95% for both groups in one Go-NoGo study (Tachibana et al., 1997), whereas SSRT deficits can be profound on challenging stop-signal tasks that induce roughly 50% error rates on stop trials (Gauggel et al., 2004; Alegre et al., 2013). Others have noted that performance on Go-NoGo tasks often is close to ceiling, and thus may not be sufficiently sensitive to detect response inhibition deficits in PD (MacDonald and Byblow, 2015). Our findings that SST effect sizes were rather large and, compared to the other three tasks, had the least heterogeneity across studies, suggesting that the SST may be a more sensitive task for identifying response inhibition deficits in PD. Lastly, attempts to boost DA transmission

in healthy adults (Hershey et al., 2004) might not improve response inhibition performance because most healthy adults should presumably already have optimal levels of DA to support task performance, based on the inverted U-shape theory of dopaminergic function in cognition (Cools and D'Esposito, 2011). In support, Colzato et al., (2016) found that L-Tyrosine (DA precursor) administration improved SSRT only in the subset of healthy adults with the T/T polymorphism of the dopamine D2 receptor (DRD2), which confers low levels of striatal DA. These considerations highlight the need for systematic assessment of how DA may support response inhibition in various populations, using a variety of tasks and medications.

While this meta-analysis finds an association between dopaminergic medication and response inhibition performance, there is substantial evidence that other neurotransmitters also play a critical role in these behaviors in PD. Animal studies have found that drugs which alter noradrenaline and serotonin can have marked effects on response inhibition behavior (for a review, see Eagle and Baunez, 2010). This has prompted researchers to find non-dopaminergic therapies for response inhibition deficits in PD. Recent studies have reported some success with noradrenergic and serotonergic drugs in SST performance in moderate-to-advanced PD (Kehagia et al., 2014; Ye et al., 2014a, 2014b). A current challenge is to find optimal combination therapies that might promote response inhibition in PD. Given the current findings on how disease duration interacts with DA-replacement therapy, it seems likely that medication regimes for cognition may need to be adjusted throughout the course of the disease. These results also highlight the great need for regenerative medicine to restore the deteriorating dopaminergic system in PD (Li et al., 2016).

There are a number of limitations to acknowledge. While all meta-analyses must deal with many sources of heterogeneity across independent studies, studies of PD may include

additional sources of variance that cannot all be accounted for. The current study examined the role of disease duration and medication status in cognitive task performance, and controlled for the possible effects of age. Yet many variables are not consistently reported that could explain additional variance, such as drug type, dosage differences, motor subtype and global assessments of cognitive function. Investigators should strive to report levodopa dose equivalency values (Tomlinson et al., 2010), as well as comprehensive data on motor (Unified Parkinson's Disease Rating Scale; Goetz et al., 2007) and cognitive (Montreal Cognitive Assessment; Nasreddine and Phillips, 2005) function to help account for these variables. Other clinical differences across patient groups may also obscure findings, such as levels of comorbid depression and fatigue, which are common in PD and may relate to response inhibition performance. Another limitation regards sample size. We chose to select only studies that used relatively pure cognitive versions of response inhibition tasks, and hence could not report on the many studies that used variations on these paradigms, e.g. reward-based Go-NoGo tasks. Some reports did not include critical information on disease duration or medication status that precluded their inclusion in this meta-analysis. Therefore, while these results demonstrate a significant interaction effect of disease duration and medication status on cognitive performance in four specific tasks, future efforts should attempt to summarize findings from a larger body of literature. This work will be essential for describing how dopaminergic medications are related to cognitive deficits in PD more broadly.

Overall, results from this meta-analysis suggest in PD, response inhibition deficits are least severe relative to controls when patients are in early-stages of PD and "on" dopaminergic medications. Deficits are more severe in later stages of PD "on" medications, and under medication withdrawal, regardless of disease duration. This pattern of findings provides indirect

evidence that dopaminergic medications may support response inhibition in early-stage PD. We evaluate this theory directly in a within-subject study in **Chapter III**.

CHAPTER III. FMRI STUDY OF THE STOP-SIGNAL TASK IN EARLY-STAGE PD: EFFECTS OF DOPAMINERGIC MEDICATION

Introduction

The meta-analysis provided evidence that DA administration produces variable effects over the course of disease duration and may improve some aspects of response inhibition behavior in early-stage PD. However, direct evidence is still lacking. To this end, we performed a within-subject fMRI experiment of the SST in early-stage PD to examine whether dopaminergic medication improves response inhibition behavior and changes brain activation patterns. If this hypothesis is confirmed, the next important goal of this study was to provide some evidence for a possible mechanism behind the beneficial effects of DA. Previous studies in healthy adults have found some evidence for a role of DA in response inhibition. Striatal DA D1- and D2-receptor availability (Ghahremani et al., 2012; Robertson et al., 2015) and genetic polymorphisms affecting striatal and cortical DA release (Congdon et al., 2008, 2009, Kasparbauer et al., 2015a, 2015b) are linked to individual differences in SST performance and prefrontal, parietal, and basal ganglia activations. However, exactly what underlying component processes DA modulates to support response inhibition has remained unclear.

Recent theories suggest that there are two broad components to successful response inhibition performance: the first is fast, reactive inhibition that is relatively well studied and shown to involve a network of critical brain regions: the inferior frontal cortex, the pre-supplementary motor area, M1, and the striatum (Verbruggen and Logan, 2008; Duann et al., 2009; Elchlepp et al., 2016). Reactive inhibition is often assumed to be measured in the SST by examining brain activation patterns from discrete events on the task, such as comparing

successful stopping with go trials, and sometimes correlating these brain activations with SSRT (e.g., Zhang et al., 2015; Manza et al., 2016a). The second component comprises proactive control: slower, ongoing processes of trial observation, error-based learning, and behavioral adjustment, which are typically associated medial and lateral fronto-parietal regions, including supplementary motor area (SMA), pre-SMA, dorsal anterior cingulate (dACC), and inferior parietal lobule, as well as the striatum (IPL; Ide et al., 2013; Zandbelt et al., 2013; Hu et al., 2015). While it is becoming clear that these ongoing computations are a critical component of successful performance on the SST (and to various extents, virtually all cognitive control tasks), it is rarely tested directly and related to brain activation to identify neural correlates in a PD cohort.

Many studies have identified a critical role of cortico-striatal DA in computing prediction error signals that motivate behavioral adjustments (Schultz and Dickinson, 2000; Pessiglione et al., 2006; Schonberg et al., 2010), even in the absence of explicit reward (Horvitz, 2000; Friston et al., 2012; Galea et al., 2012). Recent evidence suggests proactive control processes are impaired in PD, in association with abnormal brain activation in cortical and subcortical regions (Criaud et al., 2016). There has been indirect evidence that regions modulated by DA promote proactive control during response inhibition tasks without explicit rewards (Yoon et al., 2015); for instance, substantia nigra fMRI activation covaries with trial-to-trial adjustments in RT during the SST (Boehler et al., 2011). Here we provide more direct evidence for this theory by testing whether dopamine medication improves SST performance in early-stage PD via proactive control in addition to the conventional SST analyses.

To do this, we used a Bayesian computational model that tracks participants' trial-to-trial changes in anticipation and unsigned prediction error ("surprise") to salient events (Shenoy et al.,

2010; Shenoy and Yu, 2011). Through this approach we can identify subtle, ongoing patterns of behavior and brain activation that may be modulated by dopamine and related to response inhibition in PD (Ide et al., 2013; Manza et al., 2016b). Given the broad role of the dopaminergic circuitry in supporting ongoing processes of anticipation and error processing (see Ullsperger, 2010 for a review), we hypothesized that a) dopaminergic medications would improve SST performance as indexed by the SSRT and b) medication-based improvement would be accompanied by altered behavioral and neural signatures of anticipation, prediction error, and behavioral adjustment. We attempted to minimize sources of clinical variability across individuals with PD by carefully recruiting patients only in the early stages of PD (Hoehn & Yahr I or II) with a very specific profile of pharmacological treatment (levodopa monotherapy or levodopa with azilect, a mild MAO-B inhibitor).

Materials and Methods

Participants

Behavioral cohort. Twenty individuals (5 females, mean age of 62.5 ± 10.4 years) diagnosed with PD participated in the study. This cohort participated in the experiment after a 12-hour PD medications washout procedure, (i.e. in the "off" medication state; average 16.8 ± 4.2 hours since last dose). Fourteen of the 20 participants with PD also had a second visit where they took their medications as normal ("on" medication state; average 2.1 ± 1.1 hours since last dose). The order of on/off sessions was counterbalanced. Thirty-seven healthy age-matched controls (22 females, mean age of 61.8 ± 8.0 years) participated for one session. Written consent was obtained from all participants and the study was performed under protocols approved by the Stony Brook Human Investigation Review Board.

fMRI cohort. A subset of the larger behavioral cohort also completed the fMRI portion of the experiment. This included 12 individuals with PD (4 female, mean age of 61.6 ± 10.2 years) "on" and "off" medications, and 15 healthy controls (6 female, mean age 64.7 ± 7.9 years) who performed the SST during fMRI.

All participants were free from medical, psychiatric and neurological illnesses (other than PD), and denied use of illicit substances. Further, all subjects demonstrated no evidence of mild cognitive impairment or dementia (all subjects scored ≥ 24 on the Montreal Cognitive Assessment; Nasreddine and Phillips, 2005). All PD subjects were diagnosed by a practicing neurologist and currently on a stable dosage of oral carbidopa-levodopa. Seven subjects were also taking 1mg/day of the MAO-B inhibitor Azilect. Subjects were not taking any other class of PD drugs including DA agonists, or drugs for cognitive impairment. Additionally, all subjects self-reported no evidence of impulse control disorder or hallucinations. A summary of the fMRI cohort demographics and clinical characteristics is presented in **Table 2**.

Behavioral Task

During fMRI, participants performed the stop-signal task (Logan et al., 1984) as in our previous work (Li et al., 2006, 2008; Ide et al., 2013; Manza et al., 2016a, 2016b). There were two trial types: go and stop, randomly intermixed. A small dot appeared on the screen to engage attention at the beginning of a go trial. After a randomized time interval (fore-period) between 1 and 5 s, the dot turned into a circle (the go signal), prompting the subject to quickly press a button. The circle vanished at a button press or after 1 s had elapsed, whichever came first, and the trial terminated. A premature button press prior to the appearance of the circle also terminated the trial. Approximately three quarters of all trials were go trials. The remaining one

quarter were stop trials. In a stop trial, an additional X, the stop signal, appeared after and replaced the go signal. The subjects were told to withhold their button press upon seeing the stop signal. The stop-signal delay (SSD) — the time interval between the go and stop signal — started at 200 ms and varied from one stop trial to the next according to a staircase procedure, increasing and decreasing by 67 ms each after a successful or failed stop trial (Levitt, 1971; De Jong et al., 1990). There was an intertrial interval of 2 s. Subjects were instructed to respond to the go signal quickly while keeping in mind that a stop signal could come up occasionally. However, subjects were not explicitly informed about the ratio of go:stop trials or the SSD staircase procedure. In the scanner, each subject completed four 10-min runs of the task. Depending on the actual stimulus timing (trials varied in fore-period duration) and speed of response, the total number of trials varied slightly across subjects in an experiment, but participants completed approximately 300 go trials and 100 stop trials over the course of the experiment. With the staircase procedure, subjects successfully withhold their response in approximately half of the stop trials, rendering roughly 50 stop success and 50 stop error trials in total. The stop-signal reaction time (SSRT) was computed by subtracting the critical stop-signal delay, or the estimated SSD required for a subject to get half of stop trials correct, from the median go RT (Li et al., 2008).

Trial by trial Bayesian estimate of the likelihood of a stop signal

As in our previous work (Ide et al., 2013; Hu et al., 2015; Manza et al., 2016b), we used a dynamic Bayesian model (Yu and Cohen, 2009) to estimate the prior belief of an impending stop signal on each trial, based on prior stimulus history. The model assumes that subjects believe that stop signal frequency r_k on trial k has probability α of being the same as r_{k-1}, and probability (1-

α) of being re-sampled from a prior distribution $\pi(r_k)$. Subjects are also assumed to believe that trial *k* has probability r_k of being a stop trial, and probability 1- r_k of being a go trial. Based on these generative assumptions, subjects are assumed to use Bayesian inference to update their prior belief of seeing a stop signal on trial *k*, $p(r_k|\boldsymbol{s_{k-1}})$ based on the prior on the last trial $p(r_{k-1}|\boldsymbol{s_{k-1}})$ and last trial's true category (s_k=1 for stop trial, s_k=0 for go trial), where $\boldsymbol{s_k}$={ s_1,…, s_k } is short-hand for all trials 1 through *k*. Specifically, given that the posterior distribution was $p(r_{k-1}|\boldsymbol{s_{k-1}})$ on trial *k-1*, the prior distribution of stop signal in trial *k* is given by:

$$p(r_k|\boldsymbol{s_{k-1}}) = \alpha\, p(r_{k-1}|\boldsymbol{s_{k-1}}) + (1-\alpha)\, \pi(r_k),$$

where the prior distribution $\pi(r_k)$ is assumed to be a beta distribution with prior mean *pm*, and shape parameter *scale*, and the posterior distribution is computed from the prior distribution and the outcome according to the Bayes' rule:

$$p(r_k|\boldsymbol{s_k}) \propto P(s_k|r_k)\, p(r_k|\boldsymbol{s_{k-1}}).$$

The Bayesian estimate of the probability of trial k being stop trial, which we colloquially call p(Stop) in this paper, given the predictive distribution $p(r_k|\boldsymbol{s_{k-1}})$ is expressed by:

$$P(s_k = 1|\boldsymbol{s_{k-1}}) = \int P(s_k = 1|r_k) P(r_k|\boldsymbol{s_{k-1}})\, dr_k = \int r_k P(r_k|\boldsymbol{s_{k-1}})\, dr_k = (r_k|\boldsymbol{s_{k-1}})$$

$$P(s_k = 1|\boldsymbol{s_{k-1}}) = \int P(s_k = 1|r_k) P(r_k|\boldsymbol{s_{k-1}})\, dr_k = \int r_k P(r_k|\boldsymbol{s_{k-1}})\, dr_k = (r_k|\boldsymbol{s_{k-1}}).$$

In other words, the probability p(Stop) of a trial *k* being a stop trial is simply the mean of the predictive distribution $p(r_k|\boldsymbol{s_{k-1}})$. The assumption that the predictive distribution is a mixture of the previous posterior distributions and a generic prior distribution is essentially equivalent to using a causal, exponential, linear filter to estimate the current rate of stop trials (Yu and Cohen, 2009). In summary, for each subject, given a sequence of observed go/stop trials, and the three model parameters {α, *pm*, *scale*}, we estimated p(Stop) for each trial.

Imaging protocol and preprocessing of brain images

Conventional T1-weighted spin-echo sagittal anatomical images were acquired for slice localization using a 3T system (Siemens Prisma; 64-channel head and neck coil). A single high-resolution T1-weighted gradient-echo scan was obtained. One hundred and seventy-six sagittal slices covering the whole brain were acquired with TR=2400ms, TE=2.24ms, flip angle = 8°, field of view = 256x256 mm, matrix = 320x320, 0.8mm^3 isotropic voxels. Functional blood oxygenation level dependent (BOLD) signals were then acquired with a gradient-echo echo-planar imaging (EPI) sequence. Fifty-two axial slices parallel to the AC-PC line covering the whole brain were acquired with multi-slice acceleration factor ("multiband") = 4, TR=1000 ms, TE=33 ms, flip angle=52°, field of view=210×210 mm, matrix=84x84, 2.5mm^3 isotropic voxels with no gap between slices. The parameters for the BOLD images were chosen based on the optimal recommendations made from the Human Connectome Project's extensive testing (Glasser et al., 2013; Uğurbil et al., 2013). However, we implemented some changes, including somewhat larger voxels (2.5mm^3 isotropic vs. the Human Connectome Project's 2.0mm^3 isotropic) after our own pilot testing indicated that 2.0mm^3 voxels resulted in substantial loss of temporal signal-to-noise ratio and severe signal dropout in subcortical regions. There were six hundred images in each session for a total of 4 sessions. During all BOLD sessions, physiological signals were recorded via the built-in Siemens Prisma hardware and the "Online" software setting. Respiration was recorded with a breathing band, and heart rate was recorded with a pulse oximeter.

Data were analyzed with Statistical Parametric Mapping (SPM12, Wellcome Department of Imaging Neuroscience, University College London, U.K.). High-resolution, multiband BOLD data is somewhat more susceptible to physiological and motion-related artifacts than more

traditional EPI sequences with lower spatiotemporal resolution. Therefore we took extra effort to minimize the influence of these sources of noise, including regressing out respiration and heart rate using a model-based Bayesian method with the DRIFTER toolbox in SPM12 (Särkkä et al., 2012; http://becs.aalto.fi/en/research/bayes/drifter/). Briefly, the interacting multiple models filter algorithm estimated the frequency trajectories of the physiological signals. A Kalman filter and Rauch-Tung-Striebel smoother separated the BOLD time courses into a cleaned activation-related signal, physiological noise, and white noise, and we used the cleaned activation-related signal for all analyses.

In the subsequent pre-processing of BOLD data, images of each participant were corrected for slice timing and realigned (motion-corrected). A mean functional image volume was constructed for each participant for each run from the realigned image volumes. These mean images were co-registered with the high resolution structural image and then segmented for normalization to the PD25 EPI MNI (Montreal Neurological Institute) atlas (Xiao et al., 2015) with affine registration followed by nonlinear transformation (Friston et al., 1995; Ashburner and Friston, 1999). Finally, images were smoothed with a Gaussian kernel of 6 mm at Full Width at Half Maximum. Images from the first 10 TRs at the beginning of each session were discarded to enable the signal to achieve steady-state equilibrium between radio frequency pulsing and relaxation.

Generalized linear models

Our goal is to identify neural correlates associated with the effect of dopaminergic medications on conventional SST measures of stopping ability, as well as measures of proactive control in individuals with PD. There four basic types of SST trial outcomes: go success (GS), go

error (GE), stop success (SS), and stop error (SE). Conventional SST contrasts include activations related to (SS + SE) vs. go trials and SS vs. SE trials. There were three measures of proactive control: anticipation (p(Stop)) and unsigned prediction error (UPE) of a stop signal, and RT slowing on go trials. Because p(Stop) is updated on a trial by trial basis, we posited that activations related to stop signal anticipation should arise at trial (fixation) onset (i.e., pre-stimulus) whereas activations related to RT slowing and UPE arise at go signal onset. Because the onsets of fixation point and go signal were on average 3 seconds apart, and the canonical hemodynamic response peaks at 6-10 seconds, it was not feasible to include both events in a single model to identify activations specific to each event (Huettel and McCarthy, 2000, 2001; Soon et al., 2003). It is suggested that an average lag of 6 seconds between two successive events is required to allow near-full separation (Huettel et al., 2009). Therefore, in the current study, we constructed two separate generalized linear models (GLMs), one describing the events of interest with fixation point and another with go signal onsets (Hu and Li, 2012; Hu et al., 2015).

In the first GLM, we modeled BOLD signals by convolving the onsets of the fixation point – the beginning – of each trial with a canonical hemodynamic response function (HRF) and the temporal derivative of the canonical HRF (Friston et al., 1995). Realignment parameters in all 6 dimensions were entered in the model. We included the following variables as parametric modulators in the model: p(Stop) of GS trials, SSD of SS trials, p(Stop) of SS trials, SSD of SE trials, p(Stop) of SE trials, in that order. Inclusion of these variables as parametric modulators improves model fit (Büchel et al., 1998; Hu and Li, 2012) and, specifically, the parametric modulator of p(Stop) would allow us to examine the neural correlates of anticipation for each trial type. Serial autocorrelation of the time series was corrected by the FAST model, which is an improvement over first-degree autoregressive or AR(1) model for high temporal resolution

images (Todd et al., 2016). The data were high-pass filtered (1/128 Hz cutoff) to remove low-frequency signal drifts. In the first level analysis, for each participant, we generated one contrast, with "1" assigned to the parametric modulators "p(Stop)" weighted by the proportion of trial number each of GS, SS, and SE trials to examine how deviations from the average BOLD amplitude are modulated by trial-by-trial estimate of the likelihood of a stop signal (Wilson et al., 2009; St. Jacques et al., 2011). That is, this contrast identified voxels with activation increasing with the likelihood that a stop signal would appear.

In the second GLM, we modeled the BOLD signals by convolving the onsets of the go signal of each trial with a canonical HRF and its temporal derivative. There were three goals: first, to identify activations to conventional SST measures: all stop trials versus go trials, and to successful stopping versus unsuccessful stopping. The second goal was to identify regional activations related to unsigned stimulus prediction error (UPE): |stimulus – p(Stop)|, where stimulus is 1 for a stop and 0 for a go trial RT (Ide et al., 2013). Third, we sought to identify regional activations to RT slowing (parametric increases in RT) while controlling for UPE. Thus, we included the following variables as parametric modulators: |0–p(Stop)| or p(Stop) of GS trials, RT of GS trials, SSD of SS trials, |1–p(Stop)| of SS trials, SSD of SE trials, |1–p(Stop)| of SE trials, and RT of SE trials, in that order. To examine UPE-related activations, we used a contrast "1" on the parametric modulators of UPE, weighted by the number of GS, SS, and SE trials. That is, this contrast identified voxels with activation increasing with the likelihood – a Bayesian belief – that a stop signal would appear in a go trial rather than in a stop trial, reflecting the discrepancy between anticipation and the actual outcome. In other words, this Bayesian surprise signal, or UPE related to stimulus outcome, should be positively correlated with p(Stop) on go trials, and negatively correlated with p(Stop) on stop trials. We also used a contrast "1" on

the parametric modulator of go RT to identify activations to increasing go trial RT (RT slowing). Note that, in SPM, a parametric modulator is orthogonalized with respect to its preceding parametric modulator. Thus, by placing UPE before RT we effectively controlled for activations related to UPE in the contrast for go RT.

In summary, for this study, we used the F model to examine activations related to one aspect of proactive control in the SST: stop-signal anticipation, or p(Stop). We used the G model to examine conventional SST measures of stopping: (SS + SE) > Go and SS > SE, as well as proactive control measures of RT slowing and UPE.

In the second level analysis, all images were evaluated at a voxelwise threshold of $p < .001$, with a cluster-level threshold of $p < .05$ family-wise error (FWE) corrected and a minimum cluster size $k = 10$. One-sample *t*-tests were performed on contrasts to obtain the group effect of the PD "on", PD "off", and control groups. Two-sample *t*-tests between control and PD "on", as well as control and PD "off" groups identified disease effects in voxelwise responses to Stop > Go trials, SS > SE trials, RT slowing, stop-signal anticipation and UPE. Paired *t*-tests for participants with PD in the "on" versus "off" state identified differences in voxelwise responses to Stop > Go trials, SS > SE trials, RT slowing, stop-signal anticipation and UPE as a result of dopaminergic medication.

Results

Behavioral performance. Analysis of behavioral performance on the SST revealed that Go RT did not significantly differ between the three groups, but SSRT was significantly higher in the PD OFF group relative to the other two groups (see **Table 3**, **Figure 5a**). This indicates a response inhibition deficit in this early-stage PD group when "off" medications that is

ameliorated with dopamine-replacement therapy. A similar pattern emerged for the sequential effect, as quantified by a correlation between p(Stop) and Go RT: the PD OFF group showed a significantly reduced sequential effect relative to when ON medication and to controls (**Figure 5b**). To determine if medication-related improvement in response inhibition was related to medication-based differences in trial-to-trial behavioral adjustment, we ran an across-subject correlation between change in SSRT and change in sequential effect "on" vs. "off" dopaminergic medication. Indeed, greater benefits in response inhibition (reduction in SSRT) was associated with an increased sequential effect "on" compared to "off" medication (r = -.54, p = .04; **Figure 5c)**. One data point was an outlier according to the rule of thumb: Cooks' D > 4/n, where n is the number of data points (outlier is the bottom-left most point in **Figure 5c**; Cooks' D = .82, threshold = .29). Without the outlier, the correlation is stronger and remains significant (r = -.80, p = .001). Thus, dopamine-mediated improvements in response inhibition are associated with increased Bayesian trial-to-trial adjustment. Change in SSRT was not significantly associated with change in UPDRS III motor symptom severity ratings "on" vs. "off" dopaminergic medication (r = -.24; p = .41), suggesting that medication-based improvement in response inhibition performance was not tightly linked with alleviation of motor symptoms.

fMRI results. We first examined regional activations in each group that were specific to traditional measures of stop-signal inhibition (i.e., Stop vs. Go, SS vs. SE; **Figure 6a,b**) as well as Bayesian measures of trial-to-trial learning and behavioral adjustment (i.e., RT slowing, (p)Stop and UPE; **Figure 7**). In one-sample t test, each group showed significant activations to the (SS + SE) > Go contrast, with activation clusters in regions typically associated with SST performance: bilateral insula/inferior frontal gyrus (IFG), bilateral primary and association visual cortices, superior temporal gyrus, dACC, and pre-SMA. The control and "on" groups showed

additional suprathreshold activations in thalamus, caudate, and dorsolateral prefrontal cortex (dlPFC). The "on" group also showed suprathreshold activation in superior parietal lobule. In the reverse contrast (Go > Stop), all three groups showed significant activation in sensorimotor cortex. For the SS > SE contrast, the control and "on" groups showed activation in visual cortex. In the reverse contrast (SE > SS), all three groups showed significant activation in midcingulate cortex, SMA, sensorimotor cortex, middle occipital gyrus, calcarine sulcus, and cerebellum. The control and "on" groups showed additional activations in thalamus, caudate and insula/IFG, and the "on" group only showed activation in posterior cingulate. For the proactive control measures, the control group showed significant UPE-related activation in right lateral parietal cortex. The "on" group showed significant RT slowing activations in SMA, right insula/IFG, and right SMG/angular gyrus/IPL, and stop signal anticipation, or P(stop)-related activations in right dlPFC, right angular gyrus/IPL, and cerebellum. The "off" group showed no significant activations for all three proactive control measures (although some activations are seen to some extent at a much more lenient threshold of $p < .05$, uncorrected).

In two-sample t tests, voxelwise analysis revealed no significant differences between the PD groups and control group for any of the conventional SST contrasts nor the proactive control measures. Because of our relatively small sample size, it is possible that the two-sample analysis was not sufficiently powered for voxelwise analysis. Thus, to examine any weaker group differences that did not survive whole-brain correction for multiple comparisons, we performed additional region-of-interest analysis for the following key regions relevant to SST performance and PD, using masks from our previous work: SMA, pre-SMA, right IFG, primary motor cortex (M1), ventral/dorsal caudate, and anterior/posterior putamen (Leung and Cai, 2007; Hu et al., 2015; Manza et al., 2015, 2016c). For each group, we extracted a contrast value for each of the

conventional and proactive control analyses from the average of all voxels within each mask (**Figure 8**). At the uncorrected $p < .05$ level, the following effects were observed: for Stop > Go, the "on" group showed significantly higher activations in anterior putamen and pre-SMA, while for Go > Stop, the "off" group showed lower M1 activation than controls. For SE > SS, the "on" group showed significantly higher activation in caudate than controls. For RT slowing, both "on" and "off" groups showed higher activation in rIFG than controls. For P(stop), the "on" group showed higher activation in dorsal caudate. For UPE, the "off" group showed higher activation in rIFG.

In whole-brain paired t tests for PD "on" vs "off", we found no significant medication-based differences for any of the conventional SST contrasts. However, significant medication-based differences emerged for each of the three proactive control measures (**Table 4; Figure 9**). In the "on" compared to "off" medication state, PD participants showed significantly higher activation in association with RT slowing in posterior pre-SMA/SMA, left dlPFC, and bilateral IPL. Participants in the "on" state also showed higher activations in association with p(Stop) in left IPL compared to when "off" medication. However, "on" medication, PD participants showed significantly lower activations in association with UPE in left sensorimotor cortex and left premotor cortex than when "off" dopaminergic medication.

Discussion

We find that dopaminergic treatment improved SST performance in the early stages of PD, in contrast to previous studies that included participants with moderate-to-advanced PD. Bayesian modeling of SST performance coupled with fMRI provided convergent evidence for a

novel mechanism by which dopamine improves response inhibition, centered on proactive control, anticipation of salient stimuli, and trial-to-trial behavioral adjustment.

Improvement in response inhibition performance and trial-to-trial behavioral adjustment with dopaminergic medications. We observed that PD patients withdrawn from dopaminergic medications had significantly longer SSRT compared to healthy age-matched controls, replicating many previous studies showing a response inhibition deficit in PD (e.g., Gauggel et al., 2004; see meta-analysis in **Chapter II**). However, dopaminergic medication ameliorated this deficit, improving SSRT 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 in a within subject design. There is some evidence that dopaminergic medications improve patient performance on other response inhibition paradigms such as anti-saccade (Hood et al., 2007) and Go-NoGo (Pessiglione et al., 2005) tasks. We speculate that previous studies failed to see significant dopaminergic effects on SSRT because they typically used across-subject designs and tended to include participants in the later stages of PD, when dopaminergic medications are less effective (see meta-analysis in **Chapter II** for a more thorough discussion on this).

Dopaminergic improvement in SSRT may stem from an improved ability to exert proactive control: the Bayesian modeling approach revealed that medication-based improvements in SSRT were correlated with medication-based increases in sequential effect (correlation between go RT and anticipation of stop signal). This finding is consistent with recent work showing that PD patients "on" medications demonstrate relatively intact proactive control behavior on a Simon task (Wylie et al., 2010; van Wouwe et al., 2016). Interestingly, dopaminergic medications do not appear to improve proactive control on a simple visual RT task (Favre et al., 2013), which hints at a possibility that proactive control is not a unitary cognitive

resource. In PD, proactive control to support movement initiation may be less amenable to levodopa than proactive control to support response inhibition. However, it is important to note that Favre et al. (2013) recruited patients with more advanced PD than in this study, and therefore medications may have been less efficacious in these individuals more generally.

We must consider the possibility that medication-based differences in behavior were somewhat related to motivation, which is intimately linked with DA function (Berridge and Robinson, 1998; Cools, 2008; Bromberg-Martin et al., 2010; Chong et al., 2015) and has been shown to wane during dopaminergic medication withdrawal in PD (Czernecki et al., 2008; Chaudhuri and Schapira, 2009; Thobois et al., 2010; Lhommee et al., 2012). We could not directly measure levels of motivation with the current task design. Therefore we could not assess if medication-based changes in anticipation and behavioral adjustment are tied to changes in motivation. Several studies have found that enhancing motivation through reward incentives boosts proactive control (Beck et al., 2010; Chiew and Braver, 2014, 2016). In addition, there is some limited evidence from studies of schizophrenia (Zandbelt et al., 2011) and catechol-O-methyltransferase (COMT) genotyping (Jaspar et al., 2013) that optimal levels of DA may play a role in supporting proactive control processes. Still, to our knowledge, no research has bridged the gap in understanding how dopaminergic medication, proactive control processes, and levels of motivation are all interconnected. This data would be critical for understanding how the complex interplay between neurochemistry, cognition and motivation produces diverse clinical outcomes in PD and other neurological diseases such as schizophrenia.

We found no significant differences in brain activation for the conventional SST contrasts (Stop > Go and SS > SE) between the "on" and "off" medicated state in individuals with PD. Although this has not been explicitly tested before in a within-subject design, one might expect

that levodopa would boost stop-related activation in IPL and IFG, given that these brain regions show hypoactivation in drug naïve PD relative to controls during stopping in the SST (Vriend et al., 2014). Yet response inhibition studies in healthy adults have shown that fronto-parietal stop-related activations may be influenced by DA challenge (methylphenidate) in opposing directions, depending on SLC6A3 and COMT genotype (Congdon et al., 2009; Kasparbauer et al., 2015b). Thus, potential genetic differences in our sample may wash out when looking at group averages in BOLD response; future studies should examine if the differences in healthy adults extends to a PD cohort. Nevertheless, differences in brain activation were observed for each of our proactive control measures. These data cannot rule out a role for DA in the conventional SST measures of stopping efficiency, especially because we do not have genetic data for these participants. Instead, we argue that DA plays a relatively larger role in neural processing of proactive control, or at least that our proactive control measures were more sensitive to dopaminergic effects. This would be in line with reports that healthy aging in general, which is associated with marked loss of DA (Volkow et al., 1998, 2000), is associated with much greater deficits in proactive control than reactive control (Bugg, 2014).

Dopamine boosts fronto-parietal activations to proactive control. We found that in PD, dopaminergic drugs increased activations to RT slowing in posterior pre-SMA/SMA and left dlPFC, and increased activations to both RT slowing and stop-signal anticipation in IPL. We have found previously that these regions promote proactive control in the SST in healthy adults (Ide et al., 2013; Hu et al., 2015). The posterior pre-SMA/SMA cluster identified here may be a frontal locus for RT-based proactive control in the SST, as its' activation reflects trial-to-trial differences in go RT within subjects (Hu et al., 2015) as well as between-subject differences in average response times (Hu et al., 2014). Prominent theories suggest that midbrain DA cells

support the anticipation of salient stimuli, even in the absence of explicit reward (Horvitz, 2000), which send cascading signals through an insula-dorsal anterior cingulate-SMA network to generate goal-directed motor output during cognitive control (Menon and Uddin, 2010; Uddin, 2015; Cai et al., 2016). In support, a study of concurrent EEG/subthalamic nucleus recordings of PD patients reported oscillatory coherence between basal ganglia and SMA in association with dopaminergic treatment, which may promote fronto-basal ganglia circuit coordination to generate appropriate motor output (Williams et al., 2002). More recent PET and fMRI studies in healthy adults have reached similar conclusions. Increased DA release in the posterior pre-SMA was associated with faster learning of motor sequence output (Garraux et al., 2007), and depleting DA precursors (phenylalanine/tyrosine) decreased brain activation in this region along with impaired timing of motor output on a perceptual task (Coull et al., 2012). In sum, the posterior pre-SMA/SMA is heavily modulated by DA and supports proactive adjustments in RT to generate appropriate motor responses for cognitive control.

The IPL also showed DA-dependent modulation to RT slowing and additionally to anticipation, as indexed by P(stop). This region is a core node of the ventral attention network, and has been heavily implicated in the detection of salient stimuli (Bunge et al., 2002; Corbetta and Shulman, 2002). Recent behavioral work has demonstrated that patients with PD are impaired at combining prior knowledge with the evaluation of incoming sensory information to adjust decision thresholds and select appropriate actions (Perugini et al., 2016). The IPL is well-situated to integrate these behaviors, as it supports ongoing attentional demands during the SST (Cai and Leung, 2011), anticipation based on accumulation of evidence from prior experience (Ide et al., 2013; Hu et al., 2015) and salient stimulus detection (Bunge et al., 2002; Corbetta and Shulman, 2002). Our results show that IPL activation is associated with these behaviors during

SST performance and is modulated by DA. It is possible that DA release in the IPL supports the integration of anticipation and stimulus detection. Indeed, in healthy adults, DA is released in IPL during SST performance relative to a baseline go only task (Albrecht et al., 2014). Additionally, methylphenidate challenge is associated with lower IPL activation in conditions of high uncertainty/UPE (i.e., low anticipation) during probabilistic learning and SST performance (Schlösser et al., 2009; Manza et al., 2016b). A wealth of data implicates parietal dysfunction in association with various PD-related cognitive deficits (Huang et al., 2007; Weintraub et al., 2011; Ekman et al., 2012, 2014; Pereira et al., 2014; Danti et al., 2015). Our study suggests that fundamental processes of anticipation and stimulus detection in the IPL may be particularly disrupted in PD and could underlie broader cognitive impairment.

Dopamine decreases "surprise" activation in premotor cortex. The left premotor cortex showed significantly lower activations to UPE, or Bayesian surprise, in the "on" versus "off" medication state. We find that medication increases behavioral and neural signatures of anticipation/proactive control. Therefore we interpret decreased premotor activation as an increased preparation to stop when encountering a surprising stop signal. This interpretation is in line with recent behavioral studies. PD patients "off" medication showed deficits in cognitive control of movement only when they had to respond to an unexpected trial type that was presented during a mostly predictable sequence—hence, they were selectively impaired at flexibly responding to highly surprising stimuli—and this impairment was ameliorated with levodopa (Galea et al., 2012). This deficit was replicated in healthy adults who were given the D1/D2 receptor blocker haloperidol, confirming a role for DA in this behavior (Bestmann et al., 2015). These findings have been related to the active inference model, which postulates that DA both supports Bayesian belief updating (anticipation) and compares incoming sensory

information with prior expectations. This dual role allows DA to calculate UPE and generate fast reprogramming of behavior when encountering surprising stimuli (Friston et al., 2012). Here, we find a novel neural correlate of how DA deprivation impairs cognitive control in situations that elicit large prediction error, reflected in hyperactive premotor responses to UPE.

During SST performance, the premotor cortex is theorized to generate the "go" command, sending signals to the basal ganglia to disinhibit the thalamus and excite motor cortex (Aron et al., 2007; Li et al., 2008). It is possible that in the "off" state, decreased preparation to stop results in increased premotor signals to initiate an action at inappropriate times (i.e., when a surprising stop signal appears). This interpretation is broadly consistent with work showing that premotor cortex is hyperactive in PD relative to controls when initiating simple movements (Haslinger et al., 2001) and when selecting movements based on a cue (Toxopeus et al., 2012), with the hyperactivity normalized after levodopa intake. This dysfunctional activity may relate to more general issues with cortical metabolism in PD, as FDG-PET studies find that metabolic activity is disrupted in premotor cortex in association with PD-related cognitive deficit on the Stroop inhibition task (Huang et al., 2007; Mattis et al., 2016).

Another explanation for our finding relates to reliance on lateral prefrontal circuits in the DA-deprived state. A recent study using dynamic causal modeling found that "off" medication, compensatory hyperconnectivity of lateral premotor cortex with dlPFC supports cognitive control of externally-cued movements; when "on" medication, a mesial prefrontal circuit involving prefrontal-SMA connectivity is restored to support action selection (Michely et al., 2015). Our work extends the specificity of this finding by showing that DA supports cognitive control of movement via stimulus anticipation in SMA/IPL and decreased surprise activation in premotor cortex. In other words, it is possible that "off" medication, disrupted top-down

anticipatory activity in SMA/IPL renders a greater reliance on bottom-up processing of sensory stimuli, leading to slower detection of surprising stop signals and inappropriate generation of go commands in premotor cortex. Thus, by combining our computational modeling approach with fMRI, we have added empirical evidence for neural substrates of behavior predicted by the active inference model of DA (Friston et al., 2012; Galea et al., 2012), which may explain cognitive control deficits in PD more generally.

fMRI results: disease effects. We did not observe significant differences in brain activation between controls and PD "on" or "off" groups for any of our comparisons. Previous fMRI studies of the SST with larger samples have observed brain activation differences between controls and medicated (Rae et al., 2016) or *de novo* (Vriend et al., 2014) PD participants, and we suspect our null results are due to the relatively small sample size in our fMRI cohort (n = 15 controls; n = 12 PD). The hypothesis driven ROI analysis (Figure 8) did reveal some potential group differences similar to previous findings. Between-group differences will be revisited as we enroll a larger sample size that is more appropriate for this type of analysis. Within-subject comparisons benefit from lower variance than between-subject analysis, which likely explains why, in contrast to the two-sample t-tests, we were able to observe significant differences in the "on" versus "off" medication paired t-test analyses.

Limitations. A common limitation of studies that manipulate dopaminergic drug intake in PD, including the current study, is a lack of a true double-blind placebo experimental design. Additionally, patients with PD take different drug dosages, which could lead to additional between-subject variance in medication effects. However, because there is an optimal range of DA to support cognition (i.e., the inverted U-shaped theory of DA; Cools, 2015), it could be equally or more important to have each individual taking their optimal dosage for treatment.

Another important issue relates to strategies that participants use to complete the SST. The computational model here assumes that subjects use Bayesian inference to speed and slow responses following stop and go trials, even though there is a fixed ratio of stop:go trials that appears at random. Hence, trial history does not predict subsequent trial outcomes. Still, a large literature in humans and monkeys shows that individuals do seem to use this strategy for adjusting responses (Emeric et al., 2007; Shenoy et al., 2010; Shenoy and Yu, 2011; Ide et al., 2013). Further, a recent study with a modified Go/NoGo task found that even when participants knew with certainty what the upcoming trial outcome would be, they still showed a reliable sequential effect (Verbruggen et al., 2016). Therefore, healthy individuals seem to rely on this strategy for task performance, and this ability appears to be disrupted in PD.

In summary, these findings describe novel neural correlates of specific proactive control processes that may explain aberrant cognitive control behavior in PD. In early-stage PD, dopaminergic drugs improve SSRT in tandem with increased Bayesian trial-to-trial adjustments. DA appears to boost fronto-parietal activations to stimulus anticipation and adjustments in RT, and decreases premotor activation to surprise. Thus, DA appears to benefit cognitive control by supporting neural and behavioral signatures of anticipation and ongoing RT adjustments across trials.

CHAPTER IV. GENERAL DISCUSSION

The two studies presented here provide evidence that DA deserves reconsideration of its role in response inhibition, especially in PD. The meta-analysis showed that across studies, medicated patients tended to have less severe deficits in early-stage than late-stage PD. The fMRI study provided direct evidence that dopaminergic medication improves SST performance and boosts fronto-parietal proactive control processes in early-stage PD. There are several interesting possibilities for further research on this topic.

A primary limitation here is the sample size of the fMRI study; it is possible that our fMRI results are subject to type II error, and so replication in a larger cohort is necessary. With a larger sample size, we will also be able to examine subgroup performance, e.g., sex effects. This would be useful given recent findings that women display higher levels of behavioral adjustment across trials on response inhibition tasks as indexed by post-error slowing (Thakkar et al., 2014; Fischer et al., 2016), and that pre-SMA and IFG activations during the SST differ in adolescents based on a COMT genotype by sex interaction (White et al., 2014). It remains unknown how dopaminergic drug administration alters SST performance and brain activation in PD based on sex. If substantial interactive effects exist, this information would be critical for tailoring drug therapies on an individual basis to promote healthy cognition.

We cannot rule out the possibility that DA-replacement therapy affects cerebral blood flow (Lerner et al., 2016), which impacts the BOLD signal and has recently been related to cognitive impairment in Alzheimer's disease (Leeuwis et al., 2016). However, some studies have concluded that carbidopa-levodopa does not significantly alter cerebral blood flow (Henriksen and Boas, 1985; Hershey et al., 2000, 2003). Still, future studies in this domain could include arterial spin labeling (ASL) sequences to control for any subtle blood flow differences based on

medication use. Further, it remains unclear if prolonged use of dopaminergic medication actually impairs response inhibition directly, and whether this has some relationship with impulse control disorders in PD (although the extant evidence suggests that the latter suggestion is probably not the case, see Discussion section of **Chapter II**). A recent study in de novo (never medicated) PD found no significant deficit in SSRT compared to healthy controls (Vriend et al., 2014). It remains unclear if this is because a) the DA circuity is relatively intact in the very earliest stages of PD, b) long-term medication use actually has negative consequences for response inhibition, or c) compensatory effects cover up behavioral changes in the early-stage unimpaired PD patients (Poston et al., 2016). To address the first two possibilities, future studies should compare a de novo PD cohort with a medicated PD cohort in the "off" state, matched on disease severity, to disentangle effects of long-term medication use with disease-related deterioration of the DA systems. For the latter issue we suggest that the Bayesian modeling approach employed here would yield critical information about what component processes of response inhibition are disrupted first and what processes may be putatively compensatory in de novo PD.

To further specify the nature of response inhibition deficits in PD, data from multiple different analyses and imaging modalities could be combined. We collected DTI and resting state fMRI data along with the SST data. An important next step is to examine the integrity of structural and functional connections in these patients. While we previously focused on functional connectivity of the basal ganglia nuclei in PD (Manza et al., 2016c) our results here merit investigations into DA-dependent changes in fronto-parietal connectivity in association with response inhibition performance. Recent studies have found some evidence for this using broader assessments of cognition (Lebedev et al., 2014; Baggio et al., 2015). Finally, follow-up studies with simultaneous PET-fMRI could localize changes in DA release based on medication

status during task performance. It would be useful to see how these patterns differ across individuals and longitudinally. This work could be used to identify individuals who are likely to receive cognitive benefit from dopaminergic medication, and ultimately aid in tailoring treatment for the notoriously unmanageable cognitive symptoms of PD.

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Table 1. PD versus healthy control comparisons included in the meta-analysis. Forty-eight comparisons were used from 41 published studies. Med, Medication status (On or Off dopaminergic medications); CTRL, healthy controls; LEDD, Levodopa-dose equivalency; MMSE, Mini-mental state examination; A-S, Antisaccade; GNG, Go-NoGo; SST, Stop-Signal Task; N/A, Not available. NOTE: † denotes that more than one contrast was included from the same published study.

Med	Task	Author	Year	Journal	N, PD	N, CTRL	Age PD	% Female	Duration	LEDD	MMSE
Off	A-S	Amador	2006	Neurospsychologia	14	11	60.0	42.8	12.0	N/A	N/A
Off	A-S	Briand	1999	ExpBrainRes	8	8	73.9	25.0	8.5	N/A	26.8
Off	A-S	Hood†	2007	JNNP	14	14	59.9	35.7	14.7	N/A	27.9
Off	A-S	Lemos	2016	Brain Res	19	22	67.0	36.8	4.0	691	29.0
Off	A-S	Nemanich†	2016	Clin Neurophys	13	12	68.1	38.5	4.7	691	N/A
Off	GNG	Cohen	2014	J Parkinson's Dis	15	16	67.1	14.3	6.5	714	N/A
Off	GNG	Farid	2009	Mov Disord	9	9	61.0	22.2	10.0	1060	N/A
Off	GNG	Nemanich†	2016	Clin Neurophys	13	12	68.1	38.5	4.7	691	N/A
Off	SST	George†	2013	Neuroimage Clin	16	16	62.6	50.0	4.9	N/A	28.9
Off	SST	Obeso†	2011	Exp Brain Res	17	16	69.4	29.0	9.5	915	29.4
Off	Stroop	Bohnen	2006	J Neurol	13	14	70.8	0.0	5.9	N/A	28.1
Off	Stroop	Costa†	2014	Behav Neurol.	13	15	68.1	55.0	2.2	N/A	27.6
Off	Stroop	Fera†	2007	Brain Res Bull	12	10	59.9	50.0	3.5	489	28.4
On	A-S	Bonnet	2014	Pl0sOne	21	27	54.8	38.1	9.6	N/A	27.6
On	A-S	Cameron	2010	Neurospsychologia	14	12	60.1	28.6	4.9	N/A	29.1
On	A-S	Harsay	2010	Front Agi Neuro	20	18	61.8	0.5	7.0	N/A	N/A
On	A-S	Hood†	2007	JNNP	14	14	59.9	35.7	14.7	N/A	27.9

On	A-S	Rivaud-Péchoux	2007	Brain	15	10	64.3	26.7	6.6	N/A	N/A
On	A-S	vanKoningsbruggen	2009	Neuropsychologia	19	20	66.6	31.6	7.1	N/A	>27
On	A-S	vanStockum	2008	Neuropsychologia	18	18	65.7	33.3	8.8	N/A	N/A
On	A-S	Walton	2015	J Neurol	34	38	66.4	32.0	6.5	N/A	28.2
On	GNG	O'Callaghan	2013	Cortex	25	15	64.5	36.0	7.3	897	28.0
On	GNG	Tachibana	1997	J Neurol Sci	29	19	63.9	70.0	6.0	N/A	27.2
On	GNG	Ye†	2014	Brain	21	20	64.0	47.6	10.8	633	28.9
On	SST	Claassen	2015	Pharm Biochem Beh	12	12	60.8	N/A	6.1	520	29.0
On	SST	Gauggel	2004	JNNP	32	32	57.8	46.9	9.0	N/A	N/A
On	SST	George†	2013	Neuroimage Clin	16	16	62.6	50.0	4.9	N/A	28.9
On	SST	Obeso†	2011	Exp Brain Res	17	16	69.4	29.0	9.5	915	29.4
On	SST	Rae	2016	Brain	19	10	69.4	31.5	9.8	1080	28.5
On	SST	Stefanova	2014	J Int Neuro Soc	36	33	64.7	N/A	10.1	720	27.9
On	SST	Ye†	2014	Brain	21	20	64.0	47.6	10.8	633	28.9
On	Stroop	A'Campo	2012	Int J Clin Pract	35	29	65.5	43.0	6.0	N/A	27.4
On	Stroop	Bohlhalter	2009	Behav Brain Funct	12	12	59.1	33.3	7.7	766	28.5
On	Stroop	Brown	1988	Brain	16	16	60.3	31.3	11.6	566	N/A
On	Stroop	Costa†	2014	Behav Neurol.	13	15	68.1	55.0	2.2	N/A	27.6
On	Stroop	Fera†	2007	Brain Res Bull	12	10	59.9	50.0	3.5	489	28.4
On	Stroop	Hanes	1996	ArchClinNeuropsy	26	25	62.6	44.0	7.0	N/A	N/A
On	Stroop	Hsieh	2008	Kaohsiung J Med Sci	26	27	63.5	37.0	3.3	N/A	N/A

On	Stroop	Kierzynka	2011	Neual Neuochir Pol	37	40	61.0	59.5	6.2	N/A	28.7
On	Stroop	McNamara	2003	JNNP	24	15	70.2	0.0	8.0	N/A	27.0
On	Stroop	Müller-Oehring	2015	Brain Imaging Beh	11	11	63.0	54.5	3.1	473	N/A
On	Stroop	Ranchet	2011	JNNP	25	25	65.4	24.0	6.4	N/A	28.1
On	Stroop	Ranchet	2013	Mov Disord	19	21	66.1	10.5	7.5	742	N/A
On	Stroop	Relja	2006	J Neurol Sci	25	25	63.0	40.0	5.4	N/A	28.2
On	Stroop	Vandenbossche	2012	Neuroscience	14	14	68.0	21.0	8.2	N/A	28.4
On	Stroop	Wild	2013	J Neurol	18	18	69.3	55.6	8.4	N/A	26.4
On	Stroop	Witt	2006	Neuropsychologia	22	22	58.0	27.3	8.1	599	N/A
On	Stroop	Woodward	2002	Neuropsychologia	30	34	69.3	53.3	5.8	N/A	>23

	N, PD	**N, CTRL**	**Age PD**	**% Female PD**	**Duration**	**LEDD**	**MMSE**
Avg OFF	13.5	13.5	65.8	33.7	7.0	750	28.3
Avg ON	21.4	20.3	63.8	37.1	7.4	695	28.2
Avg A-S	17.2	17.2	63.7	31.2	8.4	691	28.1
Avg GNG	18.7	15.2	64.8	38.1	7.6	799	28.0
Avg SST	20.7	19.0	64.5	40.6	8.3	797	28.9
Avg Stroop	20.2	19.9	64.6	37.2	6.0	589	27.9

Table 2. Participant demographics and clinical characteristics for the stop-signal task experiment. Note: Subj, Subject; Yrs Edu, Years of Education, H&Y, Hoehn & Yahr, LEDD, Levodopa Dose Equivalency; GDS, Geriatric Depression Scale; STAI, State-Trait Anxiety Inventory (trait score only used here); BIS-11, Behavioral inhibition scale-11; TMT, Trail Making Test; MOCA, Montreal Cognitive Assessment; UPDRS, Unified Parkinson's Disease Rating Scale; Lev, Carbidopa-Levodopa Monotherapy; Lev + A = Carbidopa-Levodopa and Azilect

Subj No	Age	Sex	Yrs Edu	Hand	Yrs since diagnosis	H&Y	Drug status	LEDD	GDS	STAI	BIS-11	TMTA (on/ctl)	TMTA (off)	TMTB (on/ctl)	TMTB (off)	MOCA (on/ctl)	MOCA (off)	UPDRS III (on/ctl)	UPDRS III (off)	Time to dose (hours, on)	Time to dose (hours, off)
1	64	F	16	R	2	2	Lev	338	21	47	75	29	30	48	80	29	29	24	25	2.5	13
2	68	M	18	R	1	1.5	Lev + A	326	2	55	63	20	28	36	27	29	30	15	17	2	16
3	67	F	21	R	0.2	1.5	Lev	451	9	52	63	23	31	44	64	29	29	14	20	1	17
4	58	M	13	R	5	2	Lev + A	889	4	52	68	33	47	87	99	29	28	21	29	0.5	17
5	79	M	16	R	2	1.5	Lev	564	12	51	73	40	52	100	115	24	24	16	25	4	12
6	51	M	14	L	1	1	Lev + A	664	4	53	57	20	26	32	36	28	29	10	15	3	15
7	45	M	16	R	0.3	1	Lev + A	213	0	48	63	25	26	68	77	25	28	10	16	4	18
8	69	M	12	L	1	1	Lev + A	326	4	53	63	22	24	39	45	27	25	7	13	2	16
9	68	M	20	L	2	1	Lev + A	438	1	52	61	39	51	56	85	28	28	7	13	1	26
10	49	M	14	R	8	2	Lev + A	326	8	49	81	18	25	31	32	28	28	22	29	3	26
11	49	F	13	R	0.25	1	Lev	226	16	54	56	16	19	40	39	24	28	15	18	2	15
12	80	F	21	R	6	1.5	Lev	771	5	52	64	36	49	80	87	29	29	14	26	1	14
PD Mean (Stdev)	62.3 (11.8)	4 F, 8 M	16.2 (3.2)		2.4 (2.5)	1.4 (0.4)		461.0 (217.3)	7.2 (6.4)	51.5 (2.4)	65.6 (7.4)	26.8 (8.4)	34.0 (12.1)	55.1 (23.3)	65.5 (29.2)	27.4 (2.0)	27.9 (1.7)	14.6 (5.6)	20.5 (6.0)	2.2 (1.2)	17.1 (4.5)

CTL Mean (Stdev)	64.7 (7.9)	8 F, 8 M	15.6 (3.2)		3.9 (4.2)	51.2 (2.9)	57.2 (8.2)	27.8 (10.9)	62.6 (22.5)	27.8 (1.4)

Table 3. Behavioral results from the stop-signal task, presented as: Mean (Standard Deviation). CTRL, Control; SSRT, Stop-Signal Reaction Time; GoRT, Go Reaction Time; CoV, Coefficient of Variation; SERT, Stop-Error Reaction Time. NOTE: r(max) refers to the correlation between P(stop) and GoRT, or the sequential effect (see **Methods Chapter III**, or **Figure 5B** for more information). CTRL vs ON and CTRL vs OFF: *p*-values for two-sample *t*-tests. ON vs OFF (match): *p*-values for paired *t*-tests.

	SSRT	GoRT	GoRT CoV	GoRT-SERT	r(max)	Alpha	Prior Mean	Scale
CTRL (n=37)	243.7 (36.3)	720.8 (101.9)	0.21 (0.06)	79.5 (37.7)	0.26 (0.14)	0.89 (0.15)	0.15 (0.21)	9.81 (4.16)
PD ON: Match (n=14)	242.8 (50.0)	715.3 (112.1)	0.21 (0.03)	81.9 (33.8)	0.29 (0.16)	0.82 (0.20)	0.09 (0.15)	7.15 (5.47)
PD OFF: Match (n=14)	280.3 (51.2)	741.9 (109.1)	0.22 (0.04)	98.8 (70.7)	0.19 (0.22)	0.82 (0.21)	0.14 (0.21)	11.15 (2.76)
PD OFF: All (n=20)	279.5 (47.6)	747.2 (116.0)	0.24 (0.06)	87.1 (69.5)	0.13 (0.26)	0.82 (0.22)	0.17 (0.22)	10.16 (3.96)
CTRL vs ON	0.947	0.872	0.995	0.841	0.447	0.168	0.368	0.075
CTRL vs OFF (all)	**0.003**	0.395	0.170	0.600	**0.018**	0.166	0.700	0.765
ON vs OFF (match)	**0.001**	0.398	0.198	0.278	**0.032**	0.935	0.434	0.056

Table 4. Brain activation differences for various SST analysis in paired t-test comparison of PD participants "on" versus "off" dopaminergic medications. Results are thresholded voxelwise at $p < .001$, with a cluster-level threshold of $p < .05$ family-wise error (FWE) corrected and a minimum cluster size $k = 10$.

			MNI Coordinates (mm)			
Contrast	Cluster Size (mm^3)	z-score	X	Y	Z	Identified Region
On > Off:						
SS > SE						*(No significant results)*
Stop > Go						*(No significant results)*
p(Stop)	1703	4.55	-44	-60	40	Left IPL
		3.94	-57	-54	35	
		3.87	-42	-54	32	
RT slowing	672	4.62	-27	13	45	Left dlPFC
		3.92	-30	20	50	
	1359	4.39	0	20	50	SMA
		4.05	-7	18	55	
		3.99	0	10	52	
	1578	4.44	-42	-57	45	Left IPL
		3.96	-34	-50	32	
		3.35	-50	-47	38	
	1188	3.85	56	-52	35	Right IPL
		3.71	50	-44	45	
		3.35	43	-47	32	
UPE						*(No significant results)*
Off > On:						
SS > SE						*(No significant results)*

Stop > Go						*(No significant results)*
p(Stop)						*(No significant results)*
RT slowing						*(No significant results)*
UPE	1203	3.88	-52	-14	38	Left premotor
		3.8	-47	-12	50	
		3.74	-60	-12	35	

Figure 1. Flow chart of meta-analysis procedure.

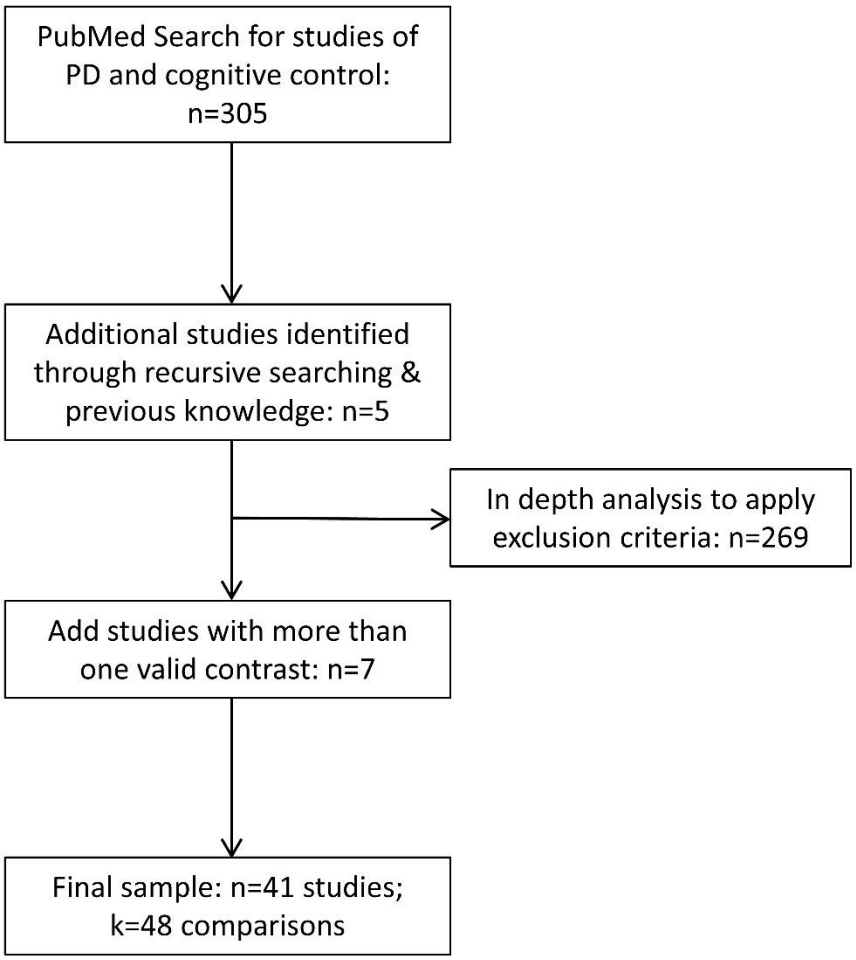

Figure 2. Forest plot of effect sizes for all studies that compared performance on a response inhibition task between a PD group and a matched healthy control group. A) Studies sorted by medication status. B) Studies sorted by task. Effect sizes to the left of the vertical dashed line indicate that performance of the PD group was poorer than controls; however, if the error bars overlap with the dashed line, it indicates that the difference in between-group performance was not statistically significant at the $p < .05$ threshold. NOTE: Avg., Average; SST, Stop-Signal Task; GNG, Go-NoGo; A-S, Anti-Saccade

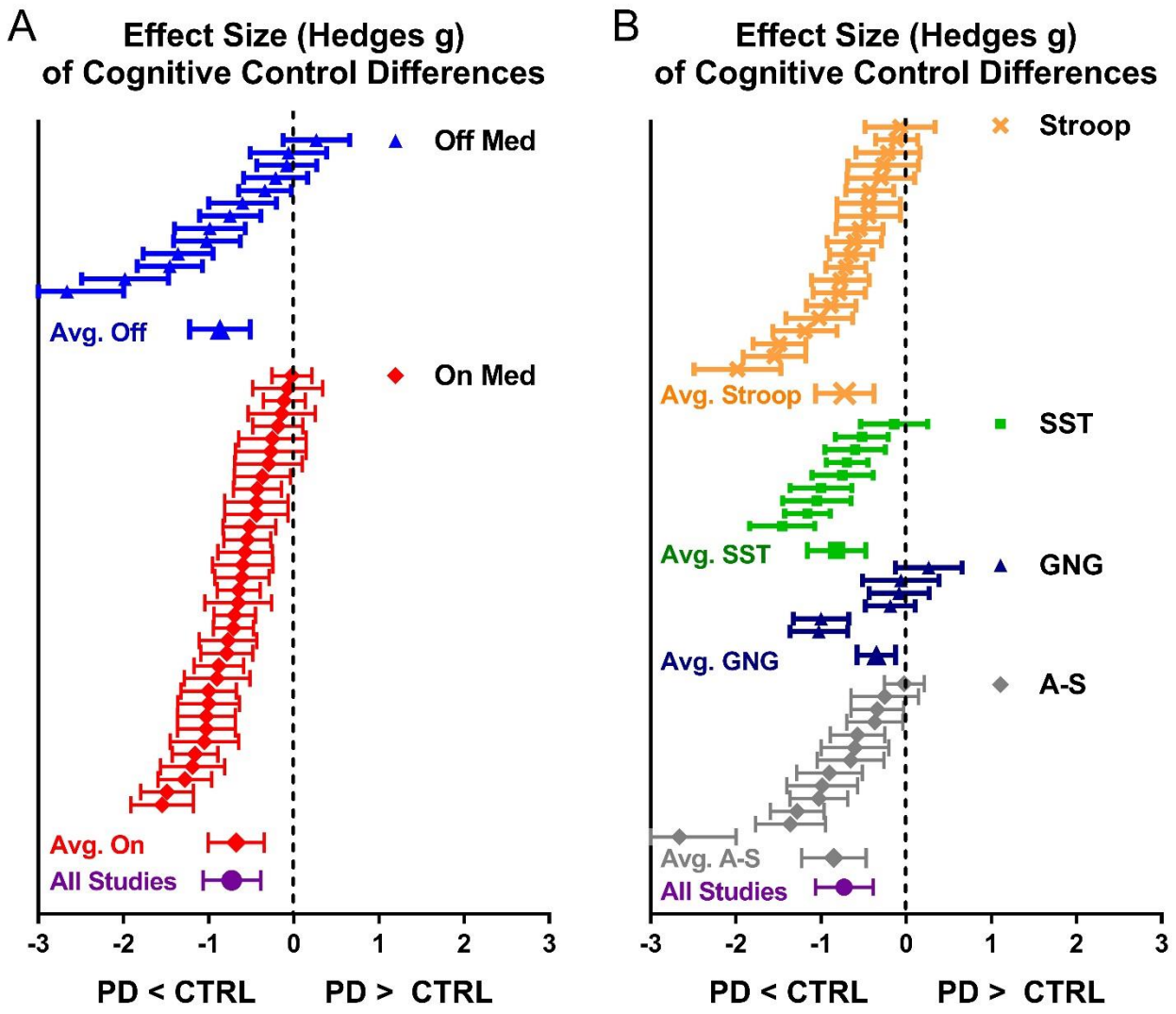

Figure 3. Regression plot of response inhibition deficits on average disease duration for the off medication (blue) and on medication (red) samples. Each bubble represents a comparison from one study, weighted by within-study variance. Smaller bubbles represent studies with higher variance than others and thus, have less influence on the regression. The regression line of best fit for each sample is also shown. *, p < .05; **, p < .01

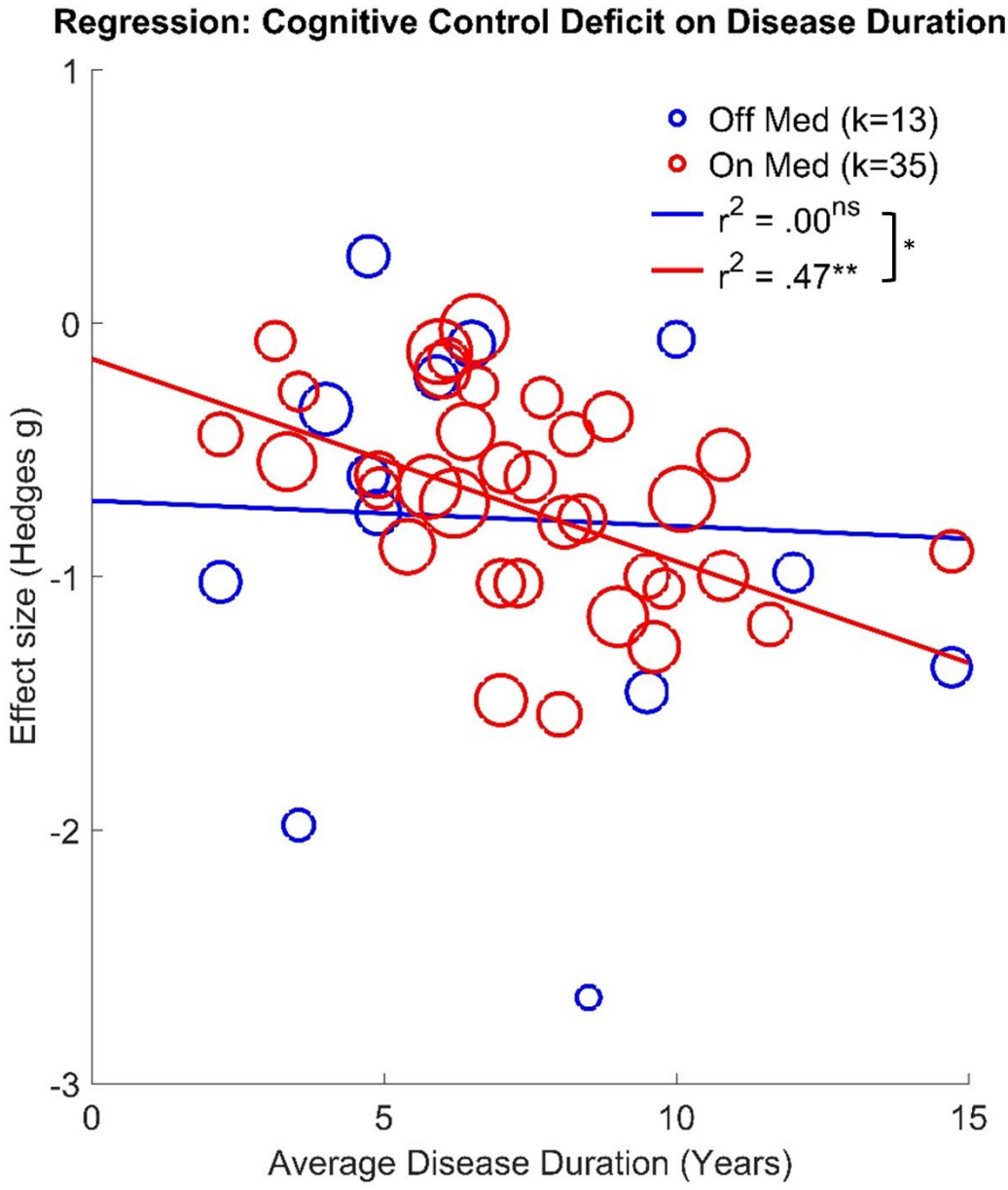

Figure 4. Stop-signal Task. A) A go stimulus (O) appears on each trial. A delayed stop signal (X) appears on 25% of the trials to instruct subjects to withhold the prepotent response. The stop-signal delay (SSD), or the amount of time between the go stimulus and the stop signal on a stop trial, is varied based on a staircase procedure. B) Schematics for the Bayesian computational model. Stimulus prediction: p(Stop) is modeled as across-trial inference (hidden Markov Model) of stop signal frequency (r_k). C) Unsigned Prediction Error, or "Bayesian surprise" is modeled as within-trial inference of both stop signal presence (z) and go stimulus identity. It is the absolute difference between the observed and expected outcome on any trial: |stimulus outcome-p(Stop)| (where for stimulus outcome, 1=stop and 0=go).

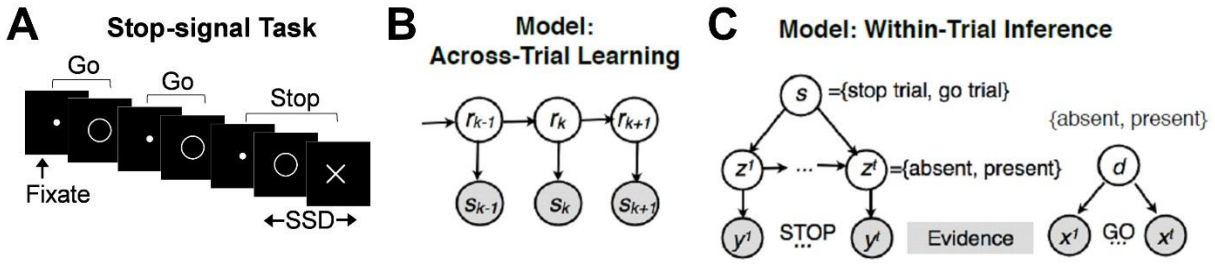

Figure 5. Behavioral performance on the stop-signal task. A) PD patients showed significantly longer SSRT in the "off" medication state (red hatch) than "on" state (red) and the control group (blue), indicating a response inhibition deficit. According to the race model, SSRT is calculated by median *go* RT - critical SSD. B) Bayesian modeling data: Compared to the controls, PD participants in the "off" but not "on" medication state showed a deficit in trial-to-trial behavioral adjustment, as indicated by a weaker sequential effect: the correlation between p(Stop) and go RT. C) Correlation between change in sequential effect and change in SSRT "on" vs. "off" dopaminergic medication. Thus, dopamine-mediated improvements in response inhibition are associated with increased Bayesian trial-to-trial adjustment.

*, p<.05; **, p<.01; ns, not significant. Error bars indicate standard error of the mean (SEM).

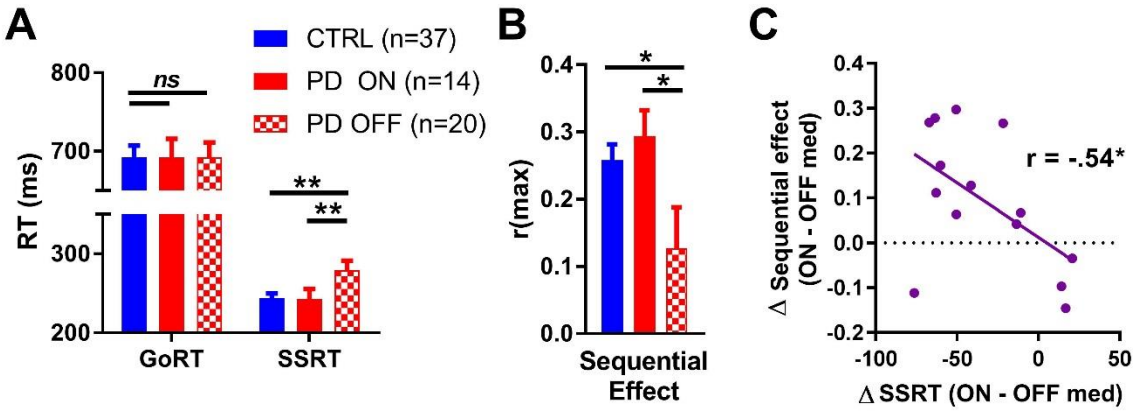

Figure 6. fMRI results: one-sample t-test results for "conventional" stop-signal task contrasts. A) Purple: contrast of stop > go trials. Green: contrast of go > stop trials. B) Purple: contrast of stop success (SS) > stop error (SE) trials. Green: contrast of SE > SS trials. Top row: healthy controls (n = 15); middle row: PD participants "on" medications (n = 12); bottom row: PD participants "off" medications (n = 12). Maps are thresholded voxelwise at $p < .001$, with a cluster-level threshold of $p < .05$ family-wise error (FWE) corrected and a minimum cluster size $k = 20$.

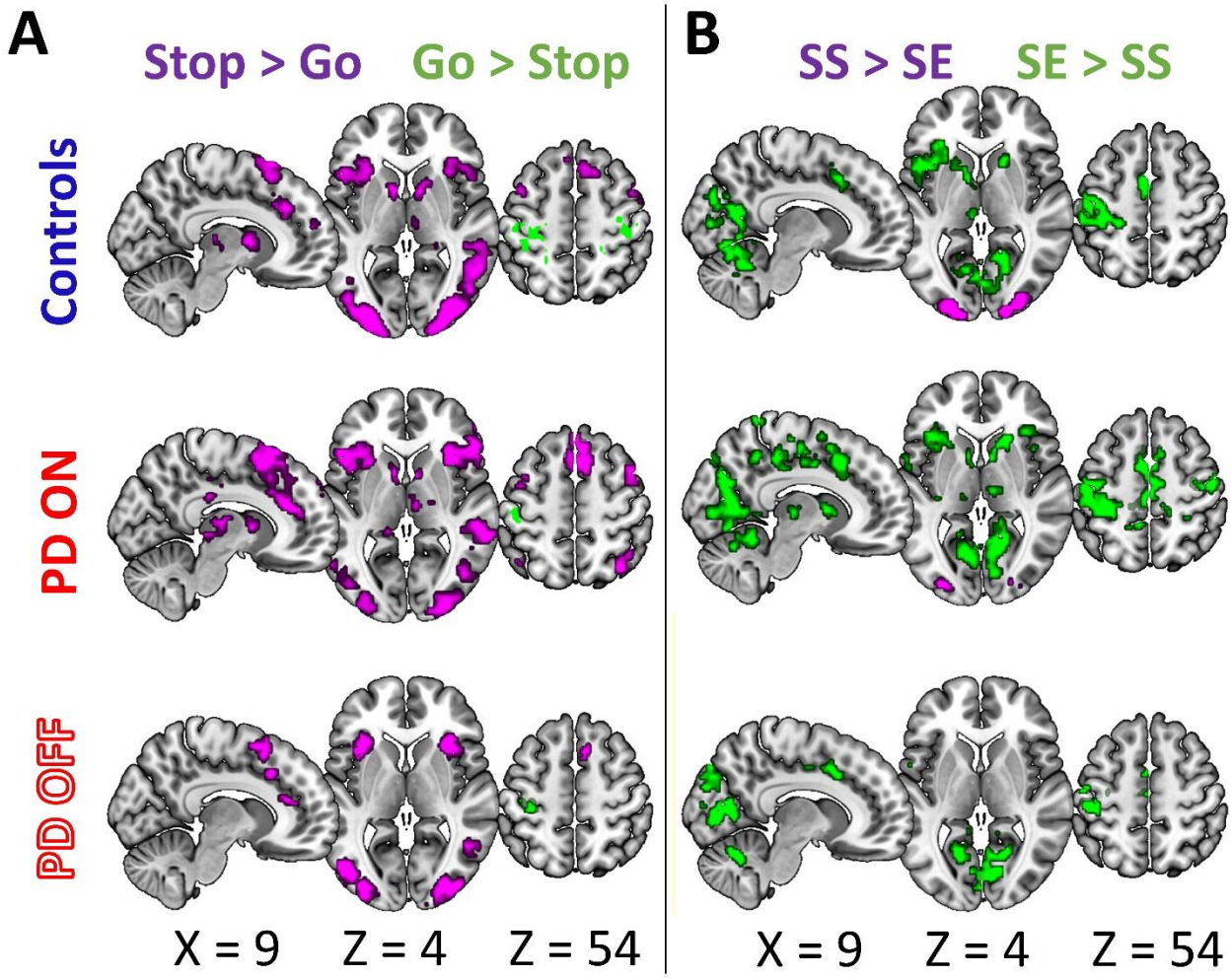

Figure **7**. fMRI results: one-sample t-test results for "proactive control" analyses. Violet: Activations to RT slowing (i.e., parametric increases in RT). Yellow: Activations to anticipation of a stop signal, or P(stop). Cyan: Activations to unsigned prediction error (UPE). Top row: healthy controls (n = 15); middle row: PD participants "on" medications (n = 12); bottom row: PD participants "off" medications (n = 12). Maps are thresholded voxelwise at $p < .001$, with a cluster-level threshold of $p < .05$ family-wise error (FWE) corrected and a minimum cluster size $k = 10$. Healthy controls showed no significant activations to RT slowing or P(stop); PD ON showed no significant activations to UPE; PD OFF showed no significant activations for all measures.

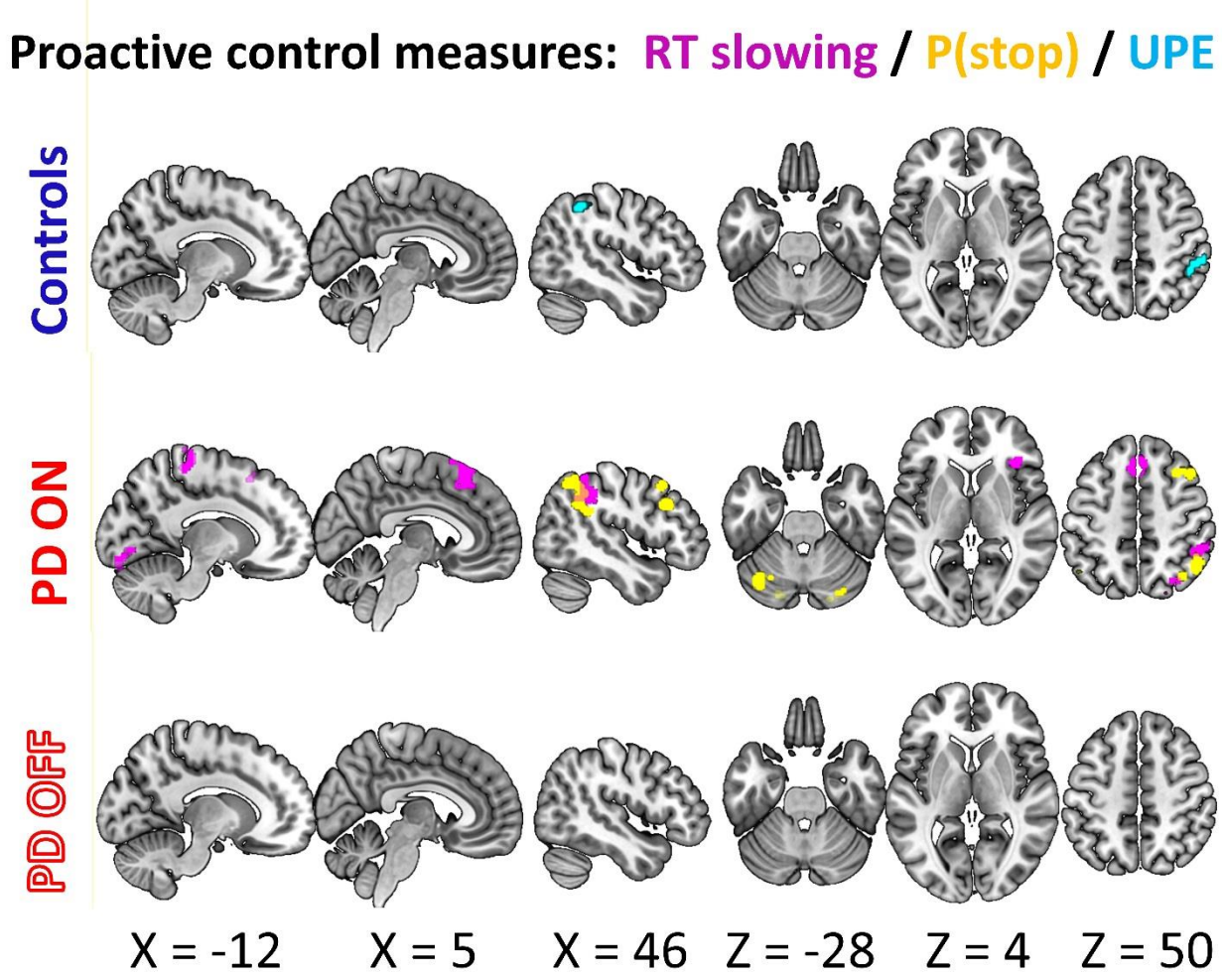

Figure 8. fMRI results: exploratory two-sample t-test results for several regions of interest (ROIs). Black asterisks denote a difference between PD "off" groups and controls, and red asterisks denote a difference between PD "on" groups and controls. All results are thresholded at $p < .05$ uncorrected for this exploratory analysis. Error bars indicate standard error of the mean (SEM). CauD, Dorsal Caudate; CauV, Ventral Caudate; PutA, Anterior Putamen, PutB, Posterior Putamen, SMA, Supplementary Motor Area, rIFG, Right Inferior Frontal Gyrus

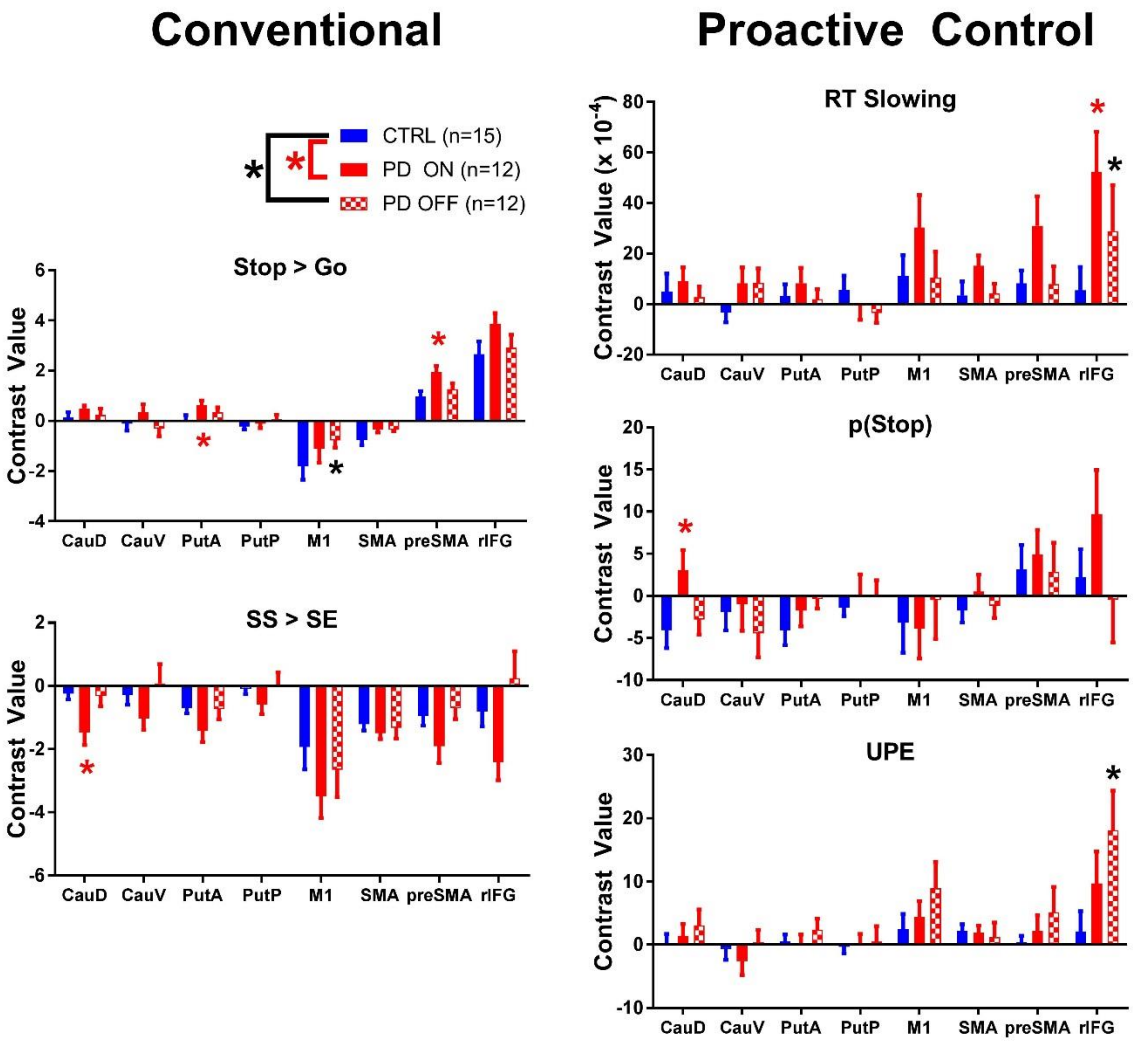

Figure 9. fMRI results: effects of dopaminergic medications in PD. A) Paired t-test results depicting brain activation differences between PD participants ON and OFF medications for proactive control analyses. Violet: Activations to RT slowing (i.e., parametric increases in RT). Yellow: Activations to anticipation of a stop signal, or P(stop). Cyan: Activations to unsigned prediction error (UPE). Top row: Activations that were greater in PD participants ON versus OFF medications; bottom row: Activations that were greater in PD participants OFF versus ON medications. Maps are thresholded voxelwise at $p < .001$, with a cluster-level threshold of $p < .05$ family-wise error (FWE) corrected and a minimum cluster size $k = 10$. B) Bar plots depicting contrast values for each group for the P(stop) IPL cluster (top) and UPE premotor cluster (bottom). Note that there were no significant differences in brain activation in paired t-test results for "conventional" SST analyses, even at a lenient threshold ($p < .005$ uncorrected). NOTE: IPL, inferior parietal lobule; SMA, supplementary motor area; dlPFC, dorsolateral prefrontal cortex.