Diffusion Imaging Analysis

of the Functional Heterogeneity in the Dopaminergic System:

Correlates with Prospective Memory

by

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ABSTRACT

Dopamine neurons are essential for several aspects of cognition. Several decades of Parkinson's Disease (PD) research have revealed that the deterioration of these neurons is associated with a wide range of cognitive deficits such as attention, motor coordination, and memory. The diversity of these deficits is a demonstration of the structural and functional heterogeneity within the dopaminergic system; projections from the substantia nigra and the ventral tegmental area to striatum have targets in the frontal and medial temporal cortices. It is known that prospective memory is negatively affected by PD, but whether the deficits originate from pathways that support attention, retrospective memory, working memory, and/or motor control has not yet been determined. For the current study, the goal is to estimate the structural integrity of these pathways by using diffusion-imaging analysis to then correlate these estimates with prospective memory performance within a standard event-based task. Two participant data sets were reported in the current study and compared with the global and target fractional anisotropy as well as seed connectivity. All the results reported here are preliminary.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER 1

INTRODUCTION

For several decades, the neuromodulator Dopamine (DA) has been primarily characterized as an essential component in neural pathways that are responsible for the encoding of reward prediction signals and the facilitation of motor control (Marsden, 2006; Schultz and Montague, 1997). Part of this narrative is supported by evidence of the effects that neurodegeneration has within Parkinson's Disease (PD) and the mechanistic paradigms that have sought to understand the structure and function of DA from a cellular and molecular perspective (Mishra et al., 2018; Henny et al., 2012). Limitations in technology have precluded the scientific community from being able to replicate and investigate these mechanistic features in live humans, however, the relationship between DA and its function is demonstrated by a multitude of observable phenomena ranging from complex cognitive behavior like decision making, to rudimentary abilities such as pupillary modulation (Van Slooten et al., 2019).

Neurons exhibit distinct morphological characteristics that relate to their role in the nervous system (Stiefel and Sejnowski, 2007; Chklovskii, 2004; Subramaniam and Roeper, 2017). In the midbrain, dopaminergic cells in the substantia nigra (SN) and the ventral tegmental area (VTA) demonstrate exceptional heterogeneity in function which translates to wide-ranging behaviors (Lammel et al., 2008; Lammel et al., 2014; Marinelli and McCutcheon, 2014); one main factor that influences this diversity is the projections to other regions and the pathways and circuits that they are embedded in (Martel et al., 2020; Subramaniam and Roeper, 2017). Through the mesolimbic and mesocortical

pathways, the VTA can act on targets such as the ventral striatum, which contains the nucleus accumbens (NAc), and the Prefrontal Cortex (PFC), respectively. The nigrostriatal pathway allows the SN to project to caudate and putamen in the dorsal striatum (Latif et al., 2021). Dopamine's function is further diversified by the genetic encoding of receptor subtypes. These DA subtypes are grouped based on their pharmacological profiles; D1 and D5 belong to the D1 class, while the D2-4 belong to the D2 class (Latif et al., 2021). Overall, there are layers of complexity within the dopaminergic system which presents a challenge in being able to ascertain specific unitary functions, especially in cognition.

In the aforementioned role of modulating decision making, DA has been shown to predict outcomes and performance in popular cognitive tasks like Delay Discounting, Go/No-go, and Serial Reaction Time (Yun et al., 2020; Peters et al., 2020; Joutsa et al., 2015). The coupling of these tasks with pharmacological interventions such as Haloperidol and L-Dopa, further exemplifies the effects of dopaminergic modulation on cognitive abilities (Freels et al., 2020;).

For several decades now, the link between DA and Attention Deficit Hyperactivity Disorder (ADHD) has elicited a movement in neuroscience and psychology, to dive into its etiology and to find enduring treatments. Methylphenidate, just one of many prescriptions available for individuals with ADHD, is thought to work by increasing DA (Gottlieb, 2001) which amplifies phasic DA firing patterns. In 2019, Fukai and colleagues were able to measure extracellular DA induced by transcranial direct current stimulation; this study also showed a positive correlation between DA

release in the striatum and performance on an attention task. Conversely, there are studies that show attention deficits are the result of too much phasic DA (Badgaiyan, 2015). Regardless of the positive or negative correlation, the significance of DA in being able to attend to stimuli is evident.

Memory subserves most aspects of executive function. A sense of identity and continuity of self is memory dependent. Engaging in routine behaviors like driving, or even using language requires memory. Episodic memory, a subtype of retrospective memory, allows previous information and experiences to be stored and remembered (Ziedman and Macguire, 2016). The ability to maintain content within cognition for even in some cases, a brief amount of time is through the use of working memory; the computational flexibility of DA is manifested in roles such as gating for relevant sensory information, maintenance of that information, and passing it along to areas responsible for motor control (D'Ardenne et al., 2012; Ott and Nieder, 2019; Spillers et al., 2012) Furthermore, these computations speak to the demonstrable loss of stability and regulation in the brains of individuals with schizophrenia (Braun et al., 2021)

Prospective memory (PM) is the storage of delayed future intentions and retrieval of those intentions at the appropriate moment (Kliegel et al.,2011). PM utilizes both attention and retrospective memory (Brewer and Marsch, 2010, which ultimately are influenced by DA (Kleigel et al., 2011; Clos et al., 2019, Cona et al., 2015). In the process model of PM, encoding–driven by attention– and retrieval are dissociable. Though previous studies have identified separate structural correlates for encoding and retrieval processes, inconclusive and varied results create a challenge in being able to

isolate the component process that accounts for PM failures (Kleigel et al., 2002; Burgess et al., 2011; Gordon et al., 2011; Spreng et al., 2018).

Currently, much of what is known about PD is centered around the idea of neurodegeneration of SN neurons and the downstream effects that this has on cognition. However, the manner in which these effects occur is not well understood (Luo et al., 2016). Much of the literature posits that SN neurons send signals along the nigrostriatal pathway, which is primarily responsible for motor control, yet the mesolimbic and mesocortical pathways are indubitably affected; deficits in working, prospective, and retrospective memory, as well as attention, and emotional regulation have been documented (Grogan et al., 2015; Luo et al., 2016; Lebowitz et al., 2020). Therefore, investigating the structural and functional overlap between these pathways is necessary for being able to provide targeted therapies based on symptoms but also to improve the diagnostic process.

Research on structural correlates of executive functioning has established that the medial temporal lobe (MTL) and PFC are key regions that support memory and attention, respectively (Race et al., 2011; Scullin et al., 2020; Tritsch and Sabatini, 2012). A subregion of the PFC, called the Orbitofrontal Cortex (OFC) has become known for its involvement in executive processes since it is so highly connected with other regions in the brain in addition to the midbrain (Yun et al 2020; Kahnt and Tobler, 2017). Previous research examining the mechanism of attention in the context of stimulus valuation points to the OFC as being a main coordinator of attention (McGinty et al., 2016; Yun et al.,

2020; Winstanley et al., 2010). Whether or not OFC is uniquely modulating attention through DA from SN or VTA is the direction that the current study intends to take.

Structural connectivity is a representation of brain tissue–axons–that physically span between regions; often, these are functionally related. Regions that exhibit high connectivity are typically dense with fibers, like the corpus callosum, which integrates information from the left and right hemispheres of the brain. In diffusion-weighted imaging, connectivity can be calculated through modeling the distribution of water molecules in 3D space. Fractional anisotropy assigns a value between 0 and 1 to voxels with water that diffuses freely in all directions or is restricted; high anisotropy is indicative of axonal tissue being present (Behrens et al, 2003; Behrens et al., 2007;).

The current study aims to extend the research done that compares the detection and retrieval components of PM failures (Ball et al, 2021) and the connectivity between midbrain DA pathways (Murty et al., 2014, Tziortzi et al., 2014; Kwon and Jang, 2014). This study hypothesizes that connectivity will be positively correlated with PM task performance. Specifically, more OFC connectivity will result in better attention (detection) performance, and that more MTL connectivity will result in better retrieval. Diffusion Imaging will be used to quantify connectivity using probabilistic tractography and tensor modeling. Another aim of this study is to investigate the differences between pathway connectivity of the SN and VTA separately, in order to probe the idea that SN DA degeneration is shared with the VTA mesocortical and mesolimbic pathways.

CHAPTER 2

METHODS

Participants

Flyers were posted around the Arizona State University campus, at Neurological clinics, and near local support groups to recruit both neurotypical and PD individuals ranging between the ages of 18-and 95. Verbal consent for a phone screening took place to determine eligibility and consent for participation in the study. Individuals Two sessions for each participant were conducted; the total time that each participant was enrolled was 3 weeks for PD participants, and 2 weeks for neurotypicals. Three participant data sets are reported in this preliminary study. Data collection will continue, and a payment of $30 per visit is provided to all participants.

Task Procedure

The design for the prospective memory tasks is a modified version from other task paradigms, which dissociate the memory and retrieval components of a standard pm task. (Ball et al., 2021; Simon et al., (2006). For the current study, participants were given two sets of pm tasks, one with words and one with shapes. Participants completed the tasks in two sessions, and they were counterbalanced by task type (detection or retrieval), task category (letters or shapes), and medication status (On/Off). As an example, if the participant completed a letter detection and shape retrieval during the first session, for the next session they would complete letter retrieval and shape detection. The specific instructions for the tasks were provided each session and several practice trials were administered to ensure that the participants understood the tasks and had the ability to complete them.

PMD-Letter. The participants were provided a series of unrelated word pairs (i.e) and the ongoing task requirement was to decide which word had more letters by pressing F for the right and J for the left word. When the words presented were semantically related, the participants would need to press the F5 key.

PMD-Shape. For the ongoing shape task, a 4x4 array was shown with a triangle and another shape. The participants needed to press the F key if the other shape was positioned to the left of the triangle or press the J key if the shape was positioned to the right of the triangle. If the shapes were arranged in the configuration of a "knight's move" (L-shape), the participants would need to press the F5 key.

PMR-Letter. The ongoing task was the same as PMD-letter however when the words were presented were both in uppercase, the participant would need to count the syllables for the both words and determine if the total number of syllables in the pair was less than or equal to four and then the participant would need to press the A key; if the syllable count was more than 4, then they would press the L key.

PMR-Shape. The ongoing task was the same as the PMD-shape, however when the shapes presented were the same color, the participants needed to count the total number of sides for the non-triangle shape; if this number was less than or equal to 5, then the participants needed to press the A key and if it was greater than 5, they needed to press the L key.

Each task block ran for 170 trials and was self-paced. Task performance was assessed by the number of correct PM responses across all trials (Figure 1).

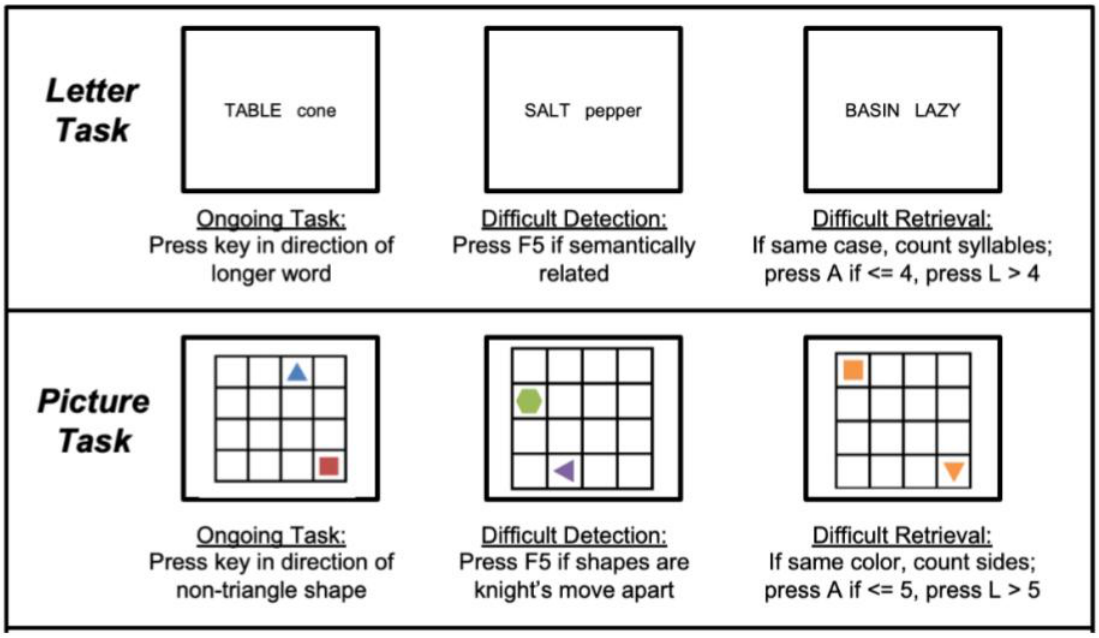

Figure 1. *Prospective Memory Task Paradigm* (modified from Ball et al., 2021)

MRI Acquisition Data

A Phillips Ingenia 3T with a 32- channel head coil was used to acquire the MRI scans at Barrow Neurological Institute in Phoenix, Arizona. T1-weighted images were captured in the sagittal plane using a single-shot, magnetization-prepared rapid gradient echo (TR= 13 ms, TE= 4.5 ms, FOV= 256 mm, slices=180).

Diffusion-weighted Image Processing and Analysis

Diffusion-weighted images were acquired in 64 directions with gradient sensitivities of b=1500 s/mm^2 in addition to a single non-diffusion B0 image, which composed a 4D 128x128x80x65 volume (voxels=1x1x2 mm^3).

To analyze the diffusion data, the FSL toolbox(www.fmrib.ox.ac.uk/fsl) and the methods used by Elliot et al., (2021), served as a framework for the steps in the processing and analysis pipeline of this study. For each participant data set, magnetic

current and motion artifacts were corrected and DTIFIT, which models the diffusion tensor in each voxel, was used to generate FA maps. Diffusion parameters were estimated within each voxel using Bedpostx. The tractography (probtrackx) was conducted from the SN and VTA seed masks to the target OFC and MTL masks using the default parameters of 5000 samples per voxel, a curvature threshold of 0.2, 2000 steps, and a 0.5mm step-length. Both sets of masks were obtained from open data sets on the website Neurovault (SN/VTA-https://identifiers.org/neurovault.collection:3145; MTL-https://neurovault.org/collections/373; Figure 2) .

For each participant, the transformation matrix created from the non-linear registration was applied to the FA map, which was then multiplied by the path distribution; the result was a FA path distribution from the seed to the target region. This volume was multiplied by the target mask to obtain the localized FA values and then averages were computed. The seed-to-target connectivity quantified during the fiber tracking was also compared between participants and regions (SN vs VTA).

CHAPTER 3

RESULTS

Tractography and Task Performance

Participant ATN002 scored significantly better on the PMD tasks compared to participant ATN006; for the second day of testing, ATN006 failed to produce the appropriate response for the picture detection task altogether. However, global FA values between the two participants were somewhat similar.

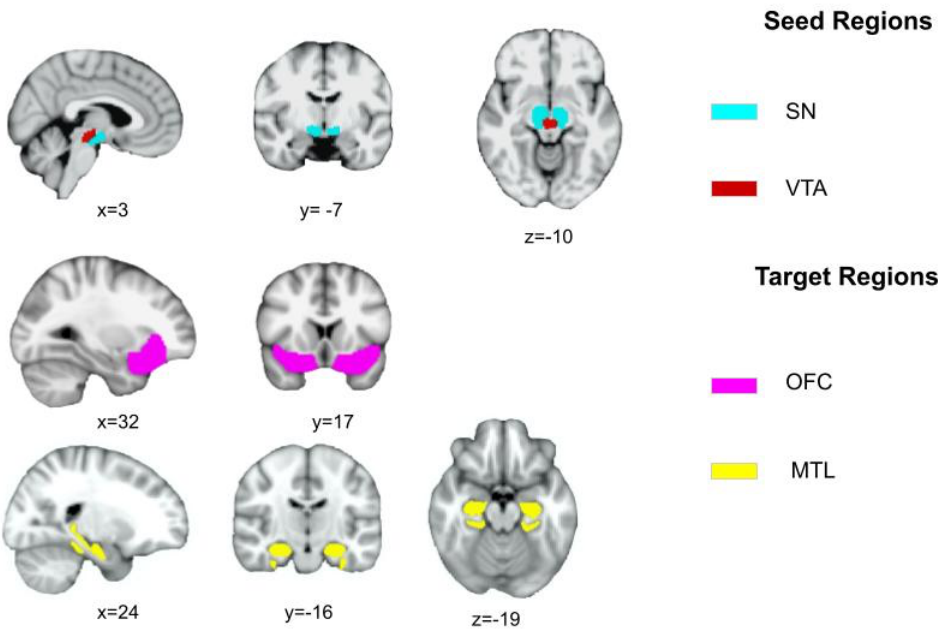

Figure 2. *Seed and Target Masks*

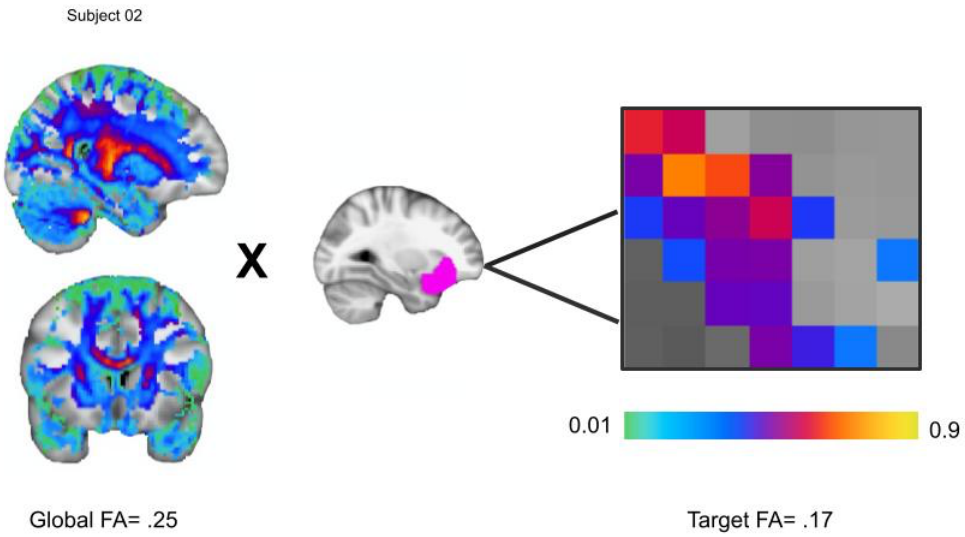

Figure 3. *SN to OFC Path Distribution*

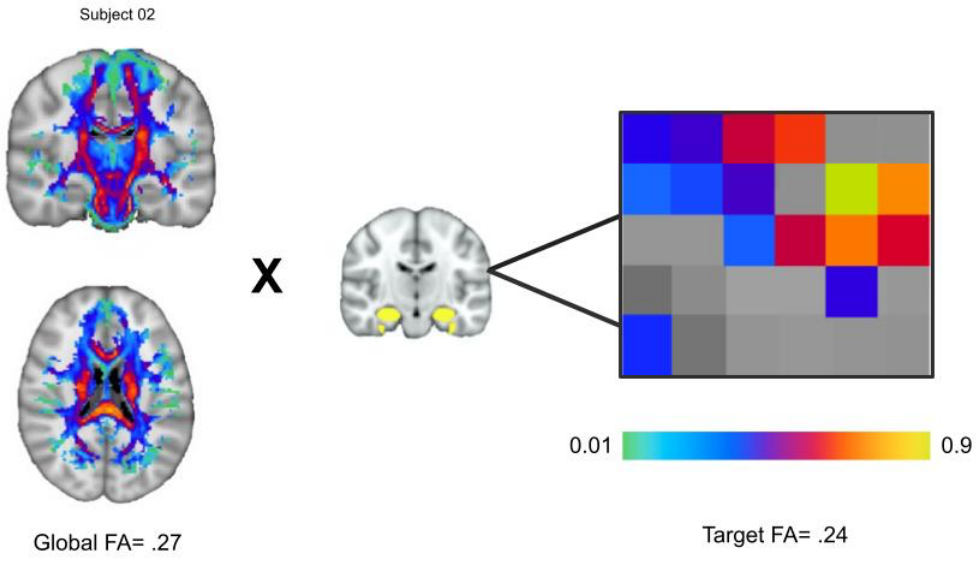

Figure 4. *VTA to MTL Path Distribution*

Moreover, the global FA distribution from VTA was higher than the FA distribution from SN in both participants. A noticeable difference is seen in the target region FA values for ATN006, as there is a decrease ranging from approximately 20-40 percent; this same reduction in FA from global to target region only ranges from approximately 20-30 percent for ATN002 (Table 1).

The SN seed connectivity was higher for both participants, but this was due to higher connectivity for the MTL overall (M=176.4, SD=56.2). This was also seen to a lesser degree with the VTA to MTL seed connectivity (M= 26.9, SD=11.8), see Table 2 for reference.

Currently, the sample size is insufficient for further statistical analysis. Upon completion of participant recruitment, t-tests for the PMDR and PMD should be used to assess if performance between the two demonstrates an effect of task type. An ANOVA

can be used to examine the influence of the DTI measures on performance, and lastly, correlations between task performance and DTI measures can help to uncover whether there is a relationship between task performance and the DTI measures obtained.

Table 1

PMDR Task Scores, Means, and Fractional Anisotropy

	PM Detection		PM Retrieval		PM Mean		Global FA				Target FA			
Subject	PMD-L	PMD-P	PMR-L	PMR-L	PMD	PMR	S:O	S:M	V:O	V:M	S:O	S:M	V:O	V:M
ATN002	0.67	1.00	0.33	0.50	0.84	0.42	0.25	0.22	0.27	0.27	0.17	0.23	0.20	0.24
ATN006	0.33	0	0.33	0.67	0.17	0.50	0.27	0.27	0.30	0.30	0.21	0.17	0.19	0.17

Note: PM Mean is calculated between the two sessions. The FA values reported in this table are statistical means which were calculated using fslstats and they are rounded up to the nearest hundredth. S:O is SN to OFC, S:M is SN to MTL, V:O is VTA to OFC and V:M is VTA to MTL.

Table 2

Seed Connectivity Profiles

					Group			
Subject	S:O	S:M	V:O	V:M	S:O	S:M	V:O	V:M
ATN002	11.8	216.2	4.62	35.21	13.78	176.45	3.34	26.85
ATN006	15.76	136.7	2.05	18.49	SD			
					2.80	56.21	1.82	11.82

Note: Seed Connectivity values are defined as samples within the seed voxel that have a high probability of terminating in the target ROI. Values are averaged over the entire volume for each subject using fslstats.

CHAPTER 4

DISCUSSION

The goal of the current study was to apply the PM component task model (Ball et al, 2021;) with diffusion tensor analysis to evaluate whether the connectivity between midbrain DA pathways could predict performances. It was specifically hypothesized that poor performance in the PM detection task could be the manifestation of loss in connectivity to the OFC, whereas poor performance in the PM-retrieval task would be accounted for by the loss in connectivity to the MTL. Due to the sample size limitation for this current study, the hypothesis that connectivity would be positively correlated with PM task performance has yet to be fully addressed. One participant, ATN006, did show decreased performance and a marked decrease in target region FA compared to ATN002. The influence of this change in global FA is notable, but there may be other factors to consider. Namely, the structural T1 images from ATN006 seem to indicate progression of PD beyond the midbrain, which translated to an absence of signal in the diffusion images. Further testing will provide insights regarding the meaningfulness of the changes between global FA and target FA and whether these changes would be indicative of pathologies.

The second goal was to assess whether the connectivity profiles between SN and VTA were substantially distinct, following the assumption that mesolimbic and mesocortical paths from the VTA project to the MTL and OFC, respectively, and that the nigrostriatal primarily projects to striatum. For the two participants, the connectivity profiles of SN and VTA in terms of global FA, were very similar. Connectivity from SN

to MTL was higher than VTA to MTL which replicates some of the findings from Kwon and Jang (2014), however, they found that MTL connectivity was about the same for both SN and VTA. The collection of more data should reveal whether this is a trend which would challenge the current ideas about the segregation of function in dopaminergic pathways.

Within many tasks, there are multiple ways of measuring performance. For the current study, the average PM score was calculated as the percent of PM targets that the participant correctly responded to, and for the hypothesis about performance, this suffices. Since myelination serves to expedite the propagation of neural signals, analyzing reaction time as a covariate for connectivity could show can contribute to the understanding of structural properties that are modulating the function of prospective memory.

The FSL tractography pipeline conducts registration across all three spaces (standard, structural, diffusion), and there are many options for optimization of the registration parameters. As a result, there is more opportunity for error in the estimation of streamlines due to miscalculation of the affine matrices for warping the regions from one space to another and this was seen to a degree, in the present study. One way this can be minimized is by using a free-hand segmentation tool to create the ROIs in the subject space(native) instead of atlases that are in the standard space.

By exploring other tools in FSL like the connectivity matrix and hard segmentation, for example, more information about the patterns of seed and target connectivity can be obtained. Moreover, there are several other diffusion and

tractography pipelines that exist and can be used as a comparison to see if the data from the current study replicates or if there are new features that can be implemented to augment the measurement profiles.

Ultimately, the goal of neuroimaging is to provide some quantifiable assessment of the structures and functions that undergird cognition and behavior; PM is crucial for being able to set, maintain and achieve goals in the context of ongoing events. Deficits in PM are seen across various psychopathologies like ADHD and OCD (Altgassen et al., 2019; Bhat et al., 2018); importantly, they are also seen in patients with PD (Kliegel et al., 2011) though DA degeneration is characterized as being nigrostriatal and mostly motor related. The relationship between PM deficits and their origins in terms of the connectivity between structures across all pathologies needs to be investigated further as this will aid in the composition of clinical models for disease prediction, diagnosis, and prognosis.

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