The Effects of Levodopa on Cognitive Control in Parkinson's Disease.

by

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ABSTRACT

The present study aimed to compare brain activity changes related to proactive and reactive control strategies patients with Parkinson's disease during "On" levodopa and "Off" levodopa conditions. The study consisted of two participants who had received a prior diagnosis of Parkinson's Disease. The participants completed AX-CPT task as a measure of attention control in two sessions: a) "On Levodopa" and b) "Off Levodopa" while they were in the fMRI scanner. Prior to the analysis, the T1- weighted anatomical scan images and the BOLD multiband functional images of both the participants were BIDS (Brain Imaging Data Structure) validated and preprocessed using the standard FMRIPrep pipeline. The imaging data was then analyzed using SPM12 (Statistical parametric mapping) software. Individual level analysis of the imaging data was conducted by creating General Linear models for both the participants on "ON" and "OFF" levodopa conditions. The BOLD responses were compared using AY>BY and BX > BY contrasts. Where BX > BY contrast measured BOLD activity related to reactive control strategy and AY> BY contrast measured BOLD activity related to proactive control strategy. It was observed that participants tended towards reactive control strategy in both "On" and "Off" levodopa conditions.

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CHAPTER 1

INTRODUCTION

Approximately one million people in the United States are presently living with Parkinson's Disease. This number is expected to rise to 1.2 million by 2030. With about 10 million people living with Parkinson's Disease globally, this is the second most common neurodegenerative disease in the world that is rapidly increasing and taking the shape of a Pandemic (Parkinson's Disease Foundation, n.d and (Dorsey et al., 2018).

Parkinson's disease progresses slowly, and its advancement has been divided into six stages. Stages 1and 2 are the pre-symptomatic stages where the pathology is confined only to the medulla oblongata and olfactory bulb. Stages 3 and 4 are the intermediate stages. During these stages, the pathology spreads to substantia nigra and other nuclear grays of the midbrain and forebrain. Finally, stages 5 and 6 are the end stages where the pathology enters the mature neocortex, and the disease manifests itself in all of its clinical dimensions(Braak et al., 2004).

Parkinson's disease is primarily characterized by motor symptoms such as postural instability, tremors, rigidity and Akinesia. In addition, People with Parkinson's disease also suffer from several non-motor symptoms such as autonomic dysfunction, sleep and sensory abnormalities, and neuropsychiatric disorders. Autonomic dysfunction may include symptoms such as orthostatic hypotension and sweating, sphincter, and erectile dysfunction. Sleep disorders may consist of insomnia and excessive daytime sleepiness as well as other sleep disturbances such as excessive sleepiness and sleep attacks. Sensory abnormalities in Parkinson's disease can involve olfactory dysfunction, pain, paresthesia, akathisia, oral pain and genital pain. Finally, many people with

Parkinson's disease are also at an increased risk of suffering from neuropsychiatric comorbidities such as dementia, depression, apathy, anxiety, hallucinations, obsessive-compulsive disorders and impulsive behavior(Jankovic, 2008). Even patients who do not suffer from psychiatric disorders show significant cognitive impairments in multiple cognitive domains. These impairments lead to reduced quality of life in Parkinson's Disease patients and pose a major challenge for the treatment of these patients(Schrag et al., 2000). Cognitive impairments in Parkinson's Disease are associated with deficits in executive functions, memory, language, visuospatial functions, processing speed and attention(Goldman et al., 2018).

One type of executive function that shows impairment in Parkinson's disease is Cognitive control. Cognitive control refers to an individual's ability to coordinate thoughts and take actions in accordance with their internal goals (Miller and Cohen, 2001). Cognitive control also allows individuals to selectively attend to the relevant information while simultaneously ignoring the irrelevant information (Fitzhugh et al., 2019). In People with Parkinson's disease, deficits in cognitive control occur prior to motor symptoms. Hence problems with cognitive control are a major determinant of Parkinson's Disease and of Mild Cognitive Impairment. One reason for this is that both cognitive control and Parkinson's Disease are regulated by dopamine (DA).

Dopamine is a neurotransmitter that plays a vital role in regulating motor control, executive functions, motivation, arousal, rewards and reinforcement. Dopamine is produced in several brain regions, such as the Ventral Tegmental Area (VTA), Substantia Nigra and Hypothalamus. Dopamine sends signals from one neuron to another through 5 different receptors- D1, D2, D3, D4 and D5. These five receptors are categorized into two

subcategories. Category 1 is the D1 like- family receptors consisting of D1 and D5 receptors. Category two is the D2 like family receptors that consist of D2.D3 and D4 receptors. There are four major Dopamine pathways through which Dopamine travels to different parts of the brain and body to convey important information: nigrostriatal pathway, mesocortical pathway, tuberoinfundibular pathway, and mesolimbic pathway (Latif et al., 2021). The nigrostriatal pathway goes from Subanstatia Nirgra to Caudate Putamen and is responsible for regulating movements such as learning new motor skills and controlling motor functions. The Mesocortical pathway starts from the Ventral Tegmental Area or A10 region of the brain and ends at the septohippocampal region and frontal cortex. This pathway plays an important role in regulating emotions and cognitive behavior such as memory and attention. The mesolimbic pathway projects dopamine from the Ventral Tegmental Area to the nucleus accumbens, amygdala and pyriform cortex. The mesolimbic pathway is majorly responsible for pleasure and reward. The Tuberoinfundibular pathway connects the paraventricular and arcuate nucleus of the hypothalamus to the median eminence in the pituitary gland. This pathway is majorly responsible for inhibiting the release of prolactin(Latif et al., 2021).

Dopamine plays an important role in regulating cognitive control that is mediated by cortico-striatal-thalamo-cortical gating loops in the brain. In the Prefrontal cortex, dopamine modulates cognitive control by gating sensory input, maintaining, and manipulating contents of the working memory, and by relaying motor commands(Ott & Nieder, 2019). In the striatum, dopamine plays a crucial role in attentional gating and shifting attention from the task-irrelevant to the unexpected task-relevant and behaviorally important stimuli(Cools, 2016).

In the past, Braver and his colleagues have proposed models to delineate how dopamine modulates goal-directed behavior. The gating model (Braver & Cohen, 1999) proposed that contextual information or goal-related information is actively maintained in the prefrontal cortex, and this serves as top-down support for control behavior. The Dopamine projection to the Prefrontal cortex serves as a gating function as it regulates access of context representations into active working memory and enables flexible updating of the active working memory in the prefrontal cortex while preventing interference from irrelevant information. Braver et al. furthered this model by proposing the connectionist computational model of cognitive control (Braver et al., 1999). This model was tested using the AX- CPT task that required participants to successfully maintain and update contextual information to succeed in the task. This model suggested that disturbances in the dopamine tonic and phasic activity levels can lead to abnormal modulation of the prefrontal cortex dynamics resulting in an inability to a) switch to a new activity state and b) sustain current states. These models were important in understanding how cognitive control is regulated in various pathologies that are related to the impairment of the dopaminergic system.

In 2012 Braver proposed the Dual Mechanisms of Cognitive Control Framework (DMC) to understand the causes of the variation in cognitive control performance. He proposed that cognitive control can operate in two primary modes: a) proactive control and b) reactive control. Proactive control occurs prior to the onset of the stimulus and involves sustaining or actively maintaining information. On the other hand, reactive control involves stimulus-driven decision-making and is characterized by transient activity that occurs in response to the changing environmental demands. The DMCC

theory proposes that in Proactive control, the contextual representations enter and are maintained in the prefrontal cortex through the phasic dopaminergic gating mechanisms. In contrast, reactive control has been proposed to operate in the absence of a gating mechanism.

The DMCC framework has extensively made use of the AX-CPT task to demonstrate proactive and reactive control strategies in the participants at both behavioral and neural levels. The task consists of two cues, A and B, that are followed by two Probes, X and Y. The participants are required to respond to the probe based on the preceding cue. Participants are asked to make a target response with they detect an AX sequence where the A cue is followed by the X probe. The participants make a non-target response when they detect AY, BY and BX sequences. In this task, the BX sequence has shown to produce the greatest interference that is marked by slow reaction times and increased error rates. However, BY trials that are characterized by both non-target probes and cues are considered control trials as they do not produce any interference. The DMCC framework proposes that AY trials reflect proactive control as these trials require the participants to maintain the information of the contextual target cue "A" that they should overcome when presented with the non-target probe "Y." In addition, the BX trials are known to reflect reactive control as the interference in these trials arises from the target probe that must be inhibited on the basis of the prior non-target contextual cue "B ." Thus, the DMC models propose that an individual's performance in the AY and BX trials can reflect an individual's tendency towards either reactive or proactive control.

Several studies in the past have used the AX-CPT task to understand how populations with dopaminergic dysregulation adapt to proactive and reactive control

strategies. For instance, Edwards et al. in 2010 used the AX-CPT task to understand the neural basis of cognitive control impairments in patients with Schizophrenia. They proposed that with instructional training, these patients can change from using reactive control strategies to proactive control strategies. In 2021, Grisetto et al. conducted a study using the AX-CPT task that demonstrated that impulsiveness is associated with less dominant proactive control and greater resilience on reactive control. In 2005, Braver et al. conducted a study to compare context processing and context maintenance in health again populations and those with early-stage dementia in Alzheimer's Disease. They found that people with Alzheimer's Disease had decreased proactive control, which was reflected through difficulty in maintaining contextual information, but relative intact reactive control.

The majority of the studies conducted to study cognitive control in patients with Parkinson's disease have also focused on the role dopaminergic medications such as Levodopa play in modulating cognitive control. This is because even though L-dopa has shown to better Parkinson's Disease patients' motor functions, it has shown variable effects on several cognitive functions. For instance, in 1986, Gotham et al. compared cognitive functions in patients with Parkinson's disease when they were on Levodopa medication and when they were off levodopa medication. The authors observed that while levodopa therapy improved performance on several cognitive functions, a higher dose of levodopa led to poor performance on the conditional associative learning task and proposed the dopamine overdose hypothesis. According to this hypothesis, dopamine medication may improve functions of motor-related brain regions but might 'overdose' other brain regions related to cognitive functions. Based on this, Cools in 2001 and

Swainson et al. in 2000 gave a theory along the lines of the Yerkes - Dodson Inverted U-shaped account and proposed that the effects of levodopa on a given brain region's function depend on the baseline dopamine levels within that region. This means that levodopa may improve functions that are mediated by dopamine-deplete brain regions, whereas it may impair the functions associated with intact dopaminergic brain regions through detrimentally overdosing them.

Studies conducted to understand how levodopa affects cognitive control have shown mixed results. For instance, Cools & D'Esposito 2011 proposed that cognitive control is a multifactorial phenomenon that requires maintaining a balance between two cognitive control components: a) cognitive stability and b) cognitive flexibility. These components are implicated in the prefrontal cortex and striatum, respectively. Manipulation of dopamine through levodopa may produce paradoxical effects by improving one cognitive control component and impairing the other. In 2011Onur and colleagues compared dopaminergic stimulation between healthy younger and older adults and found that performance on interference control worsened for younger adults under levodopa as compared to older adults. They concluded that this worsening of performance in younger adults could be associated with overstimulation of the dopaminergic system in the Anterior Cingulate Cortex. Cools et al. in 2003 found that Parkinson's disease patients on L-dopa medication showed an increase in impulsive behavior, and those off L-dopa medication increased attentional inflexibility. Finally, Moustafa et al. in 2008 compared the performance of medicated and non-medicated Parkinson's disease patients using the AX-CPT task and found that non-

medicated patients had difficulty in updating to a new attentional set, whereas medicated patients had difficulty in ignoring distractors that were previously task-relevant.

The literature suggests that dopamine plays an important role in regulating cognitive control in patients with Parkinson's Disease and that levodopa plays an important role in modulating individual components of cognitive control based on the dopaminergic concentration in the brain regions that each of the control components are associated with. Understanding the role that levodopa medication plays in regulating different components of cognitive control in patients with Parkinson's disease may play an important role in improving the pharmacological therapy given to them and in helping them to ambulate in the community effectively and safely. However, there is a scarcity of literature that assesses the role levodopa plays in modulating dopaminergic functioning in the brain regions associated with different cognitive control components.

The present study, thus, aims to compare brain activity associated with proactive and reactive cognitive control in people with Parkinson's disease with they are a) "On" levodopa medication and b) "Off" levodopa medication by using the AX-CPT task. The results of this study are expected to show that the participants will have greater reactive control in the “Off” Levodopa condition and greater proactive control in the “On” Levodopa condition. This study assumes that greater reactive control in the “Off” Levodopa condition will be indicated by reduced reaction time and error rates on the BX trials of the AX-CPT task in the “Off” levodopa condition as compared to the “On” Levodopa condition as well as by greater activations in the frontal and striatal regions in the BX>BY contrast in the “Off” levodopa condition as compared to the “On” levodopa condition. In contrast, the greater tendency towards the proactive control in the “On”

Levodopa condition will be reflected by reduced reaction times and error rates on the AY trials of the AX-CPT task in the “On” Levodopa condition as compared to the “Off”’ Levodopa condition, and through greater activations in the frontal regions in the AY>BY contrast on the “On” Levodopa condition as compared to the “Off” Levodopa condition. The present study aims to provide only preliminary results of two participants. However, in the future data from 20 participants will be collected (10 participants with Parkinson’s disease and 10 participants without Parkinson’s disease). For group level analysis the study will conduct paired sample t-test for both behavioral and neuroimaging results.

CHAPTER 2

METHODS

Participants

This study only provides preliminary results of two participants taken from the larger ongoing study that aims to recruit a total of 20 participants (10 participants with Parkinson's Disease and ten neurotypical individuals). Both the participants had a prior diagnosis of Parkinson's Disease. To be included in the study, all the participants were required to be between the ages 18-95 years, be able to ambulate continuously for 1 minute with or without the aid of the walker and have the ability to comprehend written and spoken English. Individuals were excluded from the study if a) they had any neurological pathology (other than PD) impacting their gait or balance, b) were pregnant women and/or c) showed contradictions for MRI such as indwelling Ferris metal and implanted electrical devices. The data for this study were collected at the Banner Alzheimer's Institute in downtown Phoenix. All the participants provided written informed consent to participate in the study and received a compensation of 30$ for each visit.

Protocol

After screening and consenting, participants underwent an approximately 45 minutes long fMRI scan session. The scans acquired during this session included both anatomical and functional scans. The anatomical scans included T1- weighted whole-brain images, T2-weighted whole-brain images, proton density-weighted images and diffusion-weighted images (DWI). The functional scans included T2*-weighted echo-planar images as participants viewed shapes and letters on the computer screen while the BOLD

signal was acquired. Post the scans; the participants completed 45 minutes long clinical and cognitive assessments, including the Movement Disorders Society- Unified Parkinson's Disease Rating Scale, the Mini Balance Evaluation Systems Test, and a PD-specific cognitive battery, the Scales and outcomes in Parkinson's Disease -Cognition (SCOPA-COG). Finally, participants underwent 15 minutes of mobility-related dual-tasking assessments. Neurotypical adults underwent only one scanning session. However, People with Parkinson's Disease completed these sessions both on and off their prescribed dose of levodopa on two separate days. For the "ON" sessions, the testing began about 1 hour after levodopa ingestion. For the "OFF" session, the testing began at least 12 hours after the participant's last dose of levodopa. For people with Parkinson's Disease, both "ON" Levodopa and "OFF" Levodopa Sessions were scheduled between 1 to 3 weeks apart. The order of the assessments for on and off levodopa conditions was randomized.

AX-CPT Task

Cognitive control involves maintaining and utilizing contextual information in order to minimize interference and guide goal-directed behavior. Participants in this study completed the AX-CPT task in the MRI scanner that was based on the paradigm described by D'Ardenne et al. 2012. AX-CPT task is a continuous performance task that measures attention control. This task is based on context processing and requires participants to continuously update task goals in response to rapidly shifting contextual information. This task has been used on a wide range of populations due to its simplistic design, flexibility and applicability. In the past, many studies have used this task on people with Parkinson's disease.

The AX-CPT task requires participants to respond to 2 different probes, termed X and Y, that are preceded by two cues stimuli, termed A and B. The participants always have to respond to the X- probe and never to the Y-probe. The target response requires participants to respond to the X- a probe that is followed by A- cues, and the non-target response requires participants to respond to the X- probe preceded by B-cue and Y- probe preceded by both A and B cues. However, when the X- probe is preceded by B- cue leads to higher interference as compared to the Y- probe preceded by A and B cues. Thus, both AX and BX pairing require high control ability, whereas both AY and BY pairings require low control abilities from the participants. In addition, there are no-go trials where participants do not have to respond with a keypress. On the no-go trials, the A or the B cues are followed by the numbers, and the participants do not have to make any responses on those trials.

The AX-CPT task for the present study consisted of three blocks with 24 trials in each block. Thus, there were a total of 72 trials in the experiment. Each trial lasted for approximately 5300 milliseconds. The intertrial interval between the two trials varied randomly for 1300 ms, 2500ms or 3700 ms. The interval between the two blocks was approximately 5000 ms long. The total time is taken by participants to complete the experiment while in the MRI scanner was approximately 13 minutes. The AX-CPT was programmed and presented to the participants using E-Prime software. The task was projected to the participants while they were in the MRI scanner using Glass. Participants responded using a response box.

The task consisted of six experimental conditions: A probe followed by X cue, A probe followed by Y cue, B probe followed by X cue, B probe followed by Y cue, A probe

followed by a number and B probe followed by a number. Out of these six conditions, AX pairing was the target conditions, AY, BX and BY pairings were in the non-target conditions, and Ang and Bng were no-go conditions. Within each block, there were 8 trials each for AX and BY pairings and 2 trials each for AY, BX, Ang and Bng pairings. Participants responded with an index finger for the non-target trials, with the middle finger for the target trials and did not press any button for the no-go trials.

Figure 1: Shows Trials in the AX-CPT Task.

Imaging Data Acquisition

All the imaging data were acquired on a 3.0T Phillips Ingenia scanner using a 32-channel head coil. The MRI images included both high-resolution magnetization prepared rapid gradient echo anatomical scans (T1 and T2 weighted) and BOLD functional scans. The BOLD functional scans were acquired using a multi-band acquisition sequence with a factor of 3 and a repetition time of 1000 milliseconds with alternating anterior-posterior and posterior-anterior encoding directions. In each of the imaging sessions, participants underwent one BOLD run for about 13 minutes. Each

scanning run followed an event-related design. The task trials were grouped into 3 blocks separated by approximately 5000 milliseconds long resting fixation block.

Data Analysis

For the behavioral data, the analysis focused on measuring the mean reaction times and accuracy rates of both the participants. The analysis of the imaging data was based on the T1-weighted anatomical scan and BOLD functional scans that were collected as participants performed the AX-CPT task. The imaging data acquired from the scanner was first converted into Brain Imaging Data Structure (BIDS) format. The data was then run through the BIDS validator.

Post validation the data of both the participants was preprocessed using the standard FMRIPrep pipeline. The FMRIPrep pipeline was implemented in the docker- container.

Anatomical Preprocessing: All the T1- weighted images were corrected for intensity non-uniformity (INU) with N4BiasFieldCorrection (Tustison et al. 2010), distributed with ANTs 2.3.3 (Avants et al. 2008, RRID:SCR_004757). The T1w-reference was then skull-stripped with a Nipype implementation of the antsBrainExtraction.sh workflow (from ANTs), using OASIS30ANTs as the target template. Brain tissue segmentation of cerebrospinal fluid (CSF), white-matter (WM) and gray-matter (GM) was performed on the brain-extracted T1w using fast (FSL 6.0.5.1:57b01774, RRID:SCR_002823, Zhang, Brady, and Smith 2001). A T1w-reference map was computed after registration of 2 T1w images (after INU-correction) using mri_robust_template (FreeSurfer 6.0.1, Reuter, Rosas, and Fischl 2010). Brain surfaces were reconstructed using recon-all (FreeSurfer 6.0.1, RRID:SCR_001847, Dale, Fischl, and Sereno 1999), and the brain mask estimated previously was refined with a custom variation of the method to reconcile ANTs-derived

and FreeSurfer-derived segmentations of the cortical gray-matter of Mindboggle (RRID:SCR_002438, Klein et al. 2017). Volume-based spatial normalization to one standard space (MNI152NLin2009cAsym) was performed through nonlinear registration with antsRegistration (ANTs 2.3.3), using brain-extracted versions of both T1w reference and the T1w template. The following template was selected for spatial normalization: ICBM 152 Nonlinear Asymmetrical template version 2009c [Fonov et al. (2009), RRID:SCR_008796; TemplateFlow ID: MNI152NLin2009cAsym].

Functional Preprocessing: For Each BOLD runs first, a reference volume and its skull-stripped version were generated using a custom methodology of fMRIPrep. Head-motion parameters with respect to the BOLD reference (transformation matrices, and six corresponding rotation and translation parameters) are estimated before any spatiotemporal filtering using mcflirt (FSL 6.0.5.1:57b01774, Jenkinson et al. 2002). BOLD runs were slice-time corrected to 0.464s (0.5 of slice acquisition range 0s-0.928s) using 3dTshift from AFNI ((Cox & Hyde, 1997), RRID:SCR_005927). The BOLD time-series (including slice-timing correction when applied) were resampled onto their original, native space by applying the transforms to correct for head-motion. These resampled BOLD time-series will be referred to as preprocessed BOLD in original space, or just preprocessed BOLD. The BOLD reference was then co-registered to the T1w reference using bbregister (FreeSurfer) which implements boundary-based registration (Greve and Fischl 2009). Co-registration was configured with six degrees of freedom. Several confounding time-series were calculated based on the preprocessed BOLD: framewise displacement (FD), DVARS and three region-wise global signals. FD was computed using two formulations following Power (absolute sum of relative

motions, Power et al. (2014)) and Jenkinson (relative root mean square displacement between affines, Jenkinson et al. (2002)). FD and DVARS are calculated for each functional run, both using their implementations in Nipype (following the definitions by Power et al. 2014). The three global signals are extracted within the CSF, the WM, and the whole-brain masks. Additionally, a set of physiological regressors were extracted to allow for component-based noise correction (CompCor, Behzadi et al. 2007). Principal components are estimated after high-pass filtering the preprocessed BOLD time-series (using a discrete cosine filter with 128s cut-off) for the two CompCor variants: temporal (tCompCor) and anatomical (aCompCor). tCompCor components are then calculated from the top 2% variable voxels within the brain mask. For aCompCor, three probabilistic masks (CSF, WM and combined CSF+WM) are generated in anatomical space. The implementation differs from that of Behzadi et al. in that instead of eroding the masks by 2 pixels on BOLD space, the aCompCor masks are subtracted a mask of pixels that likely contain a volume fraction of GM. This mask is obtained by dilating a GM mask extracted from the FreeSurfer's aseg segmentation, and it ensures components are not extracted from voxels containing a minimal fraction of GM. Finally, these masks are resampled into BOLD space and binarized by thresholding at 0.99 (as in the original implementation). Components are also calculated separately within the WM and CSF masks. For each CompCor decomposition, the k components with the largest singular values are retained, such that the retained components' time series are sufficient to explain 50 percent of variance across the nuisance mask (CSF, WM, combined, or temporal). The remaining components are dropped from consideration. The head-motion estimates calculated in the correction step were also placed within the corresponding

confounds file. The confound time series derived from head motion estimates and global signals were expanded with the inclusion of temporal derivatives and quadratic terms for each (Satterthwaite et al. 2013). Frames that exceeded a threshold of 0.5 mm FD or 1.5 standardized DVARS were annotated as motion outliers. The BOLD time- series were resampled into standard space, generating a preprocessed BOLD run in MNI152NLin2009cAsym space. First, a reference volume and its skull-stripped version were generated using a custom methodology of fMRIPrep. All resamplings can be performed with a single interpolation step by composing all the pertinent transformations (i.e. head-motion transform matrices, susceptibility distortion correction when available, and co-registrations to anatomical and output spaces). Gridded (volumetric) resamplings were performed using antsApplyTransforms (ANTs), configured with Lanczos interpolation to minimize the smoothing effects of other kernels (Lanczos 1964). Non-gridded (surface) resamplings were performed using mri_vol2surf (FreeSurfer).

After preprocessing in FMRIPrep, Matlab scripts (LydiaRiedl, 2021) were used for: a) creating conditions file, b) reading motion regressors from FMRIProep output, c)unzipping preprocessed functional images, and d)smoothing [6 6 6]. Following this, the 1st level analysis was conducted in SPM 12. The task-based fMRI data were analyzed using an event-related general linear model (GLM) estimation approach. To measure proactive control (AY > BY) activation, BOLD signals associated with AY trials were contrasted with BY type control trials and to measure brain activation associated with reactive control (BX > BY), BOLD signals associated with BX trials were contrasted with BOLD activation associated with BY trials.

CHAPTER 3

RESULTS

Behavioral Results

Behavioral Results

The behavior data were analyzed using SPSS software version 27. Table 1 shows the descriptive statistics for the mean reaction time and accuracy rates of two participants on the AX-CPT task in both “ON Levodopa” and “OFF Levodopa” conditions. The mean reaction time of both the patients was less on less in the “On Levodopa” condition as compared to the “Off Levodopa” condition on AX, AY and BY trials of the task. The mean reaction time for both the participants was less on the “OFF Levodopa” condition as compared to the “ON Levodopa” on the BX, Ang and Bng type trials. In addition, for the “ON Levodopa” condition, the mean reaction time of both the participants was fastest on the AX trial, followed by BY, AY and AX trials, respectively. On the “OFF Levodopa” condition, the average performance of both the participants was the fastest in the BY trials, followed by AX, AY and BX trials, respectively. The mean accuracy of both participants on both the “ON Levodopa” and “OFF Levodopa” condition was around 50% for all trial types.

As this study aims to show only the preliminary results of the two participants, conducting inferential statistics was out of scope for the present study because of the small sample size. In the future, paired sample t-test will be conducted to compare the participant’s performance on different trial types of the AX-CPT task on the “On Levodopa” and “OFF Levodopa” condition.

Task Conditions	**ON Levodopa**		**OFF Levodopa**	
	Mean Reaction Times	Accuracy Rates	Mean Reaction Time	Accuracy Rates
AX	380.00 (49.82)	0.52 (0.50)	658.83 (178.00)	0.56 (0.50)
AY	520.83 (84.66)	0.50(0.52)	806.50 (156.74)	0.58 (0.51)
BX	980.50 (264.47)	0.50 (0.52)	820.50 (103.92)	0.50 (0.52)
BY	472.00 (60.90)	0.50 (0.50)	612.29 (157.97)	0.48 (0.50)
Ang	N/A	0.33 (0.49)	N/A	0.50 (0.52)
Bng	N/A	0.33 (0.49)	N/A	0.50 (0.52)
Total	588.33 (267.88)	0.48 (0.50)	724.53 (104.63)	0.52 (0.50)

Table 1: Descriptive Statistics. Shows Mean Reaction Times and Accuracy Rates of Two Participants in "on Levodopa" and "off Levodopa" Condition. The reaction times for "Ang" and "Bng" trials are shown to be as N/A because these were no-go task conditions and reaction times for these conditions were not recorded.

Neuroimaging Results

Whole-brain analysis was conducted to identify brain regions that show the significant effects of a) Proactive cognitive control and b) reactive cognitive control. For both participants, one and two, General Linear models were created. The first-level analysis of both the participants followed an event-related design. The contrasts of interest were: a) BX-BY for reactive control and b) AY-BY for proactive control. This contrast was created for both the participants in "On Levodopa" and "Off Levodopa" conditions.

Proactive control: BOLD activations for proactive control were measured by contrasting BOLD activations associated with AY with BY trials (AY> BY). For the "ON" levodopa

condition in participant one, no brain regions showed significant activations. However, in the “Off” levodopa condition, only the right middle frontal gyrus showed activation. In the “On” levodopa condition for participant two, significant BOLD activations were seen in the left and right Precentral Gyrus, left postcentral gyrus, right Cerebellum exterior, right fusiform gyrus and superior frontal gyrus showed. In the “OFF” levodopa condition, felt and right precentral and postcentral gyrus, left and right precuneus, and superior, inferior, and middle frontal gyrus showed robust activations

Reactive Control: BOLD activations for reactive control were measured by contrasting BX with BY (BX> BY). In the “ON Levodopa” condition for participant one, the activations were shown only in the Right Cerebellum Exterior. In the “OFF Levodopa” condition, robust activations were shown in the Right middle Frontal Gyrus, Right Superior Frontal Gyrus and Right Inferior Frontal Gyrus. In the “ON Levodopa condition, participant two showed robust activations in the Right Agular Gyrus, Right Middle Frontal Gyrus, Right Cerebral White Matter, Left Cerebellum Exterior and Right Caudate. In the “Off Levodopa” condition, significant activations were seen in the Right Middle Frontal Gyrus, Right Angular Gyrus and Left Cerebral White Matter.

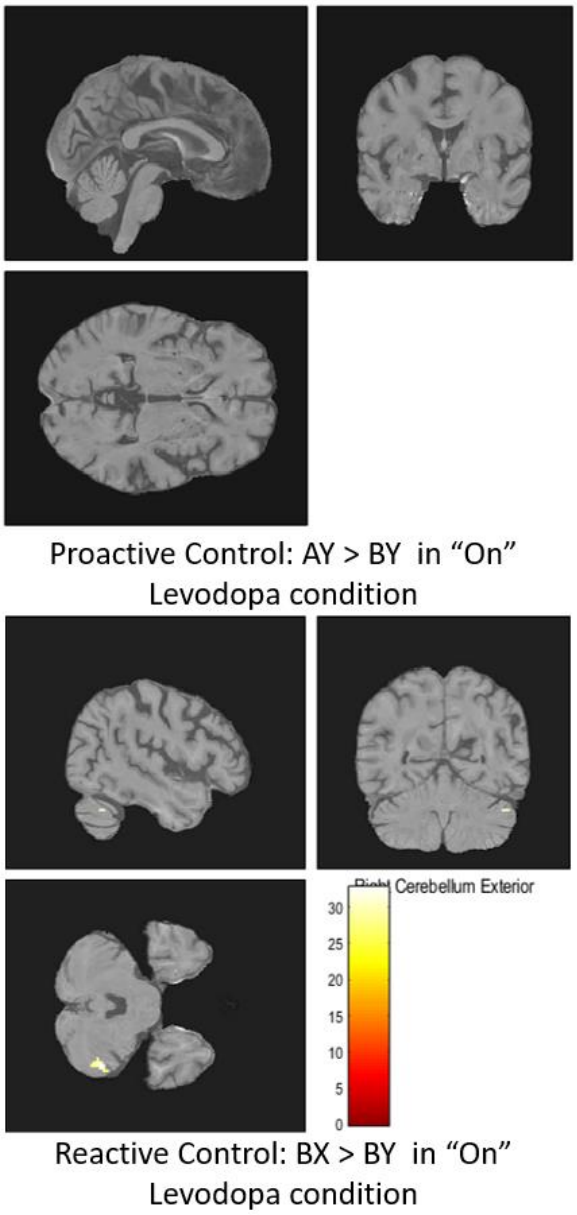
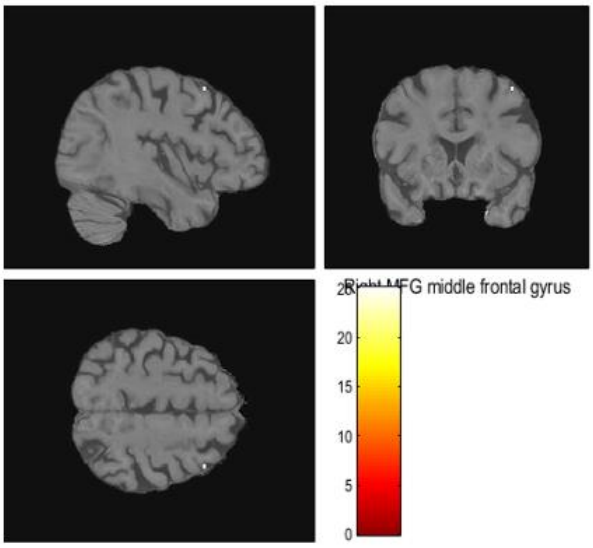
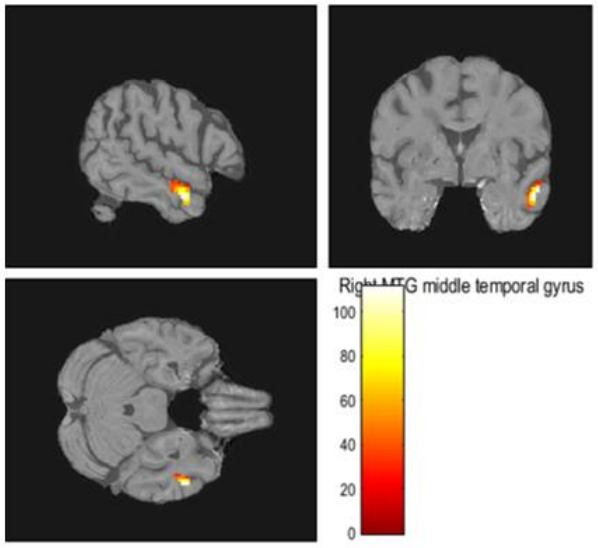


Figure 2: Shows Bold Activation for Participant 1 in the "On" Levodopa Condition for Both Proactive Control (Ay-by) and Reactive Control (Bx-by) Contrasts With FWE at P<.05. The Color Bar on the Right in Both Conditions Shows F-value.

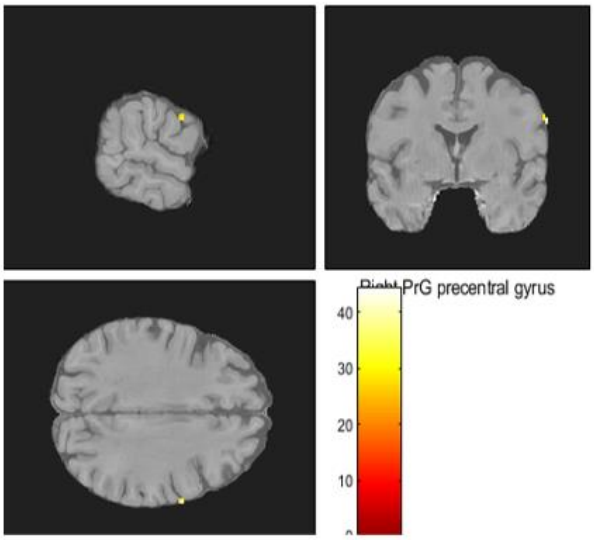


Proactive Control: AY > BY in "Off" Levodopa condition

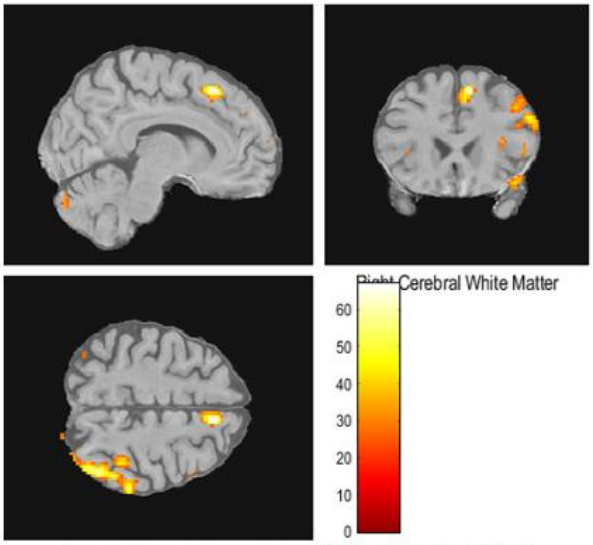


Reactive Control: BX > BY in "Off" Levodopa condition

Figure 3:Shows Bold Activation for Participant 1 in the "Off" Levodopa Condition for Both Proactive Control (Ay-by) and Reactive Control (Bx-by) Contrasts With FWE at P<.05. The Color Bar on the Right in Both Conditions Shows F-value.

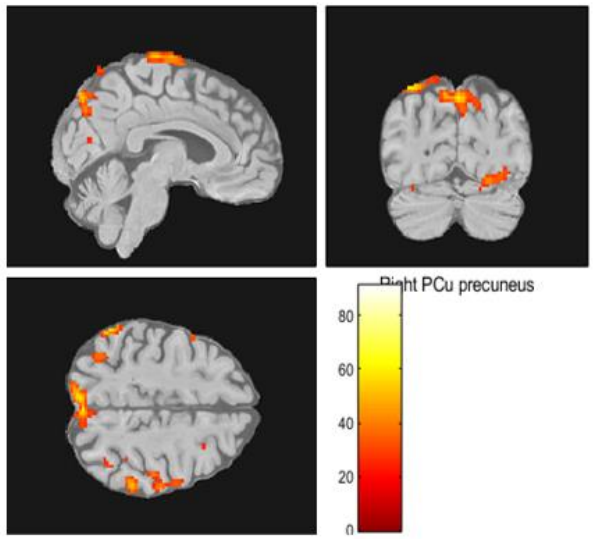


Proactive Control: AY > BY in "On" Levodopa condition

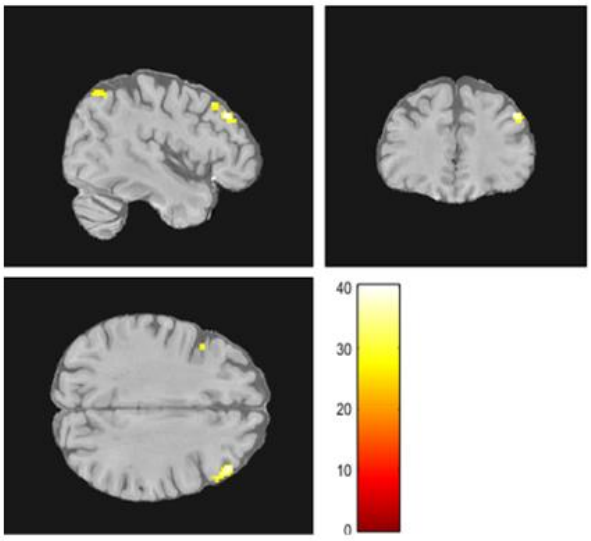


Reactive Control: BX > BY in "On" Levodopa condition

Figure 4: Shows Bold Activation for Participant 2 in the "On" Levodopa Condition for Both Proactive Control (Ay-by) and Reactive Control (Bx-by) Contrasts With FWE at P<.05. The Color Bar on the Right in Both Conditions Shows F-value.



Proactive Control: AY > BY in "Off"
Levodopa condition



Reactive Control: BX > BY in "Off"
Levodopa condition

Figure 5: Shows Bold Activation for Participant 2 in the "Off" Levodopa Condition for Both Proactive Control (Ay-by) and Reactive Control (Bx-by) Contrasts With F at P<.05. The Color Bar on the Right in Both Conditions Shows F-value.

CHAPTER 4

DISCUSSION

The present study aimed to understand the brain activity changes in patients with Parkinson's disease in relation to proactive and reactive control strategies when they were "On Levodopa" medication versus when they were "Off levodopa" medication. The study consisted of two participants who had a prior diagnosis of Parkinson's disease. The BOLD response of these participants was recorded as they performed the AX-CPT task- a measure of attention control in the fMRI scanner. The reaction times and accuracy rates of both the participants were recorded on AX, AY, BX, BY, Ang and Bng trial types on the task when they were "On" levodopa medication and when they were "Off" levodopa medication.

The behavioral results indicated that the average total mean reaction time for both participants was slower when they were off levodopa medication as compared to when they were on Levodopa medication. The mean accuracy rates for both the participants were poor in both "on" Levodopa and "off" levodopa conditions. However, the accuracy rates were slightly higher in the off-levodopa medication condition as compared to the on-levodopa medication condition. Consistent with a few previous findings, less accurate and faster reaction times in "ON" levodopa medication as compared to "OFF" levodopa medication could mean that the performance was faster due to the loss of conflict or response monitoring (Moustafa et al., 2008). The faster reaction times during the "On" condition compared to the "OFF" condition could also indicate that Levodopa was efficient in reducing Bradkinesea in Parkinson's Patients.

In the AX-CPT task, performance on the AY trials is expected to reflect proactive control as these trials require the participant to overcome the interference caused by the maintenance of the contextual information of the target cue "A" when the non-target probe "Y" is presented. Hence, the suppression of the proponent response tendency increases the reaction time in the AY trials (Chiew & Braver, 2017). Whereas performance on the BX trials is expected to reflect reactive control as the bias towards the prior non-target contextual cue "B" must be inhibited through the response bias towards the target probe "X" (Chiew & Braver, 2017). In the present study, proactive response tendency was taken as a measure of reaction times in the AY trials and reactive control strategy was taken as a measure of reaction time in the BY trials. The results indicated that the mean reaction times in the BX trials were slower than in the AY trials in both the "on" and "off" levodopa conditions. This might indicate that participants in both "on" and "off" levodopa conditions made use of the reactive control strategy rather than the proactive control strategy.

However, due to the lack of data and the absence of inferential statistics, no definitive conclusion can be drawn based only on descriptive statistics. In the future, the present study should incorporate paired sample t-test to make conclusions. In addition, the present study should also measure the Proactive Behavior Index (PBI), which is calculated by: (AY-BX)/(AY +BX). The proactive behavior Index is positive for the proactive control tendency and negative for the reactive control tendency. Even though Proactive Behavior Index was originally calculated only for the error rates, recent studies have used this index with reaction times as well (Ličen et al., 2016)

Neuroimaging analysis was conducted to understand the brain and behavior relationship of the participants as they performed the AX-CPT task. The General Linear Model was generated for both participants in “ON” and “OFF” levodopa conditions for both the participants. The AY>, BY contrast, was set to look at the BOLD activations associated with proactive interference (AY) as compared to the control condition (BY). Whereas BX - BY contrast was set to look at significant BOLD activations associated with reactive control strategy (BX) when compared with the control condition (BY). It was observed that for both the participants, robust and widespread activations were associated with reactive control as compared to proactive control. In the future, group-level analysis for the present study will include conducting paired sample t-tests to compare significant activations associated with reactive and proactive control strategies in the “On” levodopa condition and “Off” levodopa condition. Even though the present study does not make any formal conclusions, it was observed that both the behavior and brain data show participants’ tendency towards reactive control in both “On” levodopa and “Off” levodopa conditions

REFERENCES

Behzadi, Y., Restom, K., Liau, J., & Liu, T. T. (2007). A component based noise correction method (CompCor) for BOLD and perfusion based fMRI. *NeuroImage, 37*(1), 90–101. https://doi.org/10.1016/j.neuroimage.2007.04.042

Braak, H., Ghebremedhin, E., Rüb, U., Bratzke, H., & Del Tredici, K. (2004). Stages in the development of Parkinson's disease-related pathology. *Cell and Tissue Research, 318*(1), 121–134. https://doi.org/10.1007/s00441-004-0956-9

Braver, T. S. (2012). The variable nature of cognitive control: A dual mechanisms framework. *Trends in Cognitive Sciences, 16*(2), 106–113. https://doi.org/10.1016/j.tics.2011.12.010

Braver, T. S., Barch, D. M., & Cohen, J. D. (1999). Cognition and control in schizophrenia: A computational model of dopamine and prefrontal function. *Biological Psychiatry, 46*(3), 312–328. https://doi.org/10.1016/S0006-3223(99)00116-X

Braver, T. S., & Cohen, J. D. (1999). Chapter 19 Dopamine, cognitive control, and schizophrenia: The gating model. In *Progress in Brain Research* (Vol. 121, pp. 327–349). Elsevier. https://doi.org/10.1016/S0079-6123(08)63082-4

Braver, T. S., Satpute, A. B., Rush, B. K., Racine, C. A., & Barch, D. M. (2005). Context Processing and Context Maintenance in Healthy Aging and Early Stage Dementia of the Alzheimer's Type. *Psychology and Aging, 20*(1), 33–46. https://doi.org/10.1037/0882-7974.20.1.33

Chiew, K. S., & Braver, T. S. (2017). Context Processing and Cognitive Control. In *The Wiley Handbook of Cognitive Control* (pp. 143–166). John Wiley & Sons, Ltd. https://doi.org/10.1002/9781118920497.ch9

Cools, R. (2001). Enhanced or Impaired Cognitive Function in Parkinson's Disease as a Function of Dopaminergic Medication and Task Demands. *Cerebral Cortex, 11*(12), 1136–1143. https://doi.org/10.1093/cercor/11.12.1136

Cools, R. (2016). The costs and benefits of brain dopamine for cognitive control. *WIREs Cognitive Science*, *7*(5), 317–329. https://doi.org/10.1002/wcs.1401

Cools, R., Barker, R. A., Sahakian, B. J., & Robbins, T. W. (2003). L-Dopa medication remediates cognitive inflexibility, but increases impulsivity in patients with Parkinson's disease. *Neuropsychologia*, *41*(11), 1431–1441. https://doi.org/10.1016/S0028-3932(03)00117-9

Cools, R., & D'Esposito, M. (2011). Inverted-U–Shaped Dopamine Actions on Human Working Memory and Cognitive Control. *Biological Psychiatry*, *69*(12), e113–e125. https://doi.org/10.1016/j.biopsych.2011.03.028

Cox, R. W., & Hyde, J. S. (1997). Software tools for analysis and visualization of fMRI data. *NMR in Biomedicine*, *10*(4–5), 171–178. https://doi.org/10.1002/(SICI)1099-1492(199706/08)10:4/5<171::AID-NBM453>3.0.CO;2-L

Dale, A. M., Fischl, B., & Sereno, M. I. (1999). Cortical Surface-Based Analysis: I. Segmentation and Surface Reconstruction. *NeuroImage*, *9*(2), 179–194. https://doi.org/10.1006/nimg.1998.0395

Dorsey, E. R., Sherer, T., Okun, M. S., & Bloem, B. R. (2018). The Emerging Evidence of the Parkinson Pandemic. *Journal of Parkinson's Disease*, *8*(s1), S3–S8. https://doi.org/10.3233/JPD-181474

Edwards, B., Barch, D., & Braver, T. (2010). Improving prefrontal cortex function in schizophrenia through focused training of cognitive control. *Frontiers in Human Neuroscience*, *4*. https://www.frontiersin.org/article/10.3389/fnhum.2010.00032

Fonov, V., Evans, A., McKinstry, R., Almli, C., & Collins, D. (2009). Unbiased nonlinear average age-appropriate brain templates from birth to adulthood. *NeuroImage*, *47*, S102. https://doi.org/10.1016/S1053-8119(09)70884-5

Goldman, J. G., Vernaleo, B. A., Camicioli, R., Dahodwala, N., Dobkin, R. D., Ellis, T., Galvin, J. E., Marras, C., Edwards, J., Fields, J., Golden, R., Karlawish, J., Levin, B., Shulman, L., Smith, G., Tangney, C., Thomas, C. A., Tröster, A. I., Uc, E. Y., … Simmonds, D. (2018). Cognitive impairment in Parkinson's disease: A report from a multidisciplinary symposium on unmet needs and future directions to maintain cognitive health. *Npj Parkinson's Disease*, *4*(1), 19. https://doi.org/10.1038/s41531-018-0055-3

Gotham, A.-M., Brown, R. G., & Marsden, C. D. (1986). LEVODOPA TREATMENT MAY BENEFIT OR IMPAIR 'FRONTAL' FUNCTION IN PARKINSON'S

DISEASE. *The Lancet*, *328*(8513), 970–971. https://doi.org/10.1016/S0140-6736(86)90617-3

Greve, D. N., & Fischl, B. (2009). Accurate and robust brain image alignment using boundary-based registration. *NeuroImage*, *48*(1), 63–72. https://doi.org/10.1016/j.neuroimage.2009.06.060

Grisetto, F., Delevoye-Turrell, Y. N., & Roger, C. (2021). Slower adaptation of control strategies in individuals with high impulsive tendencies. *Scientific Reports*, *11*(1), 20368. https://doi.org/10.1038/s41598-021-99764-1

Jankovic, J. (2008). Parkinson's disease: Clinical features and diagnosis. *Journal of Neurology, Neurosurgery & Psychiatry*, *79*(4), 368–376. https://doi.org/10.1136/jnnp.2007.131045

Jenkinson, M., Bannister, P., Brady, M., & Smith, S. (2002). Improved Optimization for the Robust and Accurate Linear Registration and Motion Correction of Brain Images. *NeuroImage*, *17*(2), 825–841. https://doi.org/10.1006/nimg.2002.1132

Klein, A., Ghosh, S. S., Bao, F. S., Giard, J., Häme, Y., Stavsky, E., Lee, N., Rossa, B., Reuter, M., Neto, E. C., & Keshavan, A. (2017). Mindboggling morphometry of human brains. *PLOS Computational Biology*, *13*(2), e1005350. https://doi.org/10.1371/journal.pcbi.1005350

Lanczos, C. (1964). Evaluation of Noisy Data. *Journal of the Society for Industrial and Applied Mathematics Series B Numerical Analysis*, *1*(1), 76–85. https://doi.org/10.1137/0701007

Latif, S., Jahangeer, M., Maknoon Razia, D., Ashiq, M., Ghaffar, A., Akram, M., El Allam, A., Bouyahya, A., Garipova, L., Ali Shariati, M., Thiruvengadam, M., & Azam Ansari, M. (2021). Dopamine in Parkinson's disease. *Clinica Chimica Acta*, *522*, 114–126. https://doi.org/10.1016/j.cca.2021.08.009

Ličen, M., Hartmann, F., Grega, R., & Slapnicar, S. (2016). The Impact of Social Pressure and Monetary Incentive on Cognitive Control. *Frontiers in Psychology*, *7*. https://doi.org/10.3389/fpsyg.2016.00093

LydiaRiedl. (2021). *Gplus* [MATLAB]. https://github.com/LydiaRiedl/fmriprep2spm (Original work published 2021)

Moustafa, A. A., Sherman, S. J., & Frank, M. J. (2008). A dopaminergic basis for working memory, learning and attentional shifting in Parkinsonism. *Neuropsychologia*, 46(13), 3144–3156. https://doi.org/10.1016/j.neuropsychologia.2008.07.011

Onur, Ö. A., Piefke, M., Lie, C.-H., Thiel, C. M., & Fink, G. R. (2011). Modulatory effects of levodopa on cognitive control in young but not in older subjects: A pharmacological fMRI study. *Journal of Cognitive Neuroscience*, *23*(10), 2797–2810. https://doi.org/10.1162/jocn.2011.21603

Ott, T., & Nieder, A. (2019). Dopamine and Cognitive Control in Prefrontal Cortex. *Trends in Cognitive Sciences*, *23*(3), 213–234. https://doi.org/10.1016/j.tics.2018.12.006

Power, J. D., Mitra, A., Laumann, T. O., Snyder, A. Z., Schlaggar, B. L., & Petersen, S. E. (2014). Methods to detect, characterize, and remove motion artifact in resting state fMRI. *NeuroImage*, *84*, 320–341. https://doi.org/10.1016/j.neuroimage.2013.08.048

Reuter, M., Rosas, H. D., & Fischl, B. (2010). Highly accurate inverse consistent registration: A robust approach. *NeuroImage*, *53*(4), 1181–1196. https://doi.org/10.1016/j.neuroimage.2010.07.020

Satterthwaite, T. D., Elliott, M. A., Gerraty, R. T., Ruparel, K., Loughead, J., Calkins, M. E., Eickhoff, S. B., Hakonarson, H., Gur, R. C., Gur, R. E., & Wolf, D. H. (2013). An improved framework for confound regression and filtering for control of motion artifact in the preprocessing of resting-state functional connectivity data. *NeuroImage*, *64*, 240–256. https://doi.org/10.1016/j.neuroimage.2012.08.052

Schrag, A., Jahanshahi, M., & Quinn, N. (2000). What contributes to quality of life in patients with Parkinson's disease? *Journal of Neurology, Neurosurgery, and Psychiatry*, *69*(3), 308–312. https://doi.org/10.1136/jnnp.69.3.308

Swainson, R., Rogers, R. D., Sahakian, B. J., Summers, B. A., Polkey, C. E., & Robbins, T. W. (2000). *Probabilistic learning and reversal de®cits in patients with Parkinson's disease or frontal or temporal lobe lesions: Possible adverse e€ects of dopaminergic medication*. 17.

Tustison, N. J., Avants, B. B., Cook, P. A., Zheng, Y., Egan, A., Yushkevich, P. A., & Gee, J. C. (2010). N4ITK: Improved N3 Bias Correction. *IEEE Transactions on Medical Imaging*, *29*(6), 1310–1320. https://doi.org/10.1109/TMI.2010.2046908

Zhang, Y., Brady, M., & Smith, S. (2001). Segmentation of brain MR images through a hidden Markov random field model and the expectation-maximization algorithm. *IEEE Transactions on Medical Imaging*, *20*(1), 45–57. https://doi.org/10.1109/42.906424