

**The Disassociation Between Motor Output Pathway
with Reduced Parkinson's Motor Symptoms Decline
Promotes New Possibilities in Neuroimaging**

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**A Thesis submitted to the Faculty of Graduate Studies in Partial
Fulfillment of the Requirements for the Degree of Master of Arts**

Graduate Program in Interdisciplinary Studies

York University

Toronto, Ontario

June 2025

Abstract

Dance has been proven effective in slowing Parkinson's Disease (PD) progression in research and therapies. However, the neurological underpinning of how long-term dance slows PD motor decline is unknown. This study focuses on how dance benefits the brain leading to preserved motor ability. Using Diffusion Tensor Imaging (DTI), we extracted integrity measures of the motor pathway and compared them against within-subject control tracts. We found that all the white matter metrics in the motor pathway remained constant during the 3-month period. We propose that the non-motor aspects of dance are the ones that make dance superior to an intensity-controlled exercise regime. However, the limited sample size and short time between the tractography leave this idea to be validated in future data collections. This study is the first to describe the microstructural changes within PD patients with continuous dance participation. It provides valuable insight into non-invasive and non-medical PD interventions.

Acknowledgements

It has been a different life since I walked out of university and conducted my independent research; everything seems to be on my own! It has been a tough two years, and I will not be the same man now without the support from my supervisors, family, friends, pets, this faculty, and the community around me. I was a blank canvas fresh out of school, and all of you made my experience rich and full.

First and foremost, I'd like to thank my supervisor, Dr. Joseph DeSouza, for all his support and understanding along my journey, and for always having faith in me when I was under the weather. Talking with you will always inspire new ideas, not only for the project, but also for the way to succeed in life as an academic. Like we always said, I still can't believe how we pulled this off! I fully appreciate that you saw the potential in me, trusted me to work in your lab, devoted time and insight when we got stuck on problems, and offered me the opportunity that enabled me to reach a greater platform. I will cherish this invaluable time that we worked together, and it will always inspire me to move forward.

I'd also like to extend my appreciation to my supervisory committee members, Dr. Alexander Barnett and Dr. Rebecca Barnstaple, for their guidance and support along the way, with their knowledge and patience. I've worked with Dr. Barnett for 3 years, and I always see him as a role model for my academic journey. He was incredibly patient, helpful, and understanding when we got stuck on technical problems. He would always nicely answer my (sometimes dumb) questions and wouldn't mind if I made (sometimes stupid) mistakes. And thank you for continuing to let me use your lab space at the University of Toronto, which saved me lots of time and frustration in commuting. Working with Dr. Barnstaple was a charm! We had many pleasant times discussing neuroscience and dance, which exposed me to ideas and insights that I could never think of independently.

The program in Interdisciplinary Studies also offered me a unique environment and community to develop my research in. With the diverse population and point of view, I was able to think of my research more holistically, with more practical aspects and implementations. For that, I'd like to thank Fiona Fernandes and Dr. Kymberly Bird for hosting this program and protecting our little community.

My lab mates, Ashkan and Simran, were highly supportive along the way. I will never forget the days we were scratching our heads in the lab and presenting posters at conferences.

My beloved family has always supported me no matter which path I picked. They wouldn't ask for reasons, wouldn't doubt me, and have always trusted me for all the choices. I know that for 24 years, you have always wanted me to explore all the possibilities and find my cliché. Thankfully, I grew out of the troublesome little boy and can finally start to build connections and make an impact on this society.

To all my friends, I couldn't express how much I would appreciate you for all the fun and joy you brought forth. You were the people who offered me a place when I was all frustrated and spent. Toast to all the beer we had late at night!

Finally, my beloved partner Jingxuan and our four cats, Chilli, Dipsy, Lena, and Pepper, made up a great portion of my life that I would never part with. Thank you for your emotional support, all the past, present, and future moments that we had together, and all the enjoyment I had being with you. We have walked through many struggles and pain together. I wouldn't think of what I would be without all of you.

I hope I wasn't being too annoying along the way! And I also hope our cats can bring happiness to everyone!



Table of Contents

Abstract	ii
Acknowledgments	iii
Table of Contents	iv
List of Tables	v
List of Figures	vi
Abbreviation Table	vii
Preface	viii
CHAPTER 1	
1.1 History and Overview of Parkinson’s Disease	1
1.2 White Matter Imaging	9
CHAPTER 2	
2.1 Parkinson’s Disease and Dance	15
2.2 Imaging Studies in PD	26
CHAPTER 3	
3.1 Study Background and Rationale	34
3.2 Materials and Methods	37
3.3 Tractography Results	47
CHAPTER 4	
4.1 Discussions	52
Bibliography	59
APPENDIX – NOTES and CODES	83

List of Tables

Table 1: Currently recognized risk factors for elevated and decreased PD risk factors	4
Table 2: Studies involving Parkinson's Disease and Dance	21-25
Table 3: Studies involving Parkinson's disease and neuroimaging	30-33
Table 4: Sample choreography that the participants were trained on	38-39
Table 5: Paired t-test result from before/after the dance intervention in white matter data	49-51

List of Figures

Figure 1. Jean-Martin Charcot’s original lesson on atypical Parkinsonism was given on June 12, 1888	2
Figure 2. A schematic of how the pathological protein can cross the synapse through normal neurotransmission and “infect” the neighbouring neuron to propagate alpha-synuclein transmission	5
Figure 3. Simplified diagram of the go pathway within the basal ganglia to facilitate movement	7
Figure 4. An illustration of gray and white matter	10
Figure 5. An illustration of the most used tensor model, the ellipsoid tensor, and the three vectors ($\lambda_1, \lambda_2, \lambda_3$) in perpendicular space to represent its shape	11
Figure 6: Radial diffusivity is the mean of two radial vectors	12
Figure 7: Mean diffusivity is the mean of all three vectors	13
Figure 8: Fractional Anisotropy is the normalized variance of all three vectors	13
Figure 9. The affected basal ganglia go pathway in PD patients was facilitated with external cues to compensate for the dopamine deficiency	18
Figure 10. A diagram of basal ganglia dynamic in healthy subjects and PD subjects	19
Figure 11. A schematic of how external cues may benefit PD patients by introducing external cues to the go pathway within the basal ganglia	35
Figure 12. A demonstration of the CSD tensor used in this study vs the traditional ellipsoid tensor in DTI	43
Figure 13. Subject DD and his thalamus (red), M1 (green), and V1 (blue) ROI obtained from automatic parcellation using FreeSurfer	44
Figure 14. An illustration of how the ROI-based white matter tract selection is achieved using the subject DD as a sample in a 2-step process	46
Figure 15. A comparison between the right M1-thalamus white matter tract streamline count	48

Abbreviation Table

Term	Abbrivation
Parkinson's Disease	PD
Magnetic Resonance Imaging	MRI
Diffusion Tensor Imaging	DTI
White Matter	WM
Substantia Nigra	SNc
Central Nervous System	CNS
Lewy Body	LB
Axial Diffusivity	AD
Radial Diffusivity	RD
Mean Diffusivity	MD
Fractional Anisotropy	FA
Supplemental Motor Area	SMA
Primary Motor Cortex	M1
The Unified Parkinson's Disease Rating Scale	UPDRS
Voxel-based Morphometry	VBM
Structural Connectivity	SC
White Matter Hyperintensity	WMH
Fluid-attenuated Inversion Recovery	FLAIR
Superior Longitudinal Fasciculus	SLF
Postural Instability and Gait Difficulty	PIGD
Tract-based Spatial Statistics	TBSS

Ventrolateral	VL
Functional Magnetic Resonance Imaging	fMRI
Primary Visual Cortex	V1
Canada's National Ballet School	NBS
Office of Research Ethics	ORE
Diffusion Weighted Imaging	DWI
Region of Interest	ROI
Gradient Echo with Inversion Recovery	MPRAGE
Repetition Time	TR
Echo Time	TE
Inversion Time	TI
Field of View	FOV
Basic and Advanced Tractography with MRtrix for All Neurophiles	B.A.T.M.A.N.
Echo Planar Imaging	EPI
FMRIB Software Library	FSL
Five tissue types	5tt
Constrained Spherical Deconvolution	CSD
Fibre Orientation Distribution	FOD
Spherical-deconvolution-informed Filtering of Tracks	SIFT
Functional Connectivity	FC
Dance for PD [®]	(DfPD [®])

Preface

Before the initiation of my academic career, I was introduced to neuroimaging and became deeply fascinated by it when I was deeply frustrated at the wet labs. The crossing fibres and brain regions lit up, and this new way of explaining function and behaviour was very appealing. This project gave me the opportunity that I always wanted, to bring my knowledge and skills into real-world research that could benefit society more directly.

This project has also changed a few times depending on our goal, dataset, and methods of analyzing the data. Initially, we wanted to do a structural-functional cohesive comparison to visualize how the white matter changes, if any, impacts the functional connectivity between different nodes, to see which accounts for the motor function preservation that we see in effect. Luckily enough, we came into contact with the Swanson et al. paper in 2023, which provided us with a direction from their PD mouse model. Although we did not replicate the same result as the mouse studies indicate, this research may hint at more indirect mechanisms, other than the motor network itself, that the dance may benefit. We also intended to perform PCA on the white matter data using a proven method from my previous project, but the small sample size also limited that.

As this project was proceeding, I also made silly mistakes that potentially swayed the grand result, but as I was meeting with Dr. Barnett, he was able to point them out by those “too good to be true” statistical results. None of my supervisors blamed me for the dumb mistake, but I was happy about picking it out early before my thesis went public.

I guess that is also a lesson for me: never get ahead of myself and always question the process to make greater progress.

Both of these two years have been a crucial transition period for me to adjust to this society and the new lifestyle as a researcher. I've gone through those lost moments where I keep questioning myself, "Did you do enough work today?" To this day, I think it all comes down to making my time, to making every day worth living.

I hope you enjoy reading my master's thesis and my two years of work.

Xianze Meng, 2025, York University

CHAPTER 1

1.1 History and Overview of Parkinson's Disease

Over 1000 years ago, in ancient Chinese and Indian texts, there were clinical manifestations of Parkinson's disease (PD) (Manyam, 1990; Zhang et al., 2006). Quoting from Goetz (2011), the texts described the symptoms as “Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forward, and to pass from a walking to a running pace: the senses and intellects being uninjured.” which accurately resembles PD in today's perspective. In 1817, James Parkinson was the first to give a clear clinical description (Parent, 2018). But Jean-Martin Charcot was the first to identify bradykinesia as a distinguished clinical symptom of PD, and described the arthritic changes, dysautonomia, and pain that accompany PD (Charcot, 1882) (Figure 1). Further down the road, as neuroscientists associate structure with function, the discovery of dopamine by Arvid Carlsson, dopamine's producing neural structure substantia nigra (SNc) by Paul Blocq and Geogrges Marinesco, the dopaminergic nigra-striatal pathway by Kjell Fuxe and Tomas Hökfelt, and the depletion of dopamine in human PD and SNc lesion animal models tied together to reveal the neurological basis of PD (Carlsson, 1993; Duvoisin, 1987; Faull & Lavery, 1969; Fuxe & Hökfelt, 1966; Parent & Parent, 2010; Markham, 1966).

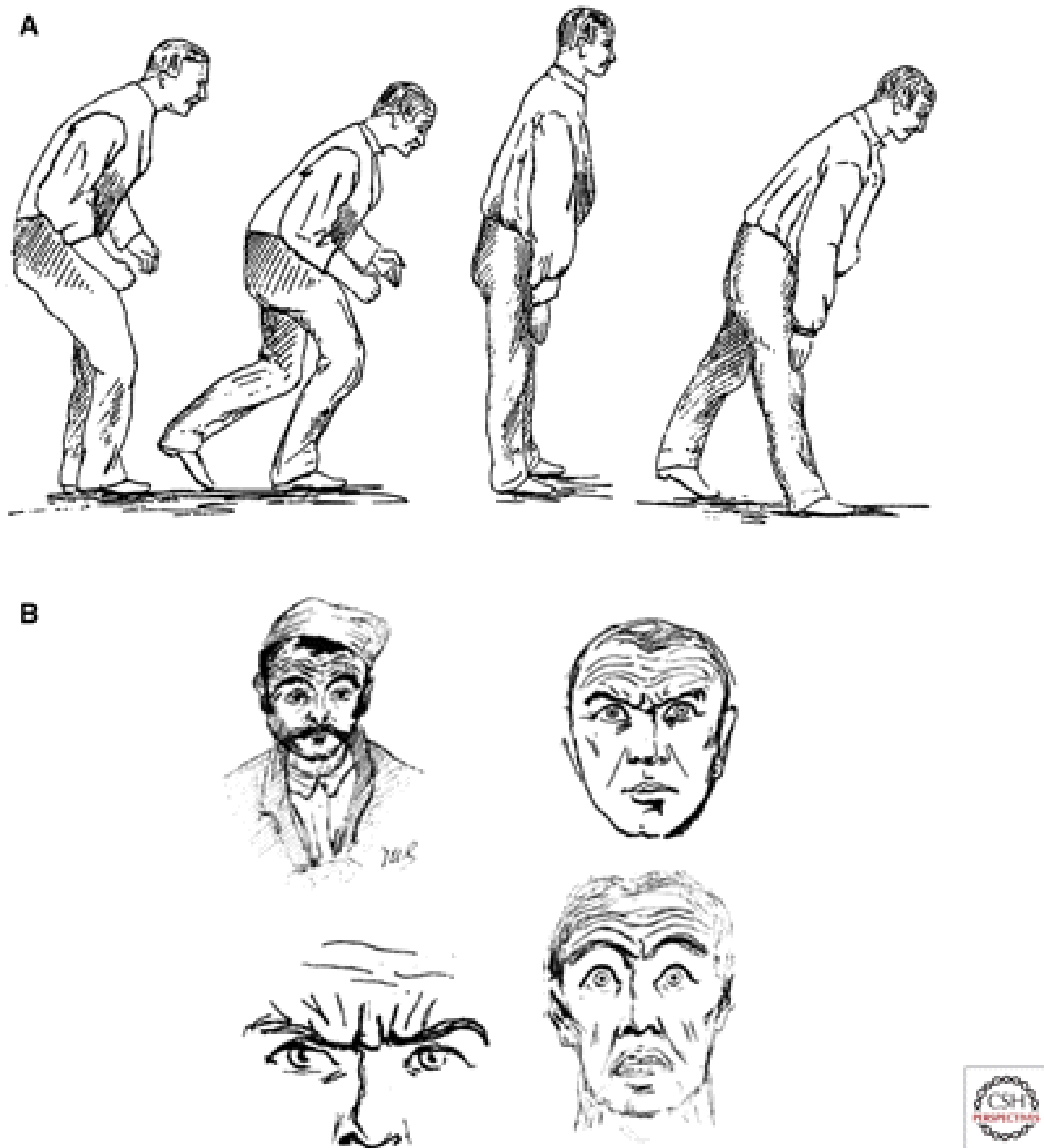


Figure 1. Jean-Martin Charcot's original lesson on atypical Parkinsonism was given on June 12, 1888. **A.** The illustration of typical PD with a tense posture on the left; Atypical Parkinson's illustration without the tremor and a more stretched posture. Both cases present abnormal walking gait and posture instability. **B.** Drawings of distinct facial expressions from Charcot's patient, Bachère, with atypical Parkinson's disease. [Source: (Charcot, 1882; Goetz, 2011)]

Nowadays, PD has become one of the most studied, age-related, neurodegenerative central nervous system (CNS) diseases in terms of disease presentation, clinical intervention, and diagnosis. There are approximately 84,000 Canadians who are 40 years or older living with diagnosed Parkinsonism, which includes 0.4% of the total population (Public Health Agency of Canada, 2018). The worldwide upward trend of Parkinson's diagnosis predicts that there will be roughly 25.2 million people living with Parkinson's by 2050, a number comparable to the entire population of Australia (Djavad Mowafaghian Centre for Brain Health, 2025). Without proper recognition and care, the patients would suffer from a significant decrease in quality of life, introducing a significant social and financial burden. However, due to the idiosyncratic nature and complexity of PD, the field has yet to localize a definitive cause of PD, nor a cure to restore the neurological damage (Blauwendraat et al., 2020; Billingsley et al., 2018; Yang et al., 2022).

After the field recognized PD as an age-related disease, genetic risk factors for PD have only come to be known within the past two decades, such as mutations close to the SNCA, LRRK2, and MAPT genes. Further, the population with a first-degree relative that was diagnosed with PD have a strong relationship with later PD diagnosis (Rybicki et al., 1999). Other developmental and environmental risk factors include a history of constipation, melanoma, traumatic brain injury, and consumption of dairy products; counterintuitively, the presence of a smoking history, caffeine consumption, higher serum urate concentrations, and the use of ibuprofen has been shown to decrease PD risk (Table 1) (Ascherio & Schwarzschild, 2016; Noyce et al., 2012). There are currently promising early detection methods using machine learning that examine

voice, retina features, and subtle motor features before clinical symptoms emerge (Govindu & Palwe, 2023; Hamedani, 2023; Pahuja & Nagabhushan, 2021; Shcherbak et al., 2023).

Increases PD risk	Decreases PD Risk
• Having a first-degree relative with PD or any relative with tremor • Constipation • History of Anxiety and Depression • History of Melanoma • History of Traumatic Brain Injury • Consumption of Dairy Products • Pesticide exposure • Farming occupation • Rural living • Well-water drinking	• Coffee Drinking • Hypertension • History of smoking • Higher serum urate concentration • Physical activity • Use of ibuprofen • Alcohol use • Use of calcium channel blockers • Use of nonsteroidal anti-inflammatory drugs

Table 1. Currently recognized risk factors for elevated and decreased PD risk factors. Note that this table only indicates risk factors for PD prevalence, but not overall patient health. [Source: (Ascherio & Schwarzschild, 2016; Noyce et al., 2012)]

Although the field has yet to outline how PD progresses and there has not been a definite cause of PD. A popular model proposed in Greffard et al. (2010) is that Lewy Bodies (LB) formation and transmission to the SNc destroys the dopaminergic neurons and causes the downstream basal ganglia circuits collapse, which triggers debilitating motor and cognitive impairments (Bloem et al., 2021, McNaught & Jenner, 2001;

Tompkins et al., 1997; Wakabayashi et al., 2006). The alpha-synuclein monomer and fibrils are actively being transported as microfluidic chambers within the cell and eventually between synapses in neuron transmission, “infecting” the correctly folded proteins in a “prion-like” fashion and eventually aggregating into cytotoxic Lewy bodies and causing damage in the dopaminergic neurons (Figure 2) (Brahic et al., 2016; Freundt et al., 2012; Greffard et al., 2010; Li et al., 2008; Peng et al., 2020; Surmeier et al., 2017). The decreased dopamine output from the SNc disrupts normal basal ganglia function, specifically in the GO pathway that initiates movements, which leads to bradykinesia, rigidity, and involuntary tremor (Figure 3); Lewy bodies could be found in diffused regions of the CNS, and have been recognized to relate with depression, dementia, and speech impairments (Galasko, 2017; Graybiel, 2000; Jellinger, 2023; Neumann et al., 2018; Patterson et al., 2019). Even though the proposed PD progression model looks promising, there has yet to be a definitive description or biomarkers of how the brain changes as the PD develops from asymptomatic to mild to severe.

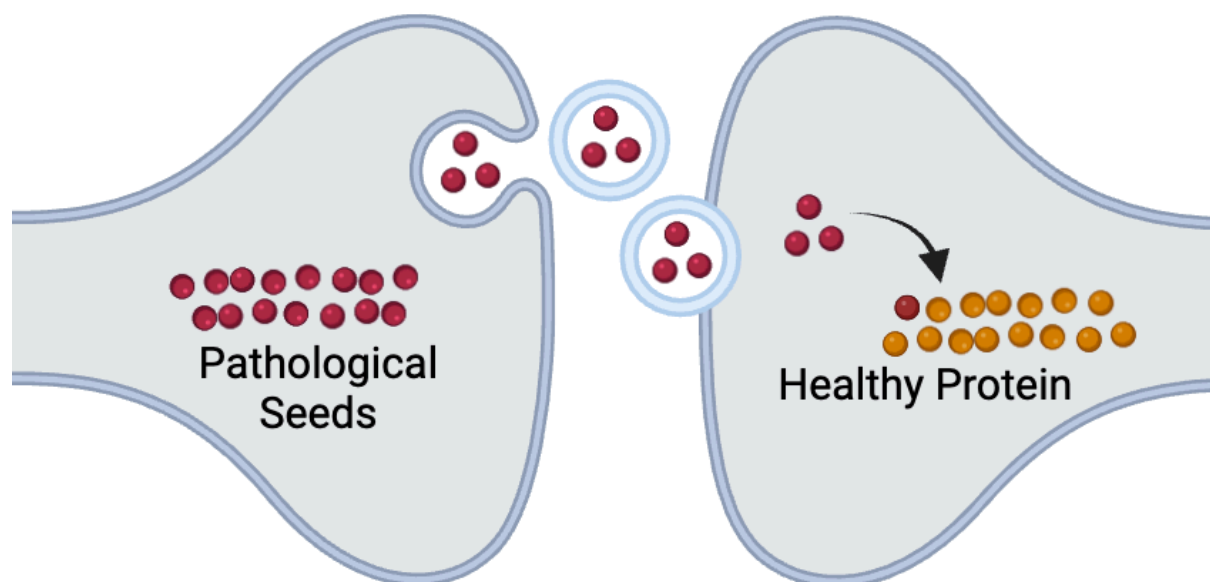
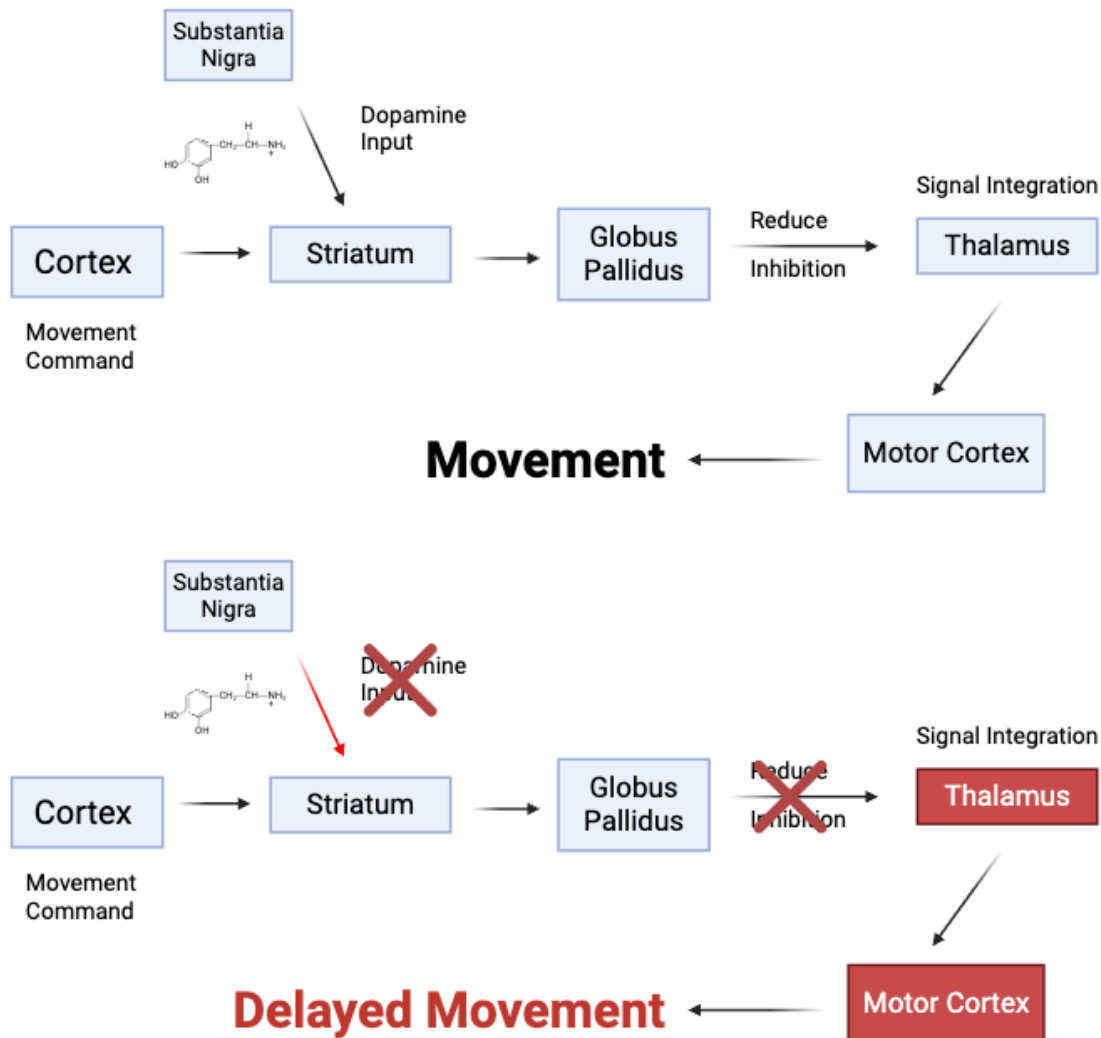


Figure 2. A schematic of how the pathological protein can cross the synapse through normal neurotransmission and “infect” the neighbouring neuron to propagate alpha-synuclein transmission. The alpha-synuclein travels via synaptic vesicles. When it came into contact with the normal protein at the neighbouring neuron, it induced misfolding of the normal protein to aggregate into cytotoxic Lewy bodies. Source: [Peng et al., 2020 but recreated and restructured with [Biorender.com](https://www.biorender.com)]

Resting tremor, bradykinesia, rigidity and loss of postural reflexes are generally considered hallmark symptoms of PD and are used to differentiate PD from other movement disorders (Jankovic, 2008). The insufficient dopamine supply to the basal ganglia to initiate the go circuit could account for the majority of motor symptoms, but the non-motor symptoms, such as autonomic dysfunction, cognitive decline, and dementia, are also apparent (Schapira et al., 2017). The current medical intervention plans, including the current gold standard, levodopa supplement, do not cure the disease or repair the brain damage, and introduce severe side effects sometimes (Armstrong & Okun, 2020). While levodopa treatment is still the priority treatment of choice for initial administration, there is a small population with atypical PD that does not respond to levodopa at all (Constantinescu et al., 2007). The simple dopamine supplement by levodopa does not improve the non-motor symptoms PD patients experience; it may also lead to levodopa-induced dyskinesia in the later stage of PD when the dose wears off (Kwon et al., 2022). The insufficient outcome and adverse side effects in current PD treatment call for a less invasive, more behaviour-based therapy that minimizes patient harm.



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Figure 3. Simplified diagram of the go pathway within the basal ganglia to facilitate movement. Each box indicates a functional brain region, and the arrows show their connectivity. The upper figure demonstrates how a functional basal ganglia go pathway functions with adequate dopamine input to the system. The cortex first generates an input signal to initiate a movement, with the assistance from substantia nigra and its dopamine output, the striatum and the

downstream globus pallidus are stimulated to signal the thalamus. The thalamus, by default, is under the influence of the stop network and works in an inhibitory state to suppress any unwanted movement. Upon stimulation, the thalamus is disinhibited and sends out a signal to the motor cortex to generate a voluntary movement. The bottom figure shows how the same go pathway functions with dopamine deficiency. When dopamine input is depleted because of substantia nigra neurodegeneration, there is not enough instant input to the striatum and globus pallidus to disinhibit the thalamus in a timely manner. These structures would depend on temporal summation (the sum of input across a time interval) from the cortex alone to activate the downstream thalamus; hence, the motor activation is delayed and causes bradykinesia and rigidity. In a low dopamine state, the abnormal basal ganglia input draws an action potential surge in the ventrolateral (VL) thalamus in the post-inhibitory period, consequently reducing their excitability during regular firing. [Kim et al., 2017, created with Biorender.com]

1.2 White Matter Tractography

As the current field shifts focus from single-region explorations to network-based analyses to explain function and behaviour, techniques like functional MRI to explore brain action synchrony and diffusion tensor imaging (DTI) to explore the physical connections between distinct regions have been gaining popularity since its introduction in 1994 to study connections via white matter integrity in healthy and pathological models (Dawson et al., 1994). When using MRI for neuroimaging, we usually view the brain in cubic millimetre voxels (volume pixels). Each single voxel may encompass innumerable thousands of neuronal axons that were wrapped by glial cells and oligodendrocytes, and the wrapping is called the myelin sheath. The fat-based myelin sheath ensures the quality and speed of signal transduction within and between neurons. The axon, combined with the white-coloured myelin sheath, fills the void between thin axons and ensures quality communication between neurons (Figure 4). There are parts of the brain that are primarily made up of neuron cell bodies that appear gray, hence the name “gray matter”; they are responsible for integrating the input from sensory systems or other neurons and output a decision. Their output is transmitted via the axon length, travels through white matter to arrive at other gray matter regions or down the spinal cord.

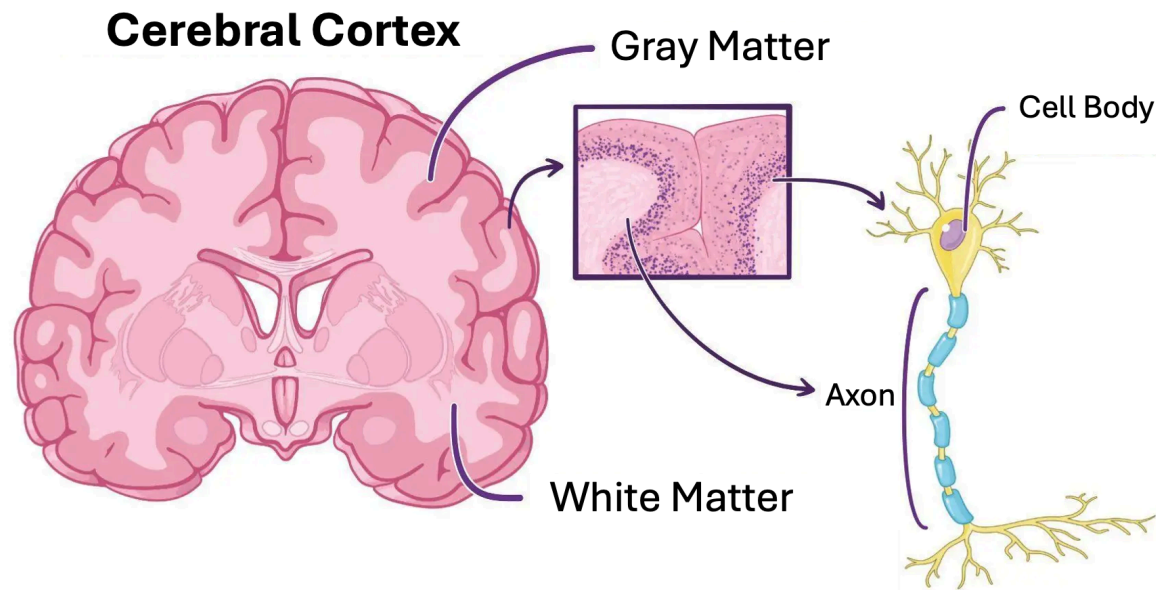


Figure 4. An illustration of gray and white matter. The cell bodies collectively make up the gray matter, and the myelin-encapsulated axon makes up the white matter that directs the communication between neurons. [Source: (Melani et al., n.d.) Recreated with Biorender.com]

As mentioned above, the axons themselves may be too small to visualize, but the myelin sheath is very hydrophobic and restricts the flow of water molecules in certain directions. The tissue-restricted water molecule is an excellent candidate for neuroimaging to trace the myelin-encapsulated axon. The water molecule is used as a proxy to reflect the neural tract shape. With advancement in Magnetic Resonance Imaging (MRI), the water diffusion change within the white matter over time can be captured, enabling us to predict the shape of axon bundles based on the water movement and continuity within the myelin sheath (Assaf & Pasternak, 2008). In every single voxel, we establish a tensor to represent the overall water molecule diffusion

within the myelin sheath. We can then use the tensor shape from multiple axons to estimate how the white matter tract maps in the brain. (Figure 5).

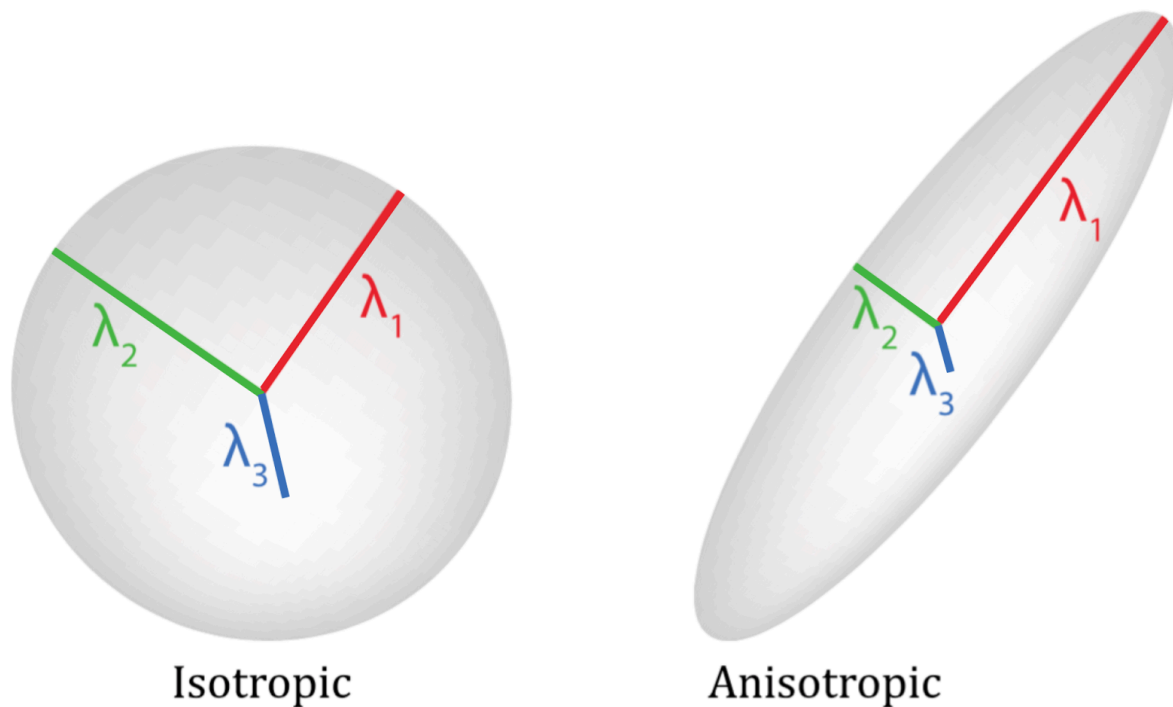


Figure 5. An illustration of the most used tensor model, the ellipsoid tensor, and the three vectors ($\lambda_1, \lambda_2, \lambda_3$) in perpendicular space to represent its shape. The tensor on the left is denoted as “Isotropic”, which means the water molecule is distributed more uniformly and randomly (i.e. represents a sphere); the tensor on the right is denoted as “Anisotropic”, which means the water molecule follows more of a pattern (shape of the myelin) and the 3 vectors appears to be more different. [Source: (Tromp, 2015)]

When describing the shape of the tensor model, we often use terms such as axial diffusivity, radial diffusivity, mean diffusivity, and fractional anisotropy to indicate the overall presence and integrity of the white matter.

Axial Diffusivity (AD, represented by λ_1) is defined as the magnitude of diffusion along the largest diffusion direction, often parallel to the axon fibre tract. This is by definition the largest among the three diffusion vectors and normally indicates the direction that axonal tracts are taking in this voxel. A reduced AD would typically indicate axonal injury, reduced axon calibre, or lack of axon coherence. There is evidence stating AD is less dependent on myelin, but relies more on the entrapment of water by the tightly packed axon bundles (Winklewski et al., 2018).

Radial Diffusivity (RD, equation 1) is defined as the mean of λ_2 and λ_3 , the average diffusivity from two radial directions perpendicular to the main axis and excluding the axial diffusivity. This measures how much water diffuses out of the main direction, and is selectively indicative of myelin damage for its reduced ability to trap water. Alternatively, the lack of axons, also representing the lack of myelin, can lead to an increase in RD.

Figure 6: Radial diffusivity is the mean of two radial vectors

$$RD = (\lambda_2 + \lambda_3)/2$$

Mean Diffusivity (MD, equation 2) is defined as the mean of all λ_1 , λ_2 , and λ_3 . This metric measures the overall fluidity of water in this voxel and indicates how “big” the tensor model would get. It has been proposed that the mean diffusivity would be lower in more complex white matter configurations (i.e. white matter bundle junctions) or in gray matter where water is restricted uniformly, but the relationship also relies on configurational and microstructural settings and image acquisition parameters (Vos et al., 2012).

Figure 7: Mean diffusivity is the mean of all three vectors

$$MD = (\lambda_1 + \lambda_2 + \lambda_3)/3$$

Fractional Anisotropy (FA, equation 3) is yielded from taking a normalized variance from all three vectors. Different from AD, RD, and MD, this metric does not simply measure the length of vectors, but gives an overall shape measurement of the tensor for this voxel between the range of 0 and 1. A FA of 0 means the tensor is shaped as a perfect sphere ($\lambda_1=\lambda_2=\lambda_3$) and means there is no directional water flow from tissue restrictions (Figure 4, left). This is typically seen in the cerebrospinal fluid because the water molecule can flow freely. As the FA gets closer to 1, the tensor resembles more like an ellipsoid, and indicates there is more restricted, directional water flow from the myelin and axons. FA is one of the most used diffusion metrics to describe the white matter property because it's more cohesive when describing the axon and the surrounding tissues. A higher FA would typically indicate more compact, better white matter properties in this region and would support better connections between gray matter regions. Lower FA would happen with age, but would also happen with axonal injury, neurodegeneration, or less pronounced white matter development.

Figure 8: Fractional Anisotropy is the normalized variance of all three vectors

$$FA = \sqrt{\frac{3}{2} \left(\frac{(\lambda_1 - \hat{\lambda})^2 + (\lambda_2 - \hat{\lambda})^2 + (\lambda_3 - \hat{\lambda})^2}{\lambda_1^2 + \lambda_2^2 + \lambda_3^2} \right)}$$

By combining the whole-brain white matter tractography with region of interest (ROI) selection, we may select specific pathways that connect multiple functional

regions and prepare for network-based analyses, which we performed in this thesis. The faster change in white matter in a matter of weeks than the neuron-body-based gray matter makes it a suitable candidate for short and long-term longitudinal studies (Newcombe et al., 2016). DTI has been implemented in tumour detection, surgical planning, and brain structure analysis (Freire et al., 2024; Froeling et al., 2016; Reiche et al., 2010).

CHAPTER 2

2.1 Parkinson's Disease and Dance

Although there has not been a definitive cure for PD, dance therapies have been a proven method for improving the PD condition and quality of life since 2009 (Aguiar et al., 2016; De Natale et al., 2017; Earhart, 2009; Michels et al., 2018). Dance is an inherently social activity involving motor participation that can enhance interpersonal, non-verbal communication and promote intra- and inter-brain synchrony (Basso et al., 2021; Dhami et al., 2015; Dyer, 2002). For PD patients, continuous dance participation has been demonstrated to drastically decelerate the motor symptom progression over 3 years compared to the non-dancing control group (Bearss & DeSouza, 2021). Dance may benefit PD patients uniquely by engaging multimodal cognitive reserve, such as the motor imagery in choreography organization, introducing multi-sensory cues, and activating the reward pathway feedback upon rehearsal and performance, which is mostly absent in an intensity-matched exercise program (Fontanesi & DeSouza, 2021; Westheimer, 2008).

The external cues associated with dance (visual, tactile, auditory, etc.) have been shown to benefit PD patients by decreasing the freezing of gait length and severity while preserving cognitive functions (Abraham et al., 2024). When the basal ganglia is affected by the low-dopamine input, the downstream supplemental motor area (SMA) is

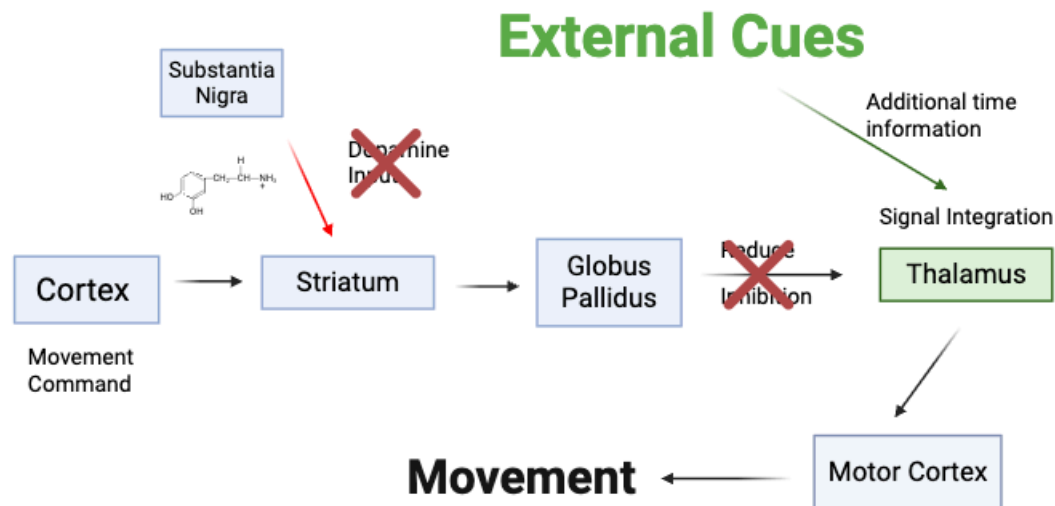
subsequently impacted, resulting in activity initiation failure and abnormal movements (Morris et al., 1996). Utilizing the external cues offers an alternative way to localize the time to initiate movements, essentially bypassing the damaged, delayed circulatory system within the basal ganglia, and promoting the preparatory process before the movement (Figure 6, Abraham et al., 2024; Morris et al., 1996). The visual external cue could enable the visual-cerebellar motor pathway to generate a better gait pattern; the auditory cues could provide a bypass of the internal rhythm deficit (the disturbance of internal rhythmic pattern formation in PD) and facilitate movement; the sensory cues could activate the voluntary dorsolateral pre-motor control system that do not utilize the damaged basal ganglia (Abraham et al., 2024; Azulay et al., 1999; McIntosh et al., 1997; Morris et al., 1996).

Within the basal ganglia circuitry, the direct (GO), indirect (STOP) together regulates the initiation of voluntary movement and the termination of an action. The pathways act in a complementary fashion while both of them depends heavily on dopamine regulation by the substantia nigra to the striatum. At resting state, the thalamus is inhibited by the globus pallidus internus (GPi) and substantia nigra pars reticulata (SNr) to prevent unwanted output activation to the motor cortex (Wichmann et al., 2011). The GPi and SNr are inhibited by the subthalamic nucleus (STN), which is inhibited by the globus pallidus externus (GPe) more upstream (Wichmann et al., 2011). The GPe receives inhibition from the indirect medium spiny neurons (iMSN) that resides in the striatum and receives dopamine input from the SNc (Figure 7). When the indirect pathway is activating, dopamine from the SNc eventually increases basal ganglia output to the thalamus via the STN, which suppresses movement (Wichmann et

al., 2011). If a voluntary movement is demanded, the striatum performs a switching activity to activate the direct medium spiny neurons (dMSN) and deactivates the iMSN in response to dopamine (Wichmann et al., 2011). This essentially terminates the indirect pathway action and mode switches to the direct pathway dynamics (Dang et al., 2012). The dMSN directly inhibits GPi and SNr when receiving dopamine input, and leads to thalamic activation and projection to the primary motor cortex to produce a voluntary movement (Figure 7). In the Parkinson's model, when dopamine production is drastically decreased in the SNc, neither the direct nor the indirect pathway receives adequate dopamine input to the striatum (Calabresi et al., 2014). When the pathways do not correctly function, the thalamus is overly active when no input is given, and is not active enough upon demand (Calabresi et al., 2014). Symptoms such as muscle rigidity and tremor are associated with malfunctioning indirect pathway; while symptoms like slowed and degraded movement, gait instability, and difficulty to speak are more associated with the failure of direct pathway (Calabresi et al., 2014).

While dancing, the strengthened cortical engagement should benefit the motor pathway and its downward projection through plasticity and manifest as preserved motor function (Hackney & Earhart, 2010). Moreover, music could also promote connectivity inside the basal ganglia to compensate for the neurodegeneration in PD and restore the affected primary motor cortex (M1) excitability (Freedland et al., 2002; Nieuwboer et al., 1997; Salimpour et al., 2011). This “detour” may access the premotor cortex via the cerebellum that “bypasses” the damaged basal ganglia (Hackney et al., 2007). Dance programs can be adjusted to different dance genres to fit different degrees of motor demand. This flexibility, combined with the generally fun atmosphere

and the social component within dance, is intrinsically rewarding and contributes to the significantly consistent and higher attendance rate (Westheimer et al., 2015).



Created in BioRender.com 

Figure 9. The affected basal ganglia go pathway in PD patients was facilitated with external cues to compensate for the dopamine deficiency. When the insufficient dopamine input forces the thalamus to rely on temporal summation to initiate motor cortex activation, the incoming external cues from other sensory cortices provide the thalamus with adequate stimulation to activate the downstream motor cortex. The external cues would drastically reduce, or sometimes eliminate, the need for temporal summation and improve bradykinesia. [Created in Biorender.com]

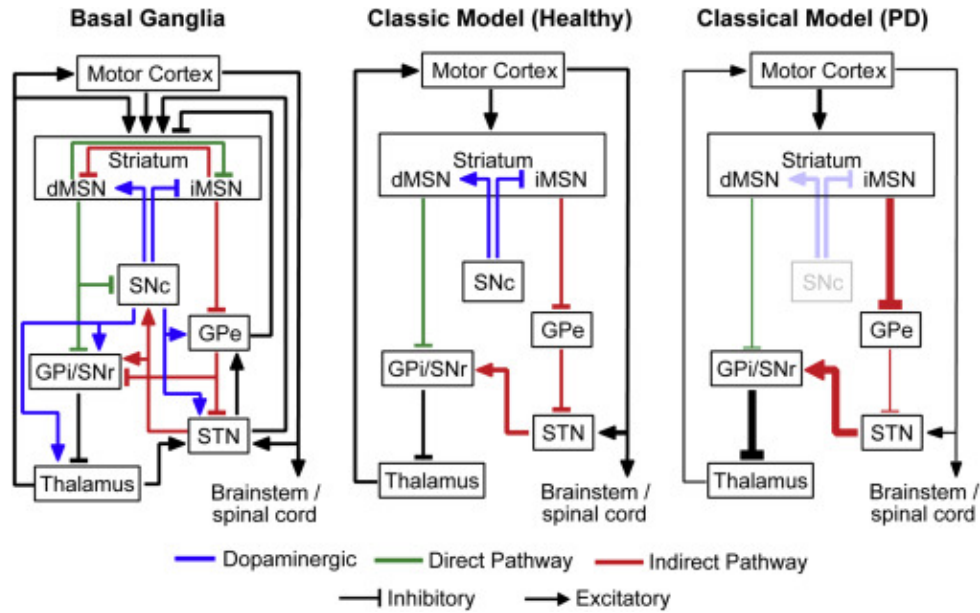


Figure 10. A diagram of basal ganglia dynamic in healthy subjects and PD subjects. The left panel describes all the dopamine cascade, with indirect and direct pathway dynamic in one picture. The dopaminergic signaling is denoted in blue, the direct pathway is denoted in green and the indirect pathway is denoted in red. The center panel demonstrates how the indirect and direct pathway functions in healthy subject. The right panel shows in a dopamine-deficient state caused by PD, how the malfunctioning basal ganglia behaves in indirect and direct pathway activation. [Source: (McGregor & Nelson, 2019)]

A three-year longitudinal study by Bearss and DeSouza (2021) demonstrated that consistent dance learning is associated with prolonged PD motor symptom progression. This study comprised 16 PD participants who maintained regular dance schedules and selected 16 age, severity, and disease duration-matched PD patients from another dataset. The dancers' unified parkinson's disease rating scale (UPDRS) score was collected to assess the degree of motor and non-motor symptoms. Bearss

and DeSouza (2021) demonstrated that motor impairment has almost stopped in the dancers' group, showing that the daily decline rate of the motor UPDRS score is non-significant from zero. This is the first dance study to show dance as a potent neurorehabilitation training method to effectively halt motor symptom decline in PD, which provided valuable insights into future intervention paradigms for PD.

Furthermore, PD patients who underwent continuous dance training had elevated levels of self-esteem and beauty recognition, enhanced interpersonal interactions, and high interest in participation in the program among the participants (Hackney & Earhart, 2009; Hackney & Earhart, 2010; Hackney et al., 2007; Hashimoto et al., 2015). One of the most prominent benefits of long-term dance participation and physical activity is the improvement in balance and functional mobility. PD patients have shown better balance ability over the no-dance group in the Mini-BESTest and the Berg Balance Scale (Duncan & Earhart, 2012; Duncan & Earhart, 2014; Hackney & Earhart, 2009; Bearss et al., 2017; Solla et al., 2019). The Movement Disorder Society United Parkinson's Disease Rating Scale Part III (MDS-UPDRS-III) has been used as one of the most common scales to measure impairments in PD, and Carapellotti et al. (2020) observed that dance could lead to positive impact in motor symptom measured by UPDRS III in their meta analysis consisting of 16 studies and 636 participants in total. However, as Carapellotti et al. (2020) stated, the exact mechanism of motor symptom alleviation is still unknown.

Table 2. Studies involving Parkinson's Disease and Dance

Study	Study type	Subjects	Outcome	Country
Abraham et al., 2024	Controlled, longitudinal study	6 PD patients were divided into internally-guided or externally-guided dance groups	5/6 patients using the external cues to dance improved upon motor symptoms, dynamic gait, global cognitive function, and freezing scores.	Australia & United Kingdom
Aguiar et al., 2016	Meta-analysis	Randomized controlled trials, quasi-randomized controlled trials, case studies (Nstudies = 18)	Dance therapy can be safe for mild to moderate to severe PD. It's beneficial for walking, freezing of gait, and quality of life.	Australia
Azulay et al., 1999	Controlled study	16 PD patients with and without external visual cues to walk	With the presence of visual cues, the PD patients were seen to increase stride length and velocity	France
Bearss & DeSouza, 2021	Longitudinal study	16 PwPD patients participated in weekly dance training for 3 years. No dance group was selected from a pool. Their UPDRS score were collected	Continuous dance training can drastically prolong the decline of PD motor and non-motor ability.	Canada
Bearss et al., 2017	Quasi-experimental study	9 PD patients underwent 12 weeks of dance training. Short-term and long-term motor scores were collected	Enhancements in balance and gait can be seen in the short- and long-term. Self-reported quality of life does not change.	United States & Canada

Carapellotti et al., 2020	Meta-analysis	Studies that exclusively used dance as the rehabilitation technique	Dance can improve motor impairments, specifically balance in mild to moderate PD patients	United Kingdom
De Natale et al., 2017	Controlled, longitudinal study	16 PD patients with a fall history were divided into two groups of 8, dance therapy or traditional rehabilitation	Significant and retained motor and cognitive improvement in the dance group.	Italy
Duncan & Earhart, 2012	Controlled study	62 PD patients were randomly assigned to the tango training program or the control group	The tango group saw a significant reduction in the UPDRS score compared to the control group, even off-medication.	United States
Duncan & Earhart, 2014	Randomized clinical trial	10 PD patients were randomly assigned to the tango group or the control group	The tango group had better UPDRS and cognitive scores 12 months and 24 months after the intervention. The control group have seen a significant decline in these metrics.	United States
Fontanesi & Desouza, 2021	Controlled study	7 PD patients, data collected before and after dance class or intensity-matched exercise	The experience of beauty, self-efficacy, and gait performance has significantly improved.	United States & Canada
Freedland et al., 2002	Controlled study	16 PD patients received different stimuli (external cues) to assist with their walking and gait	Auditory stimulation can be beneficial for PD patients to improve walking and gait. Step length and stride time are all reduced with rhythmic stimulation.	United States

Hackney & Earhart, 2009	Controlled study	58 PD patients were divided into three groups: tango, waltz/foxtrot, or control group for 13 weeks.	Both dance groups improved upon balance, 6-minute walking distance, and stride length, with the tango group yielding better results on some metrics.	United States
Hackney & Earhart, 2010	Controlled study	39 PD patients were divided into partnered or non-partnered dance groups. They danced for 10 weeks.	Both partnered and non-partnered dance groups improved upon balance, cadence, and walking velocity in comparable terms. The partnered dance group reported more enjoyment.	United States
Hackney et al., 2007	Controlled study	19 PD patients were randomly assigned to a tango group or an exercise group of matching intensity	Both groups have shown improvements in UPDRS scores, but only the tango group showed improvement in balance specifically.	United States
Hashimoto et al., 2015	Quasi-randomized pilot trial	46 PD patients were randomly assigned to dance, exercise, or no intervention for 12 weeks	Both dance and exercise groups have shown improvements in mobility and cognitive scores, but only the dance group improved on balance	Japan
McIntosh et al., 1997	Controlled study	31 PD patients were divided into two groups. n=21 walk with rhythm and n=10 without	The rhythmic external auditory cues increased the gait velocity, cadence, and stride length.	United States

Michaels et al., 2018	Controlled study	13 PD patients were randomized 2:1 to dance therapy or group control	All participants in the dance therapy group enjoyed the class and felt they were beneficial. Significant motor improvements were also observed.	United States
Morris et al., 1996	Controlled study	54 PD patients were divided into three groups: using visual floor markers, mental pictures of the stride size, or nothing at all to walk.	Both visual aids and mental imagery could help the PD patients to maintain appropriate stride length and pattern. Gait hypokinesia is a difficulty in activating the motor system.	Australia & United Kingdom
Salimpoor et al., 2011	Observational study	10 healthy participants who experienced chills at peak pleasure while listening to music were selected. The fMRI profiles were collected	Intense pleasure in response to music can lead to dopamine release in the striatal system. The anticipation of pleasure can also lead to dopamine release independent of the peak pleasure itself.	Canada
Solla et al., 2019	Controlled, longitudinal study	20 PD patients were randomly assigned to Ballu Sardu dance training and usual care for 12 weeks	The dance group shows a significant trend of improvement in mobility and gait, while the control group worsened significantly.	Italy

Westheimer et al., 2015	Preliminary, uncontrolled, longitudinal study	14 PD, first-time dancers participated in weekly dance classes taught by teachers for 8 weeks	UPDRS overall, with subscores in gait and tremor improved after the intervention, and the participants self-reported to have physical, emotional, and social benefits.	United States
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2.2 Imaging Studies in PD

DTI and white matter (WM) tractography have been implemented to examine multiple aspects of healthy aging and pathological studies. Specifically, structural connectivity (SC) metrics have proven practical in investigating disorders like multiple sclerosis and brain tumours and developing intervention plans (Kleiser et al., 2010; Roosendaal et al., 2009). Fine-grained WM changes visualized by DTI can be especially valuable in short-term longitudinal changes and predicting connectivity, as the WM change provides a more stable metric than brain functional patterns. Diffusion MRI/DTI is superior at detecting subtle brain structure changes than gray matter analysis, such as Voxel-based morphometry (VBM) (Assaf & Pasternak, 2008; Filley & Fields, 2016). As dopaminergic neuron degeneration progresses in the SNc, SC changes in the dopaminergic neurons around the SNc have been extensively studied. Within the SNc, there is a significant decrease in FA to indicate the neurodegeneration of the dopamine neurons (Hu et al., 2023; Menke et al., 2009; Vaillancourt et al., 2009). Also in the nigrostriatal tract, the main SNc output tract to the striatum, there is a significant white matter degeneration, as shown by FA decrease, indicating worse connectivity within the basal ganglia pathway (Zhang et al., 2015). Other PD studies using DTI have outlined WM differences across the brain and linked microstructural differences with multiple domains of cognitive impairments (Gorges et al., 2019; Li et al., 2017). For example, Zheng et al. (2014) showed that 1) executive function is directly correlated with better SC in most frontal white matter tracts; 2) attention impairment is related to widespread SC discrepancies across the brain; 3) memory impairment is

linked to reduced SC in the fornix. These results suggest that SC changes are more likely to emerge around the functional cortices rather than around the pathological SNc.

White matter hyperintensity (WMH) are also commonly found in PD and various small vessel disease upon visualization of T2-weighted MRI or fluid-attenuated inversion recovery (FLAIR) sequences, which may due to Wallerian degeneration (anterograde degeneration at the distal end on an neuron axon), blood-brain barrier impairment, or inflammation-based vasculature dysregulation (Bohnen & Albin, 2011; Butt et al., 2021; Leys et al., 1991; Piccini et al., 1995). This hyperintensity has been shown to negatively affect motor ability in non-dopaminergic pathways (Marshall et al., 2006). Also, PD-Dementia patients would present a higher degree of WMH than PD-normal cognition groups, suggesting WM changes could at least hint at the level of brain damage that impairs normal functions in PD (Liu et al., 2021; Wan et al., 2019). As previously mentioned, there has been evidence for inter-neuron pathological alpha-synuclein transportation along the axon that may explain the WMH in the PD-dementia group. Still, the selectivity of WMH specifically in PD-dementia groups needs further testing and explanation.

Few attempts have been made to link motor impairments with SC changes in PD patients systematically. In the bilateral superior longitudinal fasciculus (SLF), FA reduction has been exclusively observed in the postural instability and gait difficulty (PIGD) subgroup of the PD patients, but not the tremor-dominant subgroup (Gu et al., 2014; Haghshomar et al., 2018). Additionally, the PIGD subgroup of PD patients also presents reduced FA at the corpus callosum tracts and increased MD at the thalamus, putamen, and corpus callosum compared to the tremor-dominant PD subgroup and

healthy controls (Chan et al., 2014; Haghshomar et al., 2022). Yet all the research lacks the direct relationship between severity in white matter tract degeneration and motor symptom progression.

The study by Kok et al. (2020) utilized diffusion MRI in multiple imaging centres to compare local and whole-brain connectivity profiles between healthy subjects and PD patients. They demonstrated that the UPDRS motor scores negatively correlate with the SC in the posterior parietal and the sensorimotor cortices. Pietracupa et al. (2023) used tract-based spatial statistics (TBSS) to improve the spatial resolution of SC alteration to the tract level. They showed that the PD patients exhibited deficits in SC within the corticospinal tract, the internal and external capsule, the anterior and posterior thalamic radiations, the genu and body of the corpus callosum, cerebellar peduncles, and superior and inferior longitudinal and frontal-occipital fasciculi. At the same time, no significant GM changes were found in subcortical or cortical regions. Again, as previously mentioned, no systemic connections have been made between motor functional change over time and SC impairments. The results suggest that the degree of SC accompanied the severity of motor impairment, but there was no decline in gray matter.

The functional connectivity (FC) pattern in PD patients is also severely altered both within the basal ganglia and across the whole brain. Baudrexel et al. (2011) showed that the FC between the M1 and the Ventrolateral (VL) thalamus is altered in PD patients. The VL thalamus mediates the upstream cerebellar input to M1 to provide complete body representation to assist the M1 in initiating goal-directed movements (Stein, 2017; Thach, 2007). Focusing on the cerebellum-VL thalamus-M1 axis, the loss

of plasticity in M1 is directly linked with instability of coordination among the basal ganglia, cerebellum, and M1 (Kishore et al., 2014).

Moreover, Ueki et al. (2005) also showed that by stimulating the right median nerve at the wrist with subsequent TMS to the M1, they increased the ratio of motor-evoked potential amplitude, visualized by fMRI, specifically in temporally off levodopa PD patients. In this study, they successfully restored the M1 excitability via targeted stimulation between the M1 and peripheral nerve to achieve a similar effect with levodopa treatment, which hints that dopamine, even outside the basal ganglia circuits, can be responsible for promoting cortical excitability and facilitating motor movements. Given the functional change in the cerebellum-VL-M1 axis, there may be a SC change in the white matter pathway that physically connects these regions to be responsible for the phenomenon.

Table 3. Studies involving Parkinson's disease and neuroimaging

Study	Study type	Subjects	Outcome	Country
Baudrexel et al., 2011	Controlled study	31 PD patients and 44 healthy controls were scanned with fMRI in a voxel-wise manner to compare FC differences	Elevated FC between the subthalamic nucleus and cortical motor areas in PD patients. The cortical motor to subthalamic pathway might play a fundamental role in PD pathology.	Germany
Butt et al., 2021	Meta analysis	Studies reporting WMH in PD were included (nStudies = 24, nsubjects = 3860)	WMH is not prevalent in regular PD, but is significantly more prevalent in PD-Dementia models than in controls	Canada
Chan et al., 2014	Controlled study	21 PD, 25 PD with postural instability and gait disorder patients, and 19 healthy controls were scanned by DTI	FA of the corpus callosum is lower in the PD-postural instability and gait disorder compared to simple PD models. The degree of corpus callosum abnormalities is correlated with the risk of falls.	Singapore
Gu et al., 2014	Controlled study	12 PD, 12 PD with postural instability and gait disorder patients were scanned by DTI	There is a significant decrease in FA in bilateral SLF, corona radiata, and left genu of the corpus callosum in the PD-postural instability and gait disorder group. This subgroup may have significant demyelination over PD.	China

Hu et al., 2023	Controlled study	37 PD patients and 22 healthy controls were scanned with whole-brain DTI	Lowered FA can be seen in the SNc of PD patients. Increased inflammation, fibre/dendrite loss and edema can be seen in the pathological SNc.	China
Kok et al., 2020	Controlled study	19 PD patients and 18 healthy controls were scanned with diffusion-weighted and T1 MRI scans	There is a negative correlation between global and nodal brain network efficiency and UPDRS scores. The sensorimotor and posterior parietal regions show systemic connectivity differences in PD	Netherlands & Canada
Li et al., 2017	Controlled study	35 PD patients and 26 healthy controls underwent DTI and deterministic tractography to construct brain structural networks	The limbic/paralimbic/subcortical networks showed significantly decreased connections in PD. Global network efficiency is also decreased.	China
Liu et al., 2021	Meta-analysis	Clinical trials of severity and location of WMH in PD models (nStudies = 15)	PD-dementia patients have a significantly higher level of WMH burden than normal PD models.	China
Marshall et al., 2006	Controlled study	11 PD patients and 14 healthy controls underwent MRI and positron emission tomography. The presence of WMH is calculated	The presence of WMH contributes to motor and cognitive impairments in PD models.	United States

Menke et al., 2009	Controlled study	10 PD patients and 10 healthy controls underwent a T1 MRI scan	Bilateral SNc is significantly smaller in PD patients compared to controls.	United Kingdom
Piccini et al., 1995	Controlled study	102 PD patients and 68 healthy controls were scanned with MRI for WMH frequency, extent, and location	PD patients have significantly higher WMH frequency and extent than controls. Within the PD group, patients with periventricular WMH have worse disease progression.	Italy
Pietracupa et al., 2023	Controlled study	62 PD patients and 31 healthy controls were assessed with UPDRS and scanned with MRI	PD patients exhibited lower FA and higher diffusivity in most major WM bundles. Smaller cerebellar volumes were also found in PD patients.	Italy
Ueki et al., 2006	Controlled study	18 PD patients and 11 healthy controls underwent electrical stimulation and TMS to investigate the cortical excitability	Paired peripherally evoked nerve stimulation with TMS to M1 increases motor-evoked potential amplitude in levodopa-off PD patients. Dopamine may be responsible for cortical excitability.	Japan
Vaillancourt et al., 2009	Controlled study	14 PD patients and 14 healthy controls underwent DTI scans	Significant FA decrease can be seen in the SNc of the PD patients, with the caudal SNc being more sensitive to this change. Caudal SNc FA decrease can distinguish PD patients from controls very effectively.	United States

Wan et al., 2019	Association study	137 PD patients were included to scan for MRI and correlate with their symptoms	Small vessel diseases can be seen in all PD patients. Enlarged perivascular spaces in the basal ganglia can be reliably associated with tremor. Deep WMH at the frontal and occipital lobes can be negatively associated with motor scores.	China
Zhang et al., 2015	Controlled study	50 PD patients and 27 healthy controls were scanned for the nigrostriatal fibre microstructure	FA and diffusivity metrics at the nigrostriatal tract are abnormal in the PD patients. Variations in FA can be associated with motor deficit intensity.	United States
Zheng et al., 2014	Association study	16 PD patients with stereotaxic implantation of deep brain stimulators were scanned with MRI	Executive function is positively correlated with FA at the corpus callosum and the internal capsule. Language is positively correlated with frontal region connectivity. Memory is negatively correlated with MD at the fornix.	United States

CHAPTER 3

3.1 Study Background and Rationale

Although Bearss and DeSouza (2021) demonstrated dance's great potential to slow motor symptom progression behaviourally, its exact neural benefits remain unclear, as the study did not report any functional/structural evidence to support the results. A rodent study by Swanson et al. (2023) demonstrated that in an induced PD mouse model, the loss of dopaminergic neurons in the midbrain accounts for the decrease in motor thalamus input in a laminar and cell-specific fashion, and it subsequently causes the inadequate activation of M1 of mice for normal motor functioning. As introduced previously, the activity in the thalamus was disrupted by the loss of dopaminergic neurons and, subsequently, the lack of excitability in M1 in PD (Stein, 2017; Thach, 2007). The external cues that assist the thalamus in processing time-dependent information can compensate for the lack of input from the Globus Pallidus to the thalamic-cortical pathway to restore M1 excitability (Abraham et al., 2024; Morris et al., 1996). Dance should provide additional input to the thalamus and transmission via the thalamic-cortical pathway to arrive at M1; as a result, we should observe positive plasticity change in white matter between the thalamus and M1 under white matter imaging (Figure 8). The goal of this study is to visualize the white matter change between M1 and the thalamus, to provide additional evidence that continuous dance

training provides additional external input to the thalamus to restore its excitability, and subsequently benefits motor functioning. In the anatomical aspect, the M1 and VL thalamus are connected by thalamic radiation, which may affect PD, as the plasticity changes could be prevalent (Pietracupa et al., 2023).

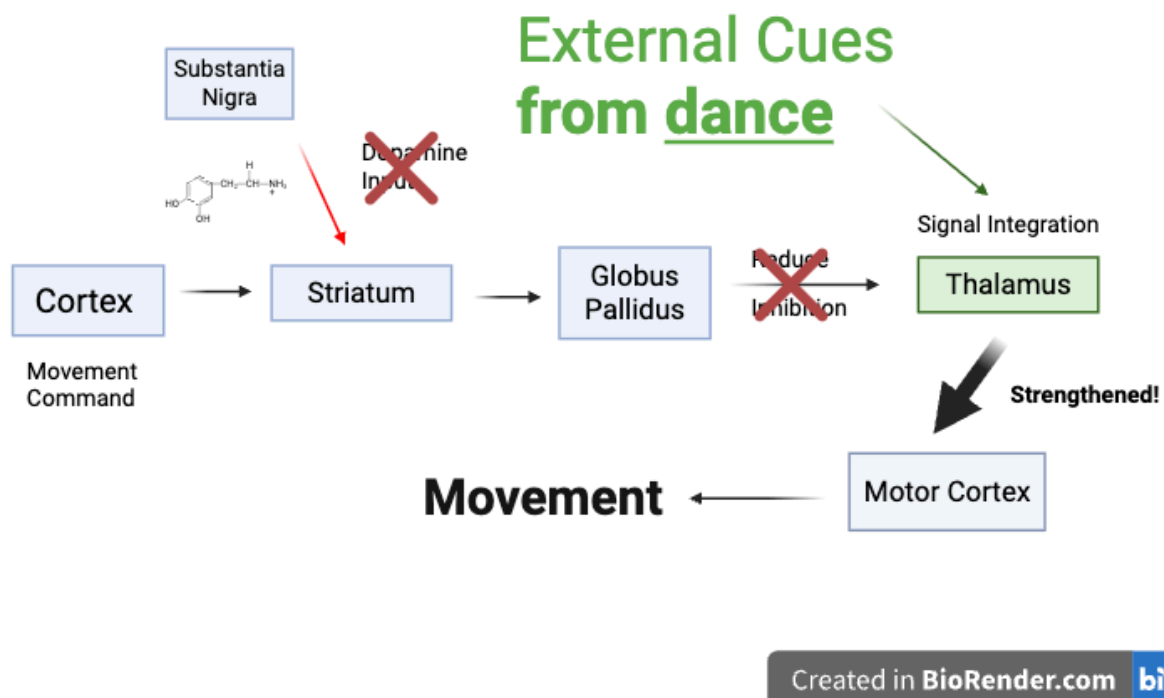


Figure 11. A schematic of how external cues may benefit PD patients by introducing external cues to the go pathway within the basal ganglia. As a result, we should observe the plasticity change within the white matter in the thalamo-cortical pathway to support M1 excitability and the restoration of motor functioning.

The current study will use the same dataset to build on the results from Bearss and DeSouza (2021) and explore the neural underpinnings that might explain the halt in motor decline. We hypothesize that dance will benefit the WM connection between the

M1 and thalamus to support the stop in motor decline, and potentially slow down neurodegeneration. To validate our hypothesis, we also selected another well-recognized white matter tract, the primary visual cortex (V1) to the thalamus tract, to act as a control, since it is not in the motor pathway and should not experience a change upon dance. We utilized DTI to study WM integrity within the Parkinsonian brain. We visualized the changes in brain SC in patients who were enrolled in a dance intervention via probabilistic tractography.

3.2 Materials and Methods

Participants

We collected data from sixteen participants with mild-severity PD. However, only participants with before and after DTI scans (Jan. 2014 & May 2014) were included in this study ($N = 4$, Mean Hoehn & Yahr Score = 1.25, $N_{males} = 3$, Age of diagnosis = 64.5, $SD = 5.3$). All participants participated in an ongoing, longitudinal, weekly participation in a 1.25-h Dance for PD class at Canada's National Ballet School (NBS) and Trinity locations in Toronto, Ontario, over 3 years. York University approved the ethical protocol, and written informed consent was obtained before data collection.

Ethical Compliance Statement

The study was approved by the Office of Research Ethics (ORE) committee at York University (STU 2025-002) prior to any data analysis.

Procedure

All subjects were trained in a weekly 1.25-h dance for PD class from January 2014 until April 2014. The class participation was also continued further in time but the brain scans occurred in January and April 2014. Classes began with live music during the seated warm-up, followed by “barre” work, and ended with moving across the floor; choreography was also learned for an upcoming performance (Table 4). This choreography was first introduced in Bearss et al. (2017).

Table 4. Sample choreography that the participants were trained on.

Exercise	Description	Purpose
Dance name introduction	The participant state their name with the corresponding dance movement. The rest of the class first watches before repeating the participants' name and movement. Standing or seated.	The participant will feel welcomed, and they will welcome everyone in the class. They could practice their choreographing skills on the spot.
Tendus	The participant will press their feet along the floor until their leg is extended. Their arms will follow a similar extension motion. Seated.	The participant warms up their feet and lower leg while working on their core strength.
Shuffle dance	The participant will perform shuffles, stamps, and ankle inversions. Seated.	The participant can enhance flexibility and mobility in the ankles and knees.
Magic dance	The participant will be “magic” dancing with an imaginary ball and scarf, while exploring motions. Seated.	This provides the participants with an opportunity for mental imagery and creative interpretation.
Rainfall cannon	The participant will simulate the sound of an approaching rainstorm using their body parts as instruments. Seated.	The participant can practice movement initiation by waiting to execute a movement in a proper sequence.
Winning the poker game	The participant will rise slowly from a chair while moving in a celebratory manner.	The participant can practice transitioning from a seated position to standing in a safe manner.

Painter and Sculptor mirrored pairs	This is a paired improvisation dance, done face-to-face. One participant would lead as a painter while the other mirrored their motion. This dance finishes with intertwined poses between the participants. Seated and standing aspects.	The participant can mirror their partner very closely and practice creative movement initiation by improvising and using unique poses.
Pliés in parallel and second position	The participant will hold on to the back of a chair, pliés (bending of the knees), and rises, which were done in parallel (feet together) and apart. Standing.	The participant can develop strength and standing balance. The legs' mobility can also be strengthened.
Lunging side to side	While holding onto the back of the chair, the participant transfers weight from side to side while the legs are in a wide pronated position. They will "brandish a fist" at a neighbouring participant. Standing.	The participant can find a centre for balance by lunging off balance and returning to a central position using their core muscle.
Waltz	The participant will perform waltz steps first on the spot and then while travelling. Standing.	The participant can dance through space safely and experience the triplet rhythm of the waltz.
Shy to confident shuffle dance	This is a standing variation of the seated shuffle dance, where the movements are done first in a demure and small manner, but it gradually increases in confidence until they are gregariously expressed.	This is a fun way of practicing moving with confidence and with clear intention.
The "Showdown Hoedown" dance	The participant will perform an approximately a 2 min choreography done facing a partner, first dancing as advisories in the "showdown" and then together as companions in the "hoedown." Standing.	This is challenging participants to recall a lengthy piece of choreography with multiple sections and changes of direction.

Image acquisition

Participants were scanned on a 3T Siemens MAGNETOM PrismaFit MRI scanner (York University, Ontario) with a 32-channel head coil. We conducted a T1 structural scan and a diffusion-weighted imaging (DWI) scan for every participant. The T1 scan was conducted to localize the brain structures, while the DWI scan was used to conduct probabilistic tractography to localize the target WM regions of interest (ROIs) and extract WM metrics. A 3D, Gradient Echo with Inversion Recovery (MPRAGE) T1-weighted sequence with repetition time (TR) = 1.9 ms, echo time (TE) = 2.52 ms, inversion time (TI) = 900 ms, flip angle = 9 degrees, field of view (FOV) = 256 mm, matrix = 256 × 256, slice thickness = 1.0 mm was acquired to delineate the gray-white matter interface and accurate Thalamus, M1, and V1 localization. DWI data were acquired with a diffusion-weighted echo planar imaging sequence with presaturation fat suppression. The DWI protocol is a 30-direction, single shell ($b = 1000 \text{ s/mm}^2$) protocol including 60 contiguous, 2 mm thick axial slices, encoded in anterior-to-posterior direction with TR = 8300 ms, TE = 100 ms, FOV = 244 mm × 244 mm × 120 mm to yield a 2.0 mm × 2.0 mm × 2.0 mm³ resolution. The DWI sequence comprised thirty $b = 1000 \text{ s/mm}^2$ volumes and one $b = 0$ volume.

Image preprocessing

DWI data were processed using the Basic and Advanced Tractography with MRtrix for All Neurophiles (B.A.T.M.A.N.) pipeline using MRTrix3 software. (Raffelt & Tabbara, 2022; Tournier et al., 2019). The schematic diagram can be found in the appendix. The raw DICOM files were converted to NIfTI format using MRlcroGL before

primary processing occurred (Rorden & Brett, 2000; Rorden et al., 2007). The pipeline included removing spatial noise, addressing Gibbs' ringing artifact, correcting for motion and distortion artifact using echo planar imaging (EPI) distortion correction, B0-field inhomogeneity correction, and eddy-current correction, offsetting the bias field, and estimating the binary brain mask before conducting probabilistic tractography to ensure the most accurate result, for probabilistic tractography is highly susceptible for artifacts (Andersson et al., 2003; Andersson & Sotiropoulos, 2016; Holland et al., 2010; Kellner et al., 2016; Smith et al., 2004; Tustison et al., 2010; Veraart et al., 2016a; Veraart et al., 2016b). The preprocessing steps mentioned above can be done using MrTrix3-included functions. The reverse encoding image required for EPI distortion correction was obtained from fMRI scans in the same dataset, but was aimed at another study.

The T1 structural scan also underwent DICOM-NIfTI conversion using MRICroGL but was preprocessed with FMRIB software library (FSL) to conduct skull stripping (Rorden & Brett, 2000; Rorden et al., 2007; Smith, 2002) with fractional intensity set to 0.3. The T1 was then automatically segmented into five tissue types (5tt) using MrTrix3 with the FSL algorithm (5ttgen fsl) to obtain the gray-white matter boundaries used in white matter tract estimation (Smith et al., 2012). Also, FreeSurfer was used to segment and preprocess the T1, in which the steps include motion correction, intensity normalization, skull striping, non-linear volumetric registration, neck removal before yielding the gray and white matter parcellations used in ROI (M1, V1, Thal) selection (Fischl, 2012).

Whole-brain tractogram estimation

We first estimated the fibre orientation in the DWI scan by fitting a constrained spherical deconvolution (CSD) model to each voxel, which has been shown to outperform the traditional ellipsoidal tensor model in regions with crossing fibres (Figure 9; Farquharson et al., 2013; Tournier et al., 2004; Tournier et al., 2007). The pipeline called for a multi-shell, multi-tissue CSD to yield the best result by visualizing the change in response function in different tissue types as time lapses, but we were only able to perform single-shell CSD as our dataset only comprises $b = 1000$ data. Global intensity differences were also corrected using MrTrix3 to make the Fibre Orientation Distribution (FOD) comparable between subjects. The global CSD tensor map was then used to generate brain-wide AD, RD, MD, and FA maps for each subject using MrTrix3 (tensor2metric). The T1-derived 5tt map and skull-stripped T1 were then registered with the DWI scan to allow for minimal alteration to the DWI to endure the fiber accuracy, then 10 million white matter estimation streamlines were generated within the whole brain using probabilistic tractography based on the gray/white matter interface from the 5tt map as seed and the FOD in each voxel as guidance. After the initial generation, spherical-deconvolution-informed filtering of tracks (SIFT) would filter out most of the longer streamlines due to the pitfall of CSD of overestimating the thickness of tracts, which leaves us 1 million streamlines in total for the ROI-based tractography.

Region of interest selection

ROIs encompassing the gray and white matter of the primary motor cortex, primary visual cortex, and the gray matter of the thalamus were obtained from T1 scan

gray and white matter parcellation in FreeSurfer using recon-all (Figure 10). The M1 and V1 ROI was obtained from combining the gray and white matter parcellation from recon-all using fslmaths from FSL to ensure the maximum number of streamlines land in the ROI. The thalamus ROI was taken from recon-all directly as a whole without combining with any white matter. The obtained ROIs were first binarized and then registered into the DWI space using the matrix produced by T1 and 5tt to DWI registration with the linear registration tool provided by FSL; the voxel size was also upsized (2mm^3) to fit into the DWI space.

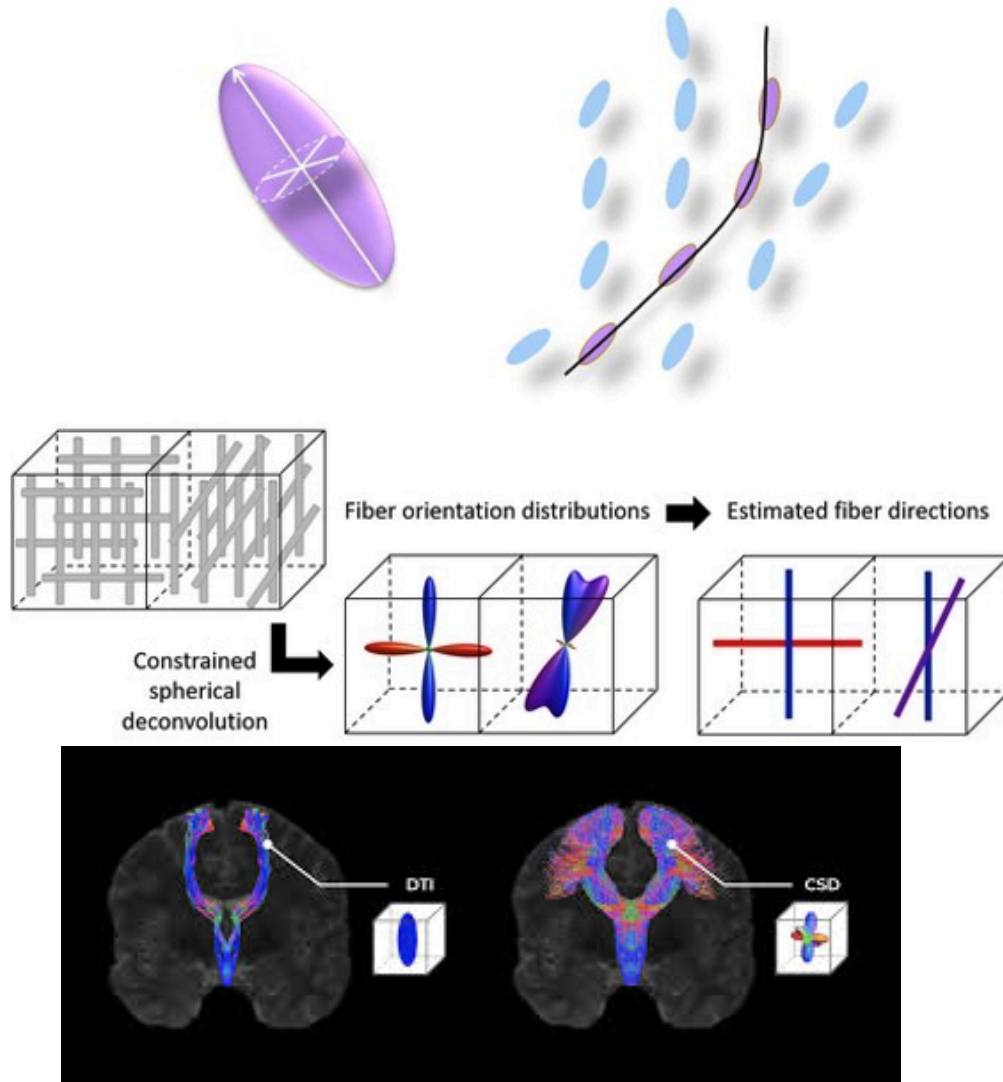


Figure 12. A demonstration of the CSD tensor used in this study vs the traditional ellipsoid tensor in DTI. The ellipsoid tensor could provide a rough estimation of fibre orientation, but only supports the tractography in one single direction (Top). This is potentially problematic when visualizing white matter fibre junctions and crossing fibres. The CSD model can provide a better estimation in crossing fibres when the fibre directionality is unclear in the ellipsoid tensors (Middle). The CSD tensor is useful in visualizing complex tractography, such as at the cortispinal tract and hence is suitable for our methodology (Bottom).

The white matter tract between V1-Thal and M1-Thal is outlined by first using the thalamus ROI to select only the streamlines that originated from this 3D ROI from the 1-million streamline whole brain tractogram. (Figure 11a) Then, we used V1 and M1 GM+WM ROI as AND gates separately to select all the streamlines that pass through these two ROIs. (Figure 11b) Then, we used the location of these WM tracts as a guide to sample the AD, RD, MD, and FA from the voxels that they pass through using MrTrix3. The whole-brain tractogram was also used to generate an AD/RD/MD/FA metric to control global changes.

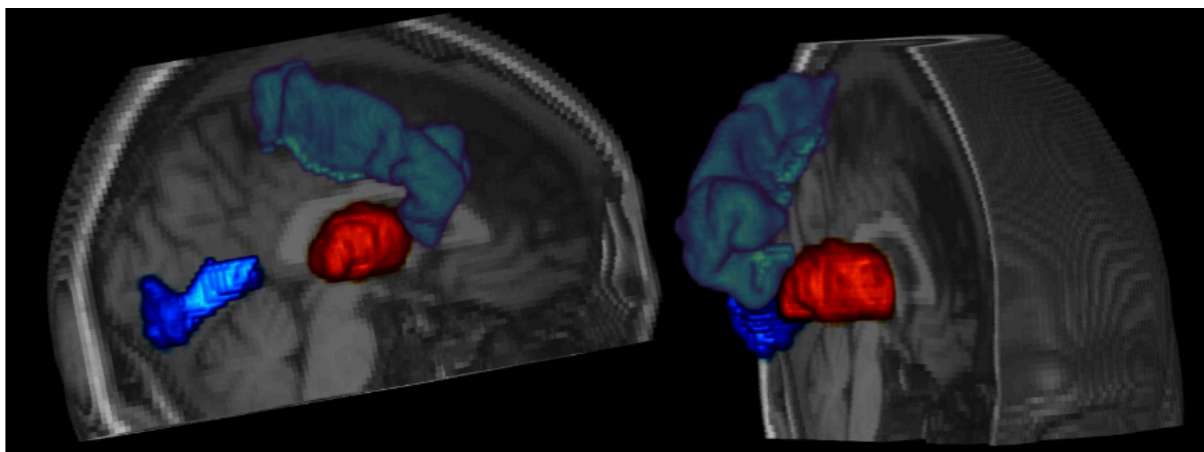


Figure 13. Subject DD and his thalamus (red), M1 (green), and V1 (blue) ROI obtained from automatic parcellation using FreeSurfer. The M1 and V1 ROIs were obtained from combining the cortex and the white matter below. The parcellations were obtained from native T1 images but then registered into DWI space to be used for subsequent tractography.

Statistical analyses

The white matter data were obtained from overlaying the outlined tract in previous steps onto AD/RD/MD/FA metric maps, and the metric from each voxel was averaged to yield a mean AD/RD/MD/FA for a particular tract. Statistical analyses were conducted in R 2025a (R Core Team, 2025). The data was handled with packages tidyverse, readr, tringr, and vroom to organize all the single-voxel metric data into tract-specific metrics and to be put into dataframes (Hester et al., 2023; Wickham, 2023; Wickham et al., 2019; Wickham et al., 2024). Paired t-tests were used to explore whether significant WM metric differences existed between January scans and April scans in 2014. The test track is part of Corona Radiata, originating from the thalamus to the M1; the control track is the visual track, originating from the thalamus to the V1, and the global WM control is the whole brain white matter data. The voxel-wise AD/RD/MD/FA were averaged to obtain a single AD/RD/MD/FA value for the single track of the whole brain. Findings with a P value of < 0.05 were considered significant. The graphs were created with ggplot2 (Wickham, 2016).

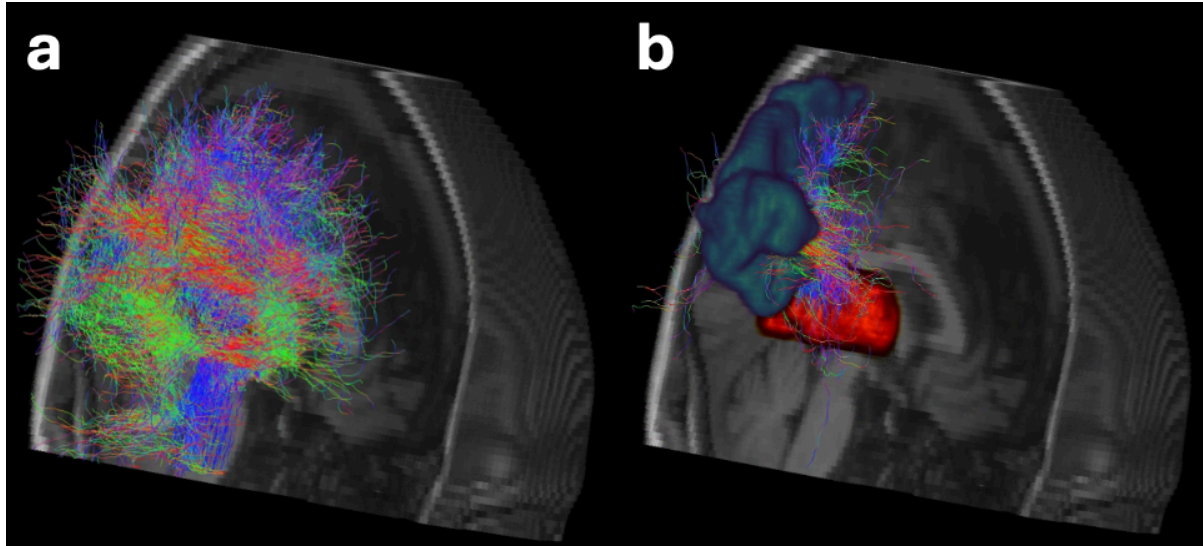


Figure 14. An illustration of how the ROI-based white matter tract selection is achieved using the subject DD as a sample in a 2-step process. **a.** From all the white matter streamlines in the brain, only the ones originating from the thalamus (red) were strictly selected. **b.** From the streamlines selected in a, only the streamlines that **pass through** M1 (green) were selected. The thalamus-V1 white matter is also selected in a similar fashion. This is the final tract to yield the white matter metric in the subsequent steps.

3.3 Tractography Results

Pathway-specific streamline counts

By simulating 10 million streamlines in 8 DTI scans and conducting WM tract selection using the mentioned ROIs (Bilateral Thalamus, V1, M1), we yielded an average of 128 (SD = 10.01) streamlines in the left Thal-M1 connection at baseline; the average number of streamlines was 134 (SD = 10.23) after the dance intervention. The t-test did not reveal a significant difference between the two timepoints, $t(3) = -0.59$, $p = .60$ (Appendix 4.1).

We yielded an average of 423 (SD = 89.22) streamlines in the right Thal-M1 connection at baseline; the average number of streamlines was 183.75 (SD = 13.28) after the dance intervention. The t-test revealed that the streamline count is significantly less after the intervention compared to baseline, $t(3) = 5.3665$, $p < .02$ (Figure 12).

We yielded an average of 3 (SD = 1.83) streamlines in the left Thal-V1 connection at baseline; the average number of streamlines was 2.5 (SD = 1) after the intervention. The t-test did not reveal a significant difference between the two timepoints, $t(3) = .42$, $p = .70$ (Appendix 4.2).

We yielded an average of 5.25 (SD = 4.65) streamlines in the right Thal-V1 connection at baseline; the average number of streamlines was 6 (SD = 5.35) after the intervention. The t-test did not reveal a significant difference between the two timepoints, $t(3) = -.18$, $p = .87$ (Appendix 4.3).

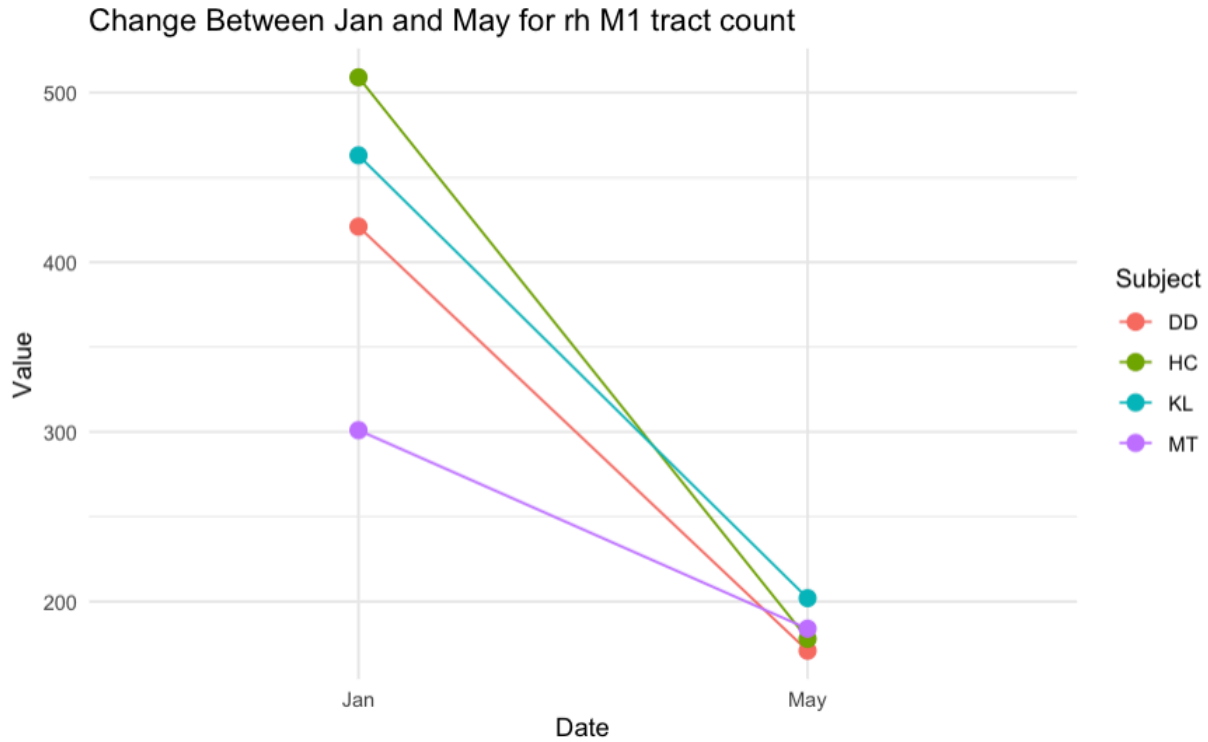


Figure 15. A comparison between the right M1-thalamus white matter tract streamline count. The streamline count in this pathway has significantly decreased from before the intervention to after ($p < .02$).

Whole-brain and pathway-specific WM metrics

After extracting the simulated streamlines from the whole-brain tractogram, we used the CSD-derived tensors to acquire the AD, RD, MD, and FA from their voxel-specific maps. Then, as the streamline paths are sampled along the voxels they pass through, we obtained an average metric for the whole tract by taking the mean of every sampled voxel. A paired t-test between the baseline and the after-intervention metrics does not reveal any significant result ($p > .05$) at the thalamus-M1 connection or

the thalamus-V1 connection. The full results are presented in Table 5. Their graphs were shown in Appendix 4.4-23 for the lack of statistical significance.

Table 5. Paired t-test result from before/after the dance intervention in white matter data.

Tract	time	metric	average	SD	t-statistic	p value
Wholebrain	January	AD	1.12×10^{-3}	1.72×10^{-5}	t(3) = -1.19	0.32
Wholebrain	April	AD	1.14×10^{-3}	3.60×10^{-5}		
Wholebrain	January	RD	6.62×10^{-4}	4.08×10^{-5}	t(3) = -1.25	0.30
Wholebrain	April	RD	6.81×10^{-4}	7.05×10^{-5}		
Wholebrain	January	MD	8.15×10^{-4}	3.16×10^{-5}	t(3) = -1.25	0.30
Wholebrain	April	MD	8.33×10^{-4}	5.89×10^{-5}		
Wholebrain	January	FA	0.35	0.03	t(3) = 1.58	0.21
Wholebrain	April	FA	0.34	0.04		
Right M1-Thalamus	January	AD	1.17×10^{-3}	3.21×10^{-5}	t(3) = 0.36	0.75
Right M1-Thalamus	April	AD	1.16×10^{-3}	3.87×10^{-5}		
Right M1-Thalamus	January	RD	5.42×10^{-4}	4.56×10^{-5}	t(3) = 0.48	0.66
Right M1-Thalamus	April	RD	5.35×10^{-4}	2.36×10^{-5}		
Right M1-Thalamus	January	MD	7.50×10^{-4}	2.93×10^{-5}	t(3) = 0.50	0.65
Right M1-Thalamus	April	MD	7.45×10^{-4}	1.04×10^{-5}		
Right M1-Thalamus	January	FA	0.48	0.05	t(3) = -0.31	0.78
Right M1-Thalamus	April	FA	0.48	0.03		

Tract	time	metric	average	SD	t-statistic	p value
Left M1-Thalamus	January	AD	$1.17 \cdot 10^{-3}$	$4.26 \cdot 10^{-5}$	t(3) = -1.30	0.28
Left M1-Thalamus	April	AD	$1.18 \cdot 10^{-3}$	$3.12 \cdot 10^{-5}$		
Left M1-Thalamus	January	RD	$5.58 \cdot 10^{-4}$	$4.42 \cdot 10^{-5}$	t(3) = 0.57	0.61
Left M1-Thalamus	April	RD	$5.53 \cdot 10^{-4}$	$2.59 \cdot 10^{-5}$		
Left M1-Thalamus	January	MD	$7.62 \cdot 10^{-4}$	$2.71 \cdot 10^{-5}$	t(3) = 0.07	0.95
Left M1-Thalamus	April	MD	$7.62 \cdot 10^{-4}$	$1.60 \cdot 10^{-5}$		
Left M1-Thalamus	January	FA	0.46	0.05	t(3) = -0.68	0.55
Left M1-Thalamus	April	FA	0.47	0.03		
Right V1-Thalamus	January	AD	$1.34 \cdot 10^{-3}$	$4.27 \cdot 10^{-5}$	t(3) = -2.27	0.11
Right V1-Thalamus	April	AD	$1.36 \cdot 10^{-3}$	$4.93 \cdot 10^{-5}$		
Right V1-Thalamus	January	RD	$6.27 \cdot 10^{-4}$	$2.34 \cdot 10^{-5}$	t(3) = 0.22	0.84
Right V1-Thalamus	April	RD	$6.24 \cdot 10^{-4}$	$3.78 \cdot 10^{-5}$		
Right V1-Thalamus	January	MD	$8.65 \cdot 10^{-4}$	$2.88 \cdot 10^{-5}$	t(3) = -0.38	0.73
Right V1-Thalamus	April	MD	$8.68 \cdot 10^{-4}$	$3.78 \cdot 10^{-5}$		
Right V1-Thalamus	January	FA	0.48	0.01	t(3) = -0.67	0.55
Right V1-Thalamus	April	FA	0.48	0.01		

Tract	time	metric	average	SD	t-statistic	p value
Left V1-Thalamus	January	AD	$1.37 \cdot 10^{-3}$	$2.77 \cdot 10^{-5}$	t(3) = -0.41	0.71
Left V1-Thalamus	April	AD	$1.39 \cdot 10^{-3}$	$7.39 \cdot 10^{-5}$		
Left V1-Thalamus	January	RD	$6.16 \cdot 10^{-4}$	$1.84 \cdot 10^{-5}$	t(3) = -1.27	0.29
Left V1-Thalamus	April	RD	$6.56 \cdot 10^{-4}$	$6.78 \cdot 10^{-5}$		
Left V1-Thalamus	January	MD	$8.69 \cdot 10^{-4}$	$4.20 \cdot 10^{-5}$	t(3) = -1.00	0.39
Left V1-Thalamus	April	MD	$9.00 \cdot 10^{-4}$	$6.44 \cdot 10^{-5}$		
Left V1-Thalamus	January	FA	0.50	0.02	t(3) = 2.64	0.08
Left V1-Thalamus	April	FA	0.47	0.03		

Chapter 4

4.1 Discussions

In this study, we examined the WM connection between the M1 and the thalamus in PD patients who participated in continuous dance training to acquire an explanation for previously-demonstrated behavioural outcomes, in which we observed a halting of motor symptom decline over three years (Bearss & DeSouza, 2021). We used advanced CSD-based probabilistic tractography to generate a whole-brain tractogram and freesurfer-based ROI selection to minimize human selection bias common in other tractography studies. This study is also the first to attempt to discuss the dynamic SC to explain a real-life response we observed in our previous studies in PD rehabilitation. Focusing on the thalamus-M1 connection and utilizing thalamus-V1 and whole-brain WM as intra-subject controls, we saw a significant decrease in streamline count at the right M1-thalamus pathway specifically. We also tested whether the WM property differs between the two time points. However, no significant difference exists in our examined metrics in AD, RD, MD, or FA, either in pathway- or whole-brain-wide measures.

The pathological hallmark of PD is the loss of dopaminergic neurons in the SNc and generation of α -synuclein-containing Lewy bodies or Lewy neurites, which are irreversible. It causes neurodegeneration in other brain regions, leading to

heterogeneous brain and behaviour pathology (John van Geest Centre for Brain Repair, Department of Clinical Neurosciences, University of Cambridge, UK, et al., 2018). The widespread and idiopathic brain damage beyond the damaged SNc has made it notoriously difficult for PD to target singular ROIs to restore physiologic functions (Agosta et al., 2013).

The conventional approach to PD intervention is administering levodopa to supplement the basal ganglia with dopamine precursor to compensate for endogenous dopamine deficiency from the loss of dopaminergic neurons in the SNc (Olanow & Stocchi, 2018). Although bearing side effects and potential addiction concerns, it is still the gold standard in PD treatment when discussing other intervention plans (Beaulieu-Boire & Lang, 2015; Borek & Friedman, 2005; Vasta et al., 2017). An emerging behavioural therapy using dance has been gaining importance for its effectiveness and absence of side effects (Westheimer et al., 2015). The original Dance for PD® (DfPD®) program was developed by the Brooklyn Parkinson Group and Mark Morris and has been adapted to countless forms to suit patients' needs and achieve the best outcome. Regular aerobic exercise has been proven to improve PD patients' brain plasticity, cognition, and motor skills; dance programs have unique advantages over traditional exercise programs (Rafferty et al., 2017; Tsukita et al., 2022; Westheimer, 2008). First, dancing encompasses components other than physical exercise, such as motor learning, social interaction, and music synchronization, that would not be utilized in simple aerobic exercises. The study by Fontanesi and DeSouza (2021) demonstrated that the intensity-controlled dance program was able to contribute more to body self-efficacy, self-beauty perception, gait symmetry, and freezing reduction, which

together can be integrated into two main functional improvements – cognitive and motor improvements over exercise programs. From that perspective, dance can significantly improve PD patients' quality of life more than exercise programs, as motor performance and cognitive decline impair the quality of life the most in PD (Schrag, 2000). The music, spatial mapping, and social components provide external cues, while dancing and cognitive and motor functions can be improved by relying on these cues (Kashyap et al., 2021). The halt in PD motor symptom progression described by Bearss and DeSouza (2021) also signifies unique superiorities in dance therapy, like little-to-no side effects and a high participation rate over drug treatment and exercise regimes.

Although the beneficial effect of physical exercise on WM integrity has been well-documented in healthy and diseased populations, this pilot study failed to reject the null hypothesis stating continuous dance participation can brought forth positive SC change in the thalamocortical pathway, as none of the white matter metric (AD, RD, MD, FA) differentiates in this pathway between the intervention; or the global white matter health in general, as the control pathway and global white matter metric were also not significantly different in the time frame. Within this data, the only significant change in white matter is the decreased streamline count within the right Thalamus-M1 connection. As Pannek et al. (2011) state, streamline number-based analysis typically shows poor reproducibility even for the same subjects, which renders them ineffective in between-subject comparisons. Given our small sample size, the interpretation of this result becomes even more challenging. The streamline count cannot be used solely as the interpolation of white matter change, but more as a supplemental tool.

There are previous studies describing regional white matter in short time frames, but not on a whole-brain scale. The study by Mielke et al. (2009) showed that three months is not sufficient to trigger whole-brain level WM metric change in Alzheimer's disease, despite the presence of regional white matter deterioration that can be correlated with cognitive impairments. Engvig et al. (2012) also examined the WM change in healthy aging participants (mean age = 61 years) in a 10-week interval with memory cognitive training. They have found a significant FA increase within the fornix correlating with memory improvements. However, in the motor circuits, white matter changes can usually be seen in long-term training. According to Schmithorst & Wilke (2002), significant FA decrease in the corona radiata and internal capsule, with FA increase in the genu of the corpus callosum, can be seen in professional musicians with excellent manual dexterity. A 10-day motor training study by Kwon et al. (2012) revealed that short-term motor training could only induce cortical activation pattern change for implicit motor learning, yet to trigger significant plasticity to remap the white matter. In our study, even though we have seen beneficial motor effects across 3 years, the lack of UPDRS score to correspond to behavioural change within 4 months could not provide sufficient evidence for immediate white matter improvement.

As a part of the corticospinal tract (CST) that controls the voluntary movement of the limbs, the Thalamus-M1 connection were more commonly studied in injury and infarction, where a total function loss like paralysis is typical when the CST is no longer intact (Cho et al., 2007; Koyama et al., 2013; Lee et al., 2010). Even though previous rodent studies render this tract subject to change in induced Parkinson's models, we believe that more complex motor symptom disruptions like tremor and movement

difficulties, rather than simple enabling and disabling limb controls, should originate from higher motor control regions rather than the direct voluntary control pathway. Minett et al. (2018) in tracking longitudinal WM changes in PD models, have previously shown that the baseline MD change is related to motor decline in a 2.5-year interval. The Lewy bodies naturally formed in PD progression may be transported along the axons into various brain regions, impacting their functionalities (Peng et al., 2020). Conversely, the more commonly observed diffuse white matter hyperintensity (increased MD, reduced FA) in PD may also be due to the trafficking of Lewy bodies compressing the myelin or surrounding gray matter damage (Taylor et al., 2018; Peng et al., 2020).

In contrast to the motor training that dance provides, cognitive planning, socializing, music perception, and self-efficacy are all important modalities that dance encompasses. There has been an ongoing debate on the additional benefits dance brought forth, with all its additional non-motor components, compared to intensity-matched aerobic exercise. There have been conflicting results on whether dance participation can lead to decreased PD motor symptoms, but dance training typically yields better mood, enjoyment, and continuous participation rate among the participants (Hackney et al., 2007; Volpe et al., 2013; Wu et al., 2015). There is theoretical evidence stating that the involvement of music could promote connectivity inside the basal ganglia to compensate for the neurodegeneration in PD (Freedland et al., 2002; Nieuwboer et al., 1997). As an integral part of dance, the synchronization between choreography and music utilizes cognitive resources to regulate movements (Jola et al., 2022). The difficulty in isolating the motor aspect of dance from other modalities in experimental design has complicated the debate significantly. However,

observing the brain structural change within the neuroimaging data, instead of controlling the involvement of non-motor modalities, we may take an alternative approach by differentiating the degree of structural changes in various functional areas to determine the importance of motor vs non-motor modalities. Another study by Karimi et al. (In preparation) that uses the same dataset, utilizing the same WM imaging method, and across the same time frame, demonstrated a significant FA improvement at the connection between Broca's area and SMA, while the M1-Thalamus connection remains relatively unchanged. Another study in this lab by Simon et al. (2023) that explores the FC in the Parkinsonian brain also reported significant activation and reduction in activity over time of the SMA while imaging the dance choreography. As the participants gradually get better with dance, the SMA becomes less and less needed since the connectivity gets better with training-induced plasticity (Olshansky et al., 2015). Previous literature relating the cognitive impairment to WM degeneration has also yielded positive results, which also leads us to shift focus onto non-motor aspects of how dance improves brain health (Hattori et al., 2012; Kim et al., 2013). This is compelling evidence that the WM is being improved in other brain regions, not in the Thalamus-M1 or Thalamus-V1 pathways. We may speculate that other non-motor aspects of dance have a more effective effect on the brain to promote active structural changes earlier in the intervention.

The major limiting factors for this current pilot study are the lack of a PD control group who did not dance and the small sample size. The original research by Bearss and DeSouza (2021) spanned across 3 years, recorded extensive behavioural data, and maintained a high participation rate among 32 volunteers. However, due to the

inconvenience of DTI imaging and difficulty staying still in movement disorders, we included all 4 participants with longitudinal data across 4 months. Given PD's idiopathic nature and challenges in recruitment and participant selection, studies face the lack of test subjects and selecting appropriate and ethical, viable control subjects, especially in longitudinal studies. This study is among the first preliminary reports to describe the WM change in continuous participation in dance practice. Despite the promising behavioural results in 3 years, the WM connection between the Thalamus and M1, which is directly responsible for voluntary limb movements, is not subject to change in 4 months for only four subjects. Dance may benefit PD patients through non-motor domains such as social, music, and cognitive aspects, but direct motor WM pathway improvement is limited. Future work in this field can include a whole-brain TBSS to investigate WM changes across different ROI. Also considering the importance of external cues that enhance the afferent pathways to the thalamus to bypass the damaged basal ganglia, we may also focus on the auditory input pathway to the thalamus to look for WM changes. It could also be valuable to compare the SC trajectory in PD with dance training with normal aging individuals to look for pattern similarities to prove the effectiveness of dance training on the neural level.

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APPENDIX

NOTES, CODES AND FIGURES

APPENDIX A - NOTES

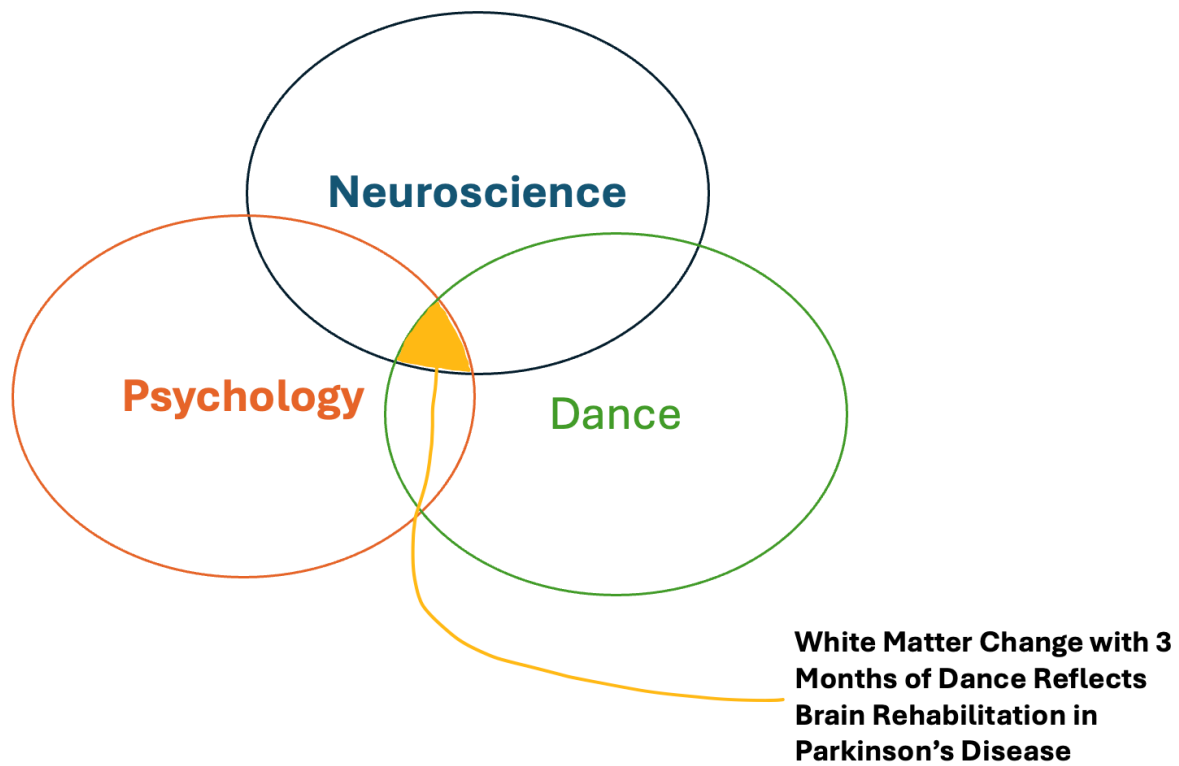
1. A Note on Interdisciplinarity in Science

When explaining a behavioural outcome, there might be complicated, multidimensional reasons that do not fit into one single discipline's realm. The factors must be considered together, in conjunction with one another, to weave a web of science that considers the problem thoroughly. Interdisciplinary research emerges naturally when scientists combine knowledge from two or more disciplines (Alvargonzález, 2011).

The current research has its roots deeply in the disciplines of neuroscience, psychology, and dance. Considering the established results that this research is based upon, neuroscience enables us to look at Parkinson's disease's pathophysiology thoroughly, and neuroimaging methods are closely associated with this discipline.

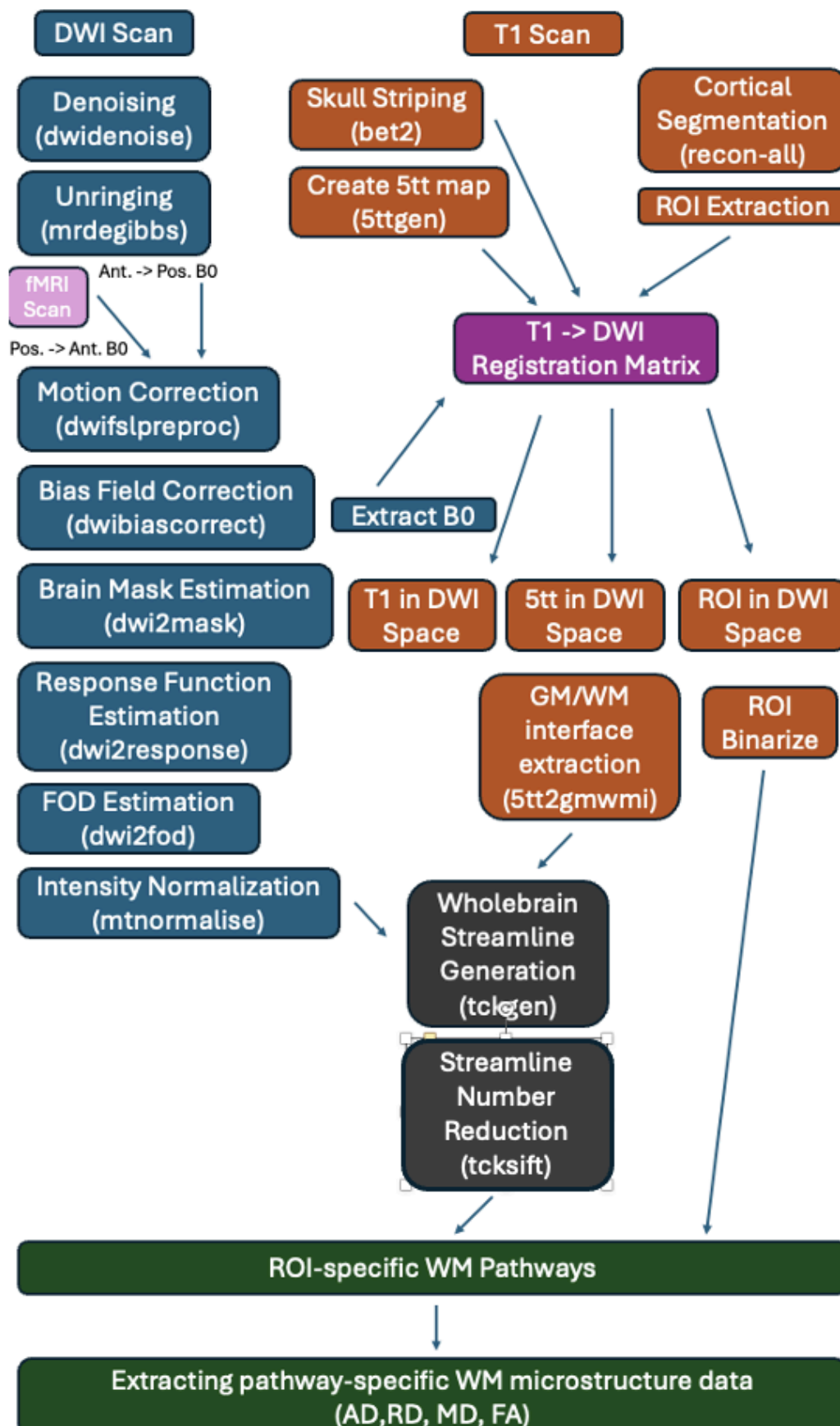
Psychology, on the other hand, studies mainly the mind and behaviour. This discipline enables me to interpret the results from neuroimaging and pair them with the real-world outcome that continuous dance training has given.

Dance is another critical discipline in my research, especially when the test subjects underwent 3 months of continuous dance training and received beneficial behavioural outcomes continuously over the 3 years. Albeit my research does not delve in depth into specific dance techniques or dance history, the highlight is in the multifactorial benefits dance can have on the brain. This research has also broken down domains of dance (e.g. aerobic exercise, social interaction, cognitive interpretation, etc.) into singular elements and linked them with changes in the brain.



Venn diagram of this thesis and its three disciplines

2. Schematic of the automated white matter tractography



APPENDIX B - CODES

3. Codes for automated white matter tractography

3.1 Local data organization

```
#!/bin/sh
```

```
sub=$(cat /Users/marcusmeng/Documents/Joe\ Lab/Bash_Script/subject_list.txt);
```

```
for i in $sub; do
```

```
    # go to master folder
```

```
    cd
```

```
    /Users/marcusmeng/Joe_lab/PD_MARCUS/PD_CohortB_Scan1_preprocessed/DESOUZA_PA  
    TIENT1*_${i}
```

```
    # go to mri folder in freesurfer
```

```
    cd ${i}3/mri
```

```
    # copy the white matter parcellation to dwi folder
```

```
    cp wmparc.mgz
```

```
    /Users/marcusmeng/Joe_lab/PD_MARCUS/PD_CohortB_Scan1_preprocessed/DESOUZA_PA  
    TIENT1*_${i}/${i}_January
```

```
    # copy the GM to ....
```

```
    cp aparc+aseg.mgz
```

```
    /Users/marcusmeng/Joe_lab/PD_MARCUS/PD_CohortB_Scan1_preprocessed/DESOUZA_PA  
    TIENT1*_${i}/${i}_January
```

```
    # same for the "after" scans
```

```
    cd
```

```
    /Users/marcusmeng/Joe_lab/PD_MARCUS/PD_CohortB_Scan2_preprocessed/DESOUZA_PA  
    TIENT1*_${i}
```

```
    cd ${i}4/mri
```

```
    cp wmparc.mgz
```

```
    /Users/marcusmeng/Joe_lab/PD_MARCUS/PD_CohortB_Scan2_preprocessed/DESOUZA_PA  
    TIENT1*_${i}/${i}_May
```

```
    cp aparc+aseg.mgz
```

```
    /Users/marcusmeng/Joe_lab/PD_MARCUS/PD_CohortB_Scan2_preprocessed/DESOUZA_PA  
    TIENT1*_${i}/${i}_May
```

```
done
```

3.2 Scan type conversion

```
#!/bin/sh
```

```
sub=$(cat /Users/marcusmeng/Documents/Joe\ Lab/Bash_Script/subject_list.txt);
```

```
for i in $sub; do
```

```
    # go to dwi folder
```

```
    cd
```

```
    /Users/marcusmeng/Joe_lab/PD_MARCUS/PD_CohortB_Scan1_preprocessed/DESOUZA_PA  
TIENT1*_${i}/${i}_January
```

```
    # convert format for wm
```

```
    mrconvert wmparc.mgz wmparc.nii.gz
```

```
    # same for "after" scans
```

```
    cd
```

```
    /Users/marcusmeng/Joe_lab/PD_MARCUS/PD_CohortB_Scan2_preprocessed/DESOUZA_PA  
TIENT1*_${i}/${i}_May
```

```
    mrconvert wmparc.mgz wmparc.nii.gz
```

```
done
```

3.3 Segmentation data type conversion

```
#!/bin/sh
```

```
sub=$(cat /Users/marcusmeng/Documents/Joe\ Lab/Bash_Script/subject_list.txt);
```

```
for i in $sub; do
```

```
    # go to dwi folder
```

```
    cd
```

```
    /Users/marcusmeng/Joe_lab/PD_MARCUS/PD_CohortB_Scan1_preprocessed/DESOUZA_PA  
TIENT1*_${i}/${i}_January
```

```
    # convert the gm parcellation file
```

```
    mrconvert aparc+aseg.mgz aparc+aseg.nii.gz
```

```
    # same for the "after" files
```

```
    cd
```

```
    /Users/marcusmeng/Joe_lab/PD_MARCUS/PD_CohortB_Scan2_preprocessed/DESOUZA_PA  
TIENT1*_${i}/${i}_May
```

```
    mrconvert aparc+aseg.mgz aparc+aseg.nii.gz
```

```
done
```

3.4 WM ROI registration

```
#!/bin/sh
```

```
sub=$(cat /Users/marcusmeng/Documents/Joe\ Lab/Bash_Script/subject_list.txt);
```

```
for i in $sub; do
```

```
    # go to dwi folder
```

```
    cd
```

```
    /Users/marcusmeng/Joe_lab/PD_MARCUS/PD_CohortB_Scan1_preprocessed/DESOUZA_PA  
TIENT1*_${i}/${i}_January
```

```
    # convert T1 file
```

```
    mrconvert T1_coreg.mif T1_coreg.nii.gz -force
```

```
    # register wm parcellation with T1, nearest neighbour interpolation, and maximum search, using  
    6 DOF because within subject
```

```
    /usr/local/fsl/bin/flirt -in wmparc.nii.gz -ref T1_coreg.nii.gz -out wmparc_xfm.nii.gz -omat  
wmparc_to_T1.mat -bins 256 -cost corratio -searchrx -180 180 -searchry -180 180 -searchrz  
-180 180 -dof 6
```

```
    # same for "after" files
```

```
    cd
```

```
    /Users/marcusmeng/Joe_lab/PD_MARCUS/PD_CohortB_Scan2_preprocessed/DESOUZA_PA  
TIENT1*_${i}/${i}_May
```

```
    mrconvert T1_coreg.mif T1_coreg.nii.gz -force
```

```
    /usr/local/fsl/bin/flirt -in wmparc.nii.gz -ref T1_coreg.nii.gz -out wmparc_xfm.nii.gz -omat  
wmparc_to_T1.mat -bins 256 -cost corratio -searchrx -180 180 -searchry -180 180 -searchrz  
-180 180 -dof 6
```

```
done
```

3.5 GM ROI registration

```
#!/bin/sh
```

```
sub=$(cat /Users/marcusmeng/Documents/Joe\ Lab/Bash_Script/subject_list.txt);
```

```
for i in $sub; do
```

```
    # go to dwi folder
```

```
    cd
```

```
    /Users/marcusmeng/Joe_lab/PD_MARCUS/PD_CohortB_Scan1_preprocessed/DESOUZA_PATIENT1*_${i}/${i}_January
```

```
    # use the transformation matrix obtained from registering wm to T1 to register GM parcellation to T1 too. Using the matrix ensures the wm-T1 and gm-T1 registration can line up
```

```
    /usr/local/fsl/bin/flirt -in aparc+aseg.nii.gz -applyxfm -init wmparc_to_T1.mat -out aparc+aseg_xfm.nii.gz -paddingsize 0.0 -interp nearestneighbour -ref T1_coreg.nii.gz
```

```
    # same for the "after" files
```

```
    cd
```

```
    /Users/marcusmeng/Joe_lab/PD_MARCUS/PD_CohortB_Scan2_preprocessed/DESOUZA_PATIENT1*_${i}/${i}_May
```

```
    /usr/local/fsl/bin/flirt -in aparc+aseg.nii.gz -applyxfm -init wmparc_to_T1.mat -out aparc+aseg_xfm.nii.gz -paddingsize 0.0 -interp nearestneighbour -ref T1_coreg.nii.gz
```

```
done
```

3.6 Thalamus ROI selection

```
#!/bin/sh
```

```
sub=$(cat /Users/marcusmeng/Documents/Joe\ Lab/Bash_Script/subject_list.txt);
```

```
for i in $sub; do
```

```
    # go to dwi folder
```

```
    cd
```

```
    /Users/marcusmeng/Joe_lab/PD_MARCUS/PD_CohortB_Scan1_preprocessed/DESOUZA_PA  
    TIENT1*_${i}/${i}_January
```

```
    # select the thalamus from GM parcellation
```

```
    fslmaths aparc+aseg_xfm.nii.gz -thr 49 -uthr 49 rh_thal.nii.gz
```

```
    fslmaths aparc+aseg_xfm.nii.gz -thr 10 -uthr 10 lh_thal.nii.gz
```

```
    # same for the "after" files
```

```
    cd
```

```
    /Users/marcusmeng/Joe_lab/PD_MARCUS/PD_CohortB_Scan2_preprocessed/DESOUZA_PA  
    TIENT1*_${i}/${i}_May
```

```
    fslmaths aparc+aseg_xfm.nii.gz -thr 49 -uthr 49 rh_thal.nii.gz
```

```
    fslmaths aparc+aseg_xfm.nii.gz -thr 10 -uthr 10 lh_thal.nii.gz
```

```
done
```

3.7 M1 WM selection

```
#!/bin/sh
```

```
sub=$(cat /Users/marcusmeng/Documents/Joe\ Lab/Bash_Script/subject_list.txt);
```

```
for i in $sub; do
```

```
    # go to dwi folder
```

```
    cd
```

```
    /Users/marcusmeng/Joe_lab/PD_MARCUS/PD_CohortB_Scan1_preprocessed/DESOUZA_PA  
    TIENT1*_${i}/${i}_January
```

```
    # select the wm from precentral cortex from WM parcellation file
```

```
    fslmaths wmparc_xfm.nii.gz -thr 4024 -uthr 4024 rh_M1.nii.gz
```

```
    fslmaths wmparc_xfm.nii.gz -thr 3024 -uthr 3024 lh_M1.nii.gz
```

```
    # same for the "after" file
```

```
    cd
```

```
    /Users/marcusmeng/Joe_lab/PD_MARCUS/PD_CohortB_Scan2_preprocessed/DESOUZA_PA  
    TIENT1*_${i}/${i}_May
```

```
    fslmaths wmparc_xfm.nii.gz -thr 4024 -uthr 4024 rh_M1.nii.gz
```

```
    fslmaths wmparc_xfm.nii.gz -thr 3024 -uthr 3024 lh_M1.nii.gz
```

```
done
```

3.8 V1 WM selection

```
#!/bin/sh
```

```
sub=$(cat /Users/marcusmeng/Documents/Joe\ Lab/Bash_Script/subject_list.txt);
```

```
for i in $sub; do
```

```
    # go to dwi folder
```

```
    cd
```

```
    /Users/marcusmeng/Joe_lab/PD_MARCUS/PD_CohortB_Scan1_preprocessed/DESOUZA_PA  
    TIENT1*_${i}/${i}_January
```

```
    # select the wm pericalcarine from WM parcellation file
```

```
    fslmaths wmparc_xfm.nii.gz -thr 4021 -uthr 4021 rh_V1.nii.gz
```

```
    fslmaths wmparc_xfm.nii.gz -thr 3021 -uthr 3021 lh_V1.nii.gz
```

```
    # same for the "after" file
```

```
    cd
```

```
    /Users/marcusmeng/Joe_lab/PD_MARCUS/PD_CohortB_Scan2_preprocessed/DESOUZA_PA  
    TIENT1*_${i}/${i}_May
```

```
    fslmaths wmparc_xfm.nii.gz -thr 4021 -uthr 4021 rh_V1.nii.gz
```

```
    fslmaths wmparc_xfm.nii.gz -thr 3021 -uthr 3021 lh_V1.nii.gz
```

```
done
```

3.9 Binarize ROIs

```
#!/bin/sh
```

```
sub=$(cat /Users/marcusmeng/Documents/Joe\ Lab/Bash_Script/subject_list.txt);
```

```
for i in $sub; do
```

```
    # go to dwi folder
```

```
    cd
```

```
    /Users/marcusmeng/Joe_lab/PD_MARCUS/PD_CohortB_Scan1_preprocessed/DESOUZA_PA  
    TIENT1*_${i}/${i}_January
```

```
    # binarize the selected M1 and V1
```

```
    fslmaths rh_V1.nii.gz -bin rh_V1_bin.nii.gz
```

```
    fslmaths lh_V1.nii.gz -bin lh_V1_bin.nii.gz
```

```
    fslmaths rh_M1.nii.gz -bin rh_M1_bin.nii.gz
```

```
    fslmaths lh_M1.nii.gz -bin lh_M1_bin.nii.gz
```

```
    fslmaths rh_thal.nii.gz -bin rh_thal_bin.nii.gz
```

```
    fslmaths lh_thal.nii.gz -bin lh_thal_bin.nii.gz
```

```
    # same for the "after" files
```

```
    cd
```

```
    /Users/marcusmeng/Joe_lab/PD_MARCUS/PD_CohortB_Scan2_preprocessed/DESOUZA_PA  
    TIENT1*_${i}/${i}_May
```

```
    fslmaths rh_V1.nii.gz -bin rh_V1_bin.nii.gz
```

```
    fslmaths lh_V1.nii.gz -bin lh_V1_bin.nii.gz
```

```
    fslmaths rh_M1.nii.gz -bin rh_M1_bin.nii.gz
```

```
    fslmaths lh_M1.nii.gz -bin lh_M1_bin.nii.gz
```

```
    fslmaths rh_thal.nii.gz -bin rh_thal_bin.nii.gz
```

```
    fslmaths lh_thal.nii.gz -bin lh_thal_bin.nii.gz
```

```
done
```

3.10 Invert transformation matrix

```
#!/bin/sh
```

```
sub=$(cat /Users/marcusmeng/Documents/Joe\ Lab/Bash_Script/subject_list.txt);
```

```
for i in $sub; do
```

```
    # go to dwi folder
```

```
    cd
```

```
    /Users/marcusmeng/Joe_lab/PD_MARCUS/PD_CohortB_Scan1_preprocessed/DESOUZA_PATIENT1*_${i}/${i}_January
```

```
    # select the diff2struct xfm from WM parcellation file and invert it to struct2diff
```

```
    /usr/local/fsl/bin/convert_xfm -omat struct2diff_fsl.mat -inverse diff2struct_fsl.mat
```

```
    # same for "after" files
```

```
    cd
```

```
    /Users/marcusmeng/Joe_lab/PD_MARCUS/PD_CohortB_Scan2_preprocessed/DESOUZA_PATIENT1*_${i}/${i}_May
```

```
    /usr/local/fsl/bin/convert_xfm -omat struct2diff_fsl.mat -inverse diff2struct_fsl.mat
```

```
done
```

3.11 Register T1 to DWI space

```
#!/bin/sh
```

```
sub=$(cat /Users/marcusmeng/Documents/Joe\ Lab/Bash_Script/subject_list.txt);
```

```
for i in $sub; do
```

```
    # go to dwi folder
```

```
    cd
```

```
    /Users/marcusmeng/Joe_lab/PD_MARCUS/PD_CohortB_Scan1_preprocessed/DESOUZA_PATIENT1*_${i}/${i}_January
```

```
    # select the diff2struct xfm from WM parcellation file and invert it to struct2diff
```

```
    /usr/local/fsl/bin/convert_xfm -omat struct2diff_fsl.mat -inverse diff2struct_fsl.mat
```

```
    # same for "after" files
```

```
    cd
```

```
    /Users/marcusmeng/Joe_lab/PD_MARCUS/PD_CohortB_Scan2_preprocessed/DESOUZA_PATIENT1*_${i}/${i}_May
```

```
    /usr/local/fsl/bin/convert_xfm -omat struct2diff_fsl.mat -inverse diff2struct_fsl.mat
```

```
done
```

3.12 Register binarized ROIs to DWI space

```
#!/bin/sh
```

```
sub=$(cat /Users/marcusmeng/Documents/Joe\ Lab/Bash_Script/subject_list.txt);
```

```
for i in $sub; do
```

```
    # go to dwi folder
```

```
    cd
```

```
    /Users/marcusmeng/Joe_lab/PD_MARCUS/PD_CohortB_Scan1_preprocessed/DESOUZA_PA  
TIENT1*_${i}/${i}_January
```

```
    # using the inverted transformation matrix, and the b0 reference image to transform the  
    binarized ROI into diffusion space
```

```
    /usr/local/fsl/bin/flirt -in lh_V1_bin.nii.gz -applyxfm -init struct2diff_fsl.mat -out  
    lh_V1_bin_diff_space.nii.gz -paddingsize 0.0 -interp trilinear -ref mean_b0_preprocessed.nii.gz
```

```
    /usr/local/fsl/bin/flirt -in rh_V1_bin.nii.gz -applyxfm -init struct2diff_fsl.mat -out  
    rh_V1_bin_diff_space.nii.gz -paddingsize 0.0 -interp trilinear -ref mean_b0_preprocessed.nii.gz
```

```
    /usr/local/fsl/bin/flirt -in lh_M1_bin.nii.gz -applyxfm -init struct2diff_fsl.mat -out  
    lh_M1_bin_diff_space.nii.gz -paddingsize 0.0 -interp trilinear -ref mean_b0_preprocessed.nii.gz
```

```
    /usr/local/fsl/bin/flirt -in rh_M1_bin.nii.gz -applyxfm -init struct2diff_fsl.mat -out  
    rh_M1_bin_diff_space.nii.gz -paddingsize 0.0 -interp trilinear -ref mean_b0_preprocessed.nii.gz
```

```
    /usr/local/fsl/bin/flirt -in lh_thal_bin.nii.gz -applyxfm -init struct2diff_fsl.mat -out  
    lh_thal_bin_diff_space.nii.gz -paddingsize 0.0 -interp trilinear -ref mean_b0_preprocessed.nii.gz
```

```
    /usr/local/fsl/bin/flirt -in rh_thal_bin.nii.gz -applyxfm -init struct2diff_fsl.mat -out  
    rh_thal_bin_diff_space.nii.gz -paddingsize 0.0 -interp trilinear -ref mean_b0_preprocessed.nii.gz
```

```
    cd
```

```
    /Users/marcusmeng/Joe_lab/PD_MARCUS/PD_CohortB_Scan2_preprocessed/DESOUZA_PA  
TIENT1*_${i}/${i}_May
```

```
    /usr/local/fsl/bin/flirt -in lh_V1_bin.nii.gz -applyxfm -init struct2diff_fsl.mat -out  
    lh_V1_bin_diff_space.nii.gz -paddingsize 0.0 -interp trilinear -ref mean_b0_preprocessed.nii.gz
```

```
    /usr/local/fsl/bin/flirt -in rh_V1_bin.nii.gz -applyxfm -init struct2diff_fsl.mat -out  
    rh_V1_bin_diff_space.nii.gz -paddingsize 0.0 -interp trilinear -ref mean_b0_preprocessed.nii.gz
```

```
    /usr/local/fsl/bin/flirt -in lh_M1_bin.nii.gz -applyxfm -init struct2diff_fsl.mat -out  
    lh_M1_bin_diff_space.nii.gz -paddingsize 0.0 -interp trilinear -ref mean_b0_preprocessed.nii.gz
```

```
/usr/local/fsl/bin/flirt -in rh_M1_bin.nii.gz -applyxfm -init struct2diff_fsl.mat -out  
rh_M1_bin_diff_space.nii.gz -paddingsize 0.0 -interp trilinear -ref mean_b0_preprocessed.nii.gz
```

```
/usr/local/fsl/bin/flirt -in lh_thal_bin.nii.gz -applyxfm -init struct2diff_fsl.mat -out  
lh_thal_bin_diff_space.nii.gz -paddingsize 0.0 -interp trilinear -ref mean_b0_preprocessed.nii.gz
```

```
/usr/local/fsl/bin/flirt -in rh_thal_bin.nii.gz -applyxfm -init struct2diff_fsl.mat -out  
rh_thal_bin_diff_space.nii.gz -paddingsize 0.0 -interp trilinear -ref mean_b0_preprocessed.nii.gz  
done
```

3.13 Cleaning up ROIs by thresholding

```
#!/bin/sh
```

```
sub=$(cat /Users/marcusmeng/Documents/Joe\ Lab/Bash_Script/subject_list.txt);
```

```
for i in $sub; do
```

```
    # go to dwi folder
```

```
    cd
```

```
    /Users/marcusmeng/Joe_lab/PD_MARCUS/PD_CohortB_Scan1_preprocessed/DESOUZA_PA  
    TIENT1*_${i}/${i}_January
```

```
    # we are going to use thresholding to exclude the outlier voxels, each lower bound will be  
    different (V1 = 0.37, M1 = 0.42)
```

```
    fslmaths lh_V1_bin_diff_space.nii.gz -thr 0.46 -uthr 1.0 lh_V1_bin_diff_space_cleanup.nii.gz
```

```
    fslmaths rh_V1_bin_diff_space.nii.gz -thr 0.46 -uthr 1.0 rh_V1_bin_diff_space_cleanup.nii.gz
```

```
    fslmaths lh_M1_bin_diff_space.nii.gz -thr 0.53 -uthr 1.0 lh_M1_bin_diff_space_cleanup.nii.gz
```

```
    fslmaths rh_M1_bin_diff_space.nii.gz -thr 0.53 -uthr 1.0 rh_M1_bin_diff_space_cleanup.nii.gz
```

```
    # no need to threshold thal
```

```
    cd
```

```
    /Users/marcusmeng/Joe_lab/PD_MARCUS/PD_CohortB_Scan2_preprocessed/DESOUZA_PA  
    TIENT1*_${i}/${i}_May
```

```
    fslmaths lh_V1_bin_diff_space.nii.gz -thr 0.46 -uthr 1.0 lh_V1_bin_diff_space_cleanup.nii.gz
```

```
    fslmaths rh_V1_bin_diff_space.nii.gz -thr 0.46 -uthr 1.0 rh_V1_bin_diff_space_cleanup.nii.gz
```

```
    fslmaths lh_M1_bin_diff_space.nii.gz -thr 0.53 -uthr 1.0 lh_M1_bin_diff_space_cleanup.nii.gz
```

```
    fslmaths rh_M1_bin_diff_space.nii.gz -thr 0.53 -uthr 1.0 rh_M1_bin_diff_space_cleanup.nii.gz
```

```
done
```

3.14 Merging the GM and WM ROIs

```
#!/bin/sh
```

```
sub=$(cat /Users/marcusmeng/Documents/Joe\ Lab/Bash_Script/subject_list.txt);
```

```
for i in $sub; do
```

```
    # go to dwi folder
```

```
    cd
```

```
    /Users/marcusmeng/Joe_lab/PD_MARCUS/PD_CohortB_Scan1_preprocessed/DESOUZA_PA  
    TIENT1*_${i}/${i}_January
```

```
    # Due to the selectiveness of the M1 and V1 ROI, we need to combine the GM and WM ROI  
    and use -ends only option on the V1 ROI to visualize the streamlines
```

```
    # Select the M1 ROI from gm parcellation
```

```
    fslmaths aparc+aseg_xfm.nii.gz -thr 1024 -uthr 1024 lh_M1_GM.nii.gz
```

```
    fslmaths aparc+aseg_xfm.nii.gz -thr 2024 -uthr 2024 rh_M1_GM.nii.gz
```

```
    # Select the V1 ROI from gm parcellation
```

```
    fslmaths aparc+aseg_xfm.nii.gz -thr 1021 -uthr 1021 lh_V1_GM.nii.gz
```

```
    fslmaths aparc+aseg_xfm.nii.gz -thr 2021 -uthr 2021 rh_V1_GM.nii.gz
```

```
    #binarize new GM ROIs
```

```
    fslmaths rh_V1_GM.nii.gz -bin rh_V1_GM_bin.nii.gz
```

```
    fslmaths lh_V1_GM.nii.gz -bin lh_V1_GM_bin.nii.gz
```

```
    fslmaths rh_M1_GM.nii.gz -bin rh_M1_GM_bin.nii.gz
```

```
    fslmaths lh_M1_GM.nii.gz -bin lh_M1_GM_bin.nii.gz
```

```
    # register new M1 and V1 with DWI space
```

```
    /usr/local/fsl/bin/flirt -in rh_V1_GM_bin.nii.gz -applyxfm -init struct2diff_fsl.mat -out  
    rh_V1_GM_bin_diff_space.nii.gz -paddingsize 0.0 -interp trilinear -ref  
    mean_b0_preprocessed.nii.gz
```

```
    /usr/local/fsl/bin/flirt -in lh_V1_GM_bin.nii.gz -applyxfm -init struct2diff_fsl.mat -out  
    lh_V1_GM_bin_diff_space.nii.gz -paddingsize 0.0 -interp trilinear -ref  
    mean_b0_preprocessed.nii.gz
```

```
    /usr/local/fsl/bin/flirt -in rh_M1_GM_bin.nii.gz -applyxfm -init struct2diff_fsl.mat -out  
    rh_M1_GM_bin_diff_space.nii.gz -paddingsize 0.0 -interp trilinear -ref  
    mean_b0_preprocessed.nii.gz
```

```

/usr/local/fsl/bin/flirt -in lh_M1_GM_bin.nii.gz -applyxfm -init struct2diff_fsl.mat -out
lh_M1_GM_bin_diff_space.nii.gz -paddingsize 0.0 -interp trilinear -ref
mean_b0_preprocessed.nii.gz
# merge the old V1 and M1 with new M1 and V1 after thresholding
fslmaths lh_V1_bin_diff_space_cleanup.nii.gz -add lh_V1_GM_bin_diff_space.nii.gz
lh_V1_merge.nii.gz

fslmaths rh_V1_bin_diff_space_cleanup.nii.gz -add rh_V1_GM_bin_diff_space.nii.gz
rh_V1_merge.nii.gz

fslmaths lh_M1_bin_diff_space_cleanup.nii.gz -add lh_M1_GM_bin_diff_space.nii.gz
lh_M1_merge.nii.gz

fslmaths rh_M1_bin_diff_space_cleanup.nii.gz -add rh_M1_GM_bin_diff_space.nii.gz
rh_M1_merge.nii.gz
# same for "after" files
cd
/Users/marcusmeng/Joe_lab/PD_MARCUS/PD_CohortB_Scan2_preprocessed/DESOUZA_PA
TIENT1*_${i}/${i}_May

# Select the M1 ROI from gm parcellation
fslmaths aparc+aseg_xfm.nii.gz -thr 1024 -uthr 1024 lh_M1_GM.nii.gz

fslmaths aparc+aseg_xfm.nii.gz -thr 2024 -uthr 2024 rh_M1_GM.nii.gz
# Select the V1 ROI from gm parcellation
fslmaths aparc+aseg_xfm.nii.gz -thr 1021 -uthr 1021 lh_V1_GM.nii.gz

fslmaths aparc+aseg_xfm.nii.gz -thr 2021 -uthr 2021 rh_V1_GM.nii.gz
#binarize new GM ROIs
fslmaths rh_V1_GM.nii.gz -bin rh_V1_GM_bin.nii.gz

fslmaths lh_V1_GM.nii.gz -bin lh_V1_GM_bin.nii.gz

fslmaths rh_M1_GM.nii.gz -bin rh_M1_GM_bin.nii.gz

fslmaths lh_M1_GM.nii.gz -bin lh_M1_GM_bin.nii.gz
# register new M1 and V1 with DWI space
/usr/local/fsl/bin/flirt -in rh_V1_GM_bin.nii.gz -applyxfm -init struct2diff_fsl.mat -out
rh_V1_GM_bin_diff_space.nii.gz -paddingsize 0.0 -interp trilinear -ref
mean_b0_preprocessed.nii.gz

/usr/local/fsl/bin/flirt -in lh_V1_GM_bin.nii.gz -applyxfm -init struct2diff_fsl.mat -out
lh_V1_GM_bin_diff_space.nii.gz -paddingsize 0.0 -interp trilinear -ref
mean_b0_preprocessed.nii.gz

```

```
/usr/local/fsl/bin/flirt -in rh_M1_GM_bin.nii.gz -applyxfm -init struct2diff_fsl.mat -out  
rh_M1_GM_bin_diff_space.nii.gz -paddingsize 0.0 -interp trilinear -ref  
mean_b0_preprocessed.nii.gz
```

```
/usr/local/fsl/bin/flirt -in lh_M1_GM_bin.nii.gz -applyxfm -init struct2diff_fsl.mat -out  
lh_M1_GM_bin_diff_space.nii.gz -paddingsize 0.0 -interp trilinear -ref  
mean_b0_preprocessed.nii.gz
```

```
# merge the old V1 and M1 with new M1 and V1 after thresholding
```

```
fslmaths lh_V1_bin_diff_space_cleanup.nii.gz -add lh_V1_GM_bin_diff_space.nii.gz  
lh_V1_merge.nii.gz
```

```
fslmaths rh_V1_bin_diff_space_cleanup.nii.gz -add rh_V1_GM_bin_diff_space.nii.gz  
rh_V1_merge.nii.gz
```

```
fslmaths lh_M1_bin_diff_space_cleanup.nii.gz -add lh_M1_GM_bin_diff_space.nii.gz  
lh_M1_merge.nii.gz
```

```
fslmaths rh_M1_bin_diff_space_cleanup.nii.gz -add rh_M1_GM_bin_diff_space.nii.gz  
rh_M1_merge.nii.gz  
done
```

3.15 ROI data type conversion

```
#!/bin/sh
```

```
sub=$(cat /Users/marcusmeng/Documents/Joe\ Lab/Bash_Script/subject_list.txt);
```

```
for i in $sub; do
```

```
    # go to dwi folder
```

```
    cd
```

```
    /Users/marcusmeng/Joe_lab/PD_MARCUS/PD_CohortB_Scan1_preprocessed/DESOUZA_PA
```

```
    TIENT1*_${i}/${i}_January
```

```
    # ROI data type conversion
```

```
    mrconvert lh_V1_merge.nii.gz lh_V1_bin_diff_space_cleanup.mif -force
```

```
    mrconvert rh_V1_merge.nii.gz rh_V1_bin_diff_space_cleanup.mif -force
```

```
    mrconvert lh_M1_merge.nii.gz lh_M1_bin_diff_space_cleanup.mif -force
```

```
    mrconvert rh_M1_merge.nii.gz rh_M1_bin_diff_space_cleanup.mif -force
```

```
    mrconvert lh_thal_bin_diff_space.nii.gz lh_thal_bin_diff_space.mif -force
```

```
    mrconvert rh_thal_bin_diff_space.nii.gz rh_thal_bin_diff_space.mif -force
```

```
    cd
```

```
    /Users/marcusmeng/Joe_lab/PD_MARCUS/PD_CohortB_Scan2_preprocessed/DESOUZA_PA
```

```
    TIENT1*_${i}/${i}_May
```

```
    mrconvert lh_V1_merge.nii.gz lh_V1_bin_diff_space_cleanup.mif -force
```

```
    mrconvert rh_V1_merge.nii.gz rh_V1_bin_diff_space_cleanup.mif -force
```

```
    mrconvert lh_M1_merge.nii.gz lh_M1_bin_diff_space_cleanup.mif -force
```

```
    mrconvert rh_M1_merge.nii.gz rh_M1_bin_diff_space_cleanup.mif -force
```

```
    mrconvert lh_thal_bin_diff_space.nii.gz lh_thal_bin_diff_space.mif -force
```

```
    mrconvert rh_thal_bin_diff_space.nii.gz rh_thal_bin_diff_space.mif -force
```

```
done
```

3.16 Tract selection

```
#!/bin/sh
```

```
sub=$(cat /Users/marcusmeng/Documents/Joe\ Lab/Bash_Script/subject_list.txt);
```

```
for i in $sub; do
```

```
    # go to dwi folder
```

```
    cd
```

```
    /Users/marcusmeng/Joe_lab/PD_MARCUS/PD_CohortB_Scan1_preprocessed/DESOUZA_PA  
    TIENT1*_${i}/${i}_January
```

```
    # track edit using clean ROIs and thalamus, we first select the tracks originating in the Thal ROI  
    tckedit sift_1mio.tck -include lh_thal_bin_diff_space.mif -ends_only lh_thal_step1.tck
```

```
    tckedit sift_1mio.tck -include rh_thal_bin_diff_space.mif -ends_only rh_thal_step1.tck
```

```
    # we then select the tracts passing through cortex from all the tracks originated in the Thalamus  
    tckedit lh_thal_step1.tck -include lh_V1_bin_diff_space_cleanup.mif lh_V1_thal.tck
```

```
    tckedit lh_thal_step1.tck -include lh_M1_bin_diff_space_cleanup.mif lh_M1_thal.tck
```

```
    tckedit rh_thal_step1.tck -include rh_V1_bin_diff_space_cleanup.mif rh_V1_thal.tck
```

```
    tckedit rh_thal_step1.tck -include rh_M1_bin_diff_space_cleanup.mif rh_M1_thal.tck -force
```

```
    cd
```

```
    /Users/marcusmeng/Joe_lab/PD_MARCUS/PD_CohortB_Scan2_preprocessed/DESOUZA_PA  
    TIENT1*_${i}/${i}_May
```

```
    tckedit sift_1mio.tck -include lh_thal_bin_diff_space.mif -ends_only lh_thal_step1.tck
```

```
    tckedit sift_1mio.tck -include rh_thal_bin_diff_space.mif -ends_only rh_thal_step1.tck
```

```
    # we then select the tracts passing through cortex from all the tracks originated in the Thalamus  
    tckedit lh_thal_step1.tck -include lh_V1_bin_diff_space_cleanup.mif lh_V1_thal.tck
```

```
    tckedit lh_thal_step1.tck -include lh_M1_bin_diff_space_cleanup.mif lh_M1_thal.tck
```

```
    tckedit rh_thal_step1.tck -include rh_V1_bin_diff_space_cleanup.mif rh_V1_thal.tck
```

```
    tckedit rh_thal_step1.tck -include rh_M1_bin_diff_space_cleanup.mif rh_M1_thal.tck
```

```
done
```

3.17 Getting the wholebrain metric

```
#!/bin/sh
```

```
sub=$(cat /Users/marcusmeng/Documents/Joe\ Lab/Bash_Script/subject_list.txt);
```

```
for i in $sub; do
```

```
    # go to dwi folder
```

```
    cd
```

```
    /Users/marcusmeng/Joe_lab/PD_MARCUS/PD_CohortB_Scan1_preprocessed/DESOUZA_PA  
TIENT1*_${i}/${i}_January
```

```
    # convert DWI 2 Tensor
```

```
    dwi2tensor dwi_den_unr_preproc_unbiased.mif tensor.mif
```

```
    # convert Tensor 2 metric
```

```
    # getting colour FA map
```

```
    tensor2metric tensor.mif -vec dec.nii | mrcalc -abs dec.nii
```

```
    # getting FA
```

```
    tensor2metric tensor.mif -fa fa.mif
```

```
    # getting MD
```

```
    tensor2metric tensor.mif -adc md.mif
```

```
    # getting AD
```

```
    tensor2metric tensor.mif -ad ad.mif
```

```
    # getting RD
```

```
    tensor2metric tensor.mif -rd rd.mif
```

```
    cd
```

```
    /Users/marcusmeng/Joe_lab/PD_MARCUS/PD_CohortB_Scan2_preprocessed/DESOUZA_PA  
TIENT1*_${i}/${i}_May
```

```
    dwi2tensor dwi_den_unr_preproc_unbiased.mif tensor.mif
```

```
    tensor2metric tensor.mif -vec dec.nii | mrcalc -abs dec.nii
```

```
    tensor2metric tensor.mif -fa fa.mif
```

```
    tensor2metric tensor.mif -adc md.mif
```

```
    tensor2metric tensor.mif -ad ad.mif
```

```
    tensor2metric tensor.mif -rd rd.mif
```

```
done
```

3.18 Getting the tract-specific metrics

```
#!/bin/sh
```

```
sub=$(cat /Users/marcusmeng/Documents/Joe\ Lab/Bash_Script/subject_list.txt);
```

```
for i in $sub; do
```

```
    # go to dwi folder
```

```
    cd
```

```
    /Users/marcusmeng/Joe_lab/PD_MARCUS/PD_CohortB_Scan1_preprocessed/DESOUZA_PA  
    TIENT1*_${i}/${i}_January
```

```
    # use tcksample to extract FA of LH M1 test track
```

```
    tcksample lh_M1_thal.tck fa.mif lh_M1_fa.ascii
```

```
    # use tcksample to extract AD of LH M1 test track
```

```
    tcksample lh_M1_thal.tck ad.mif lh_M1_ad.ascii
```

```
    # use tcksample to extract RD of LH M1 test track
```

```
    tcksample lh_M1_thal.tck rd.mif lh_M1_rd.ascii
```

```
    # use tcksample to extract MD of LH M1 test track
```

```
    tcksample lh_M1_thal.tck md.mif lh_M1_md.ascii
```

```
    # use tcksample to extract FA of RH M1 test track
```

```
    tcksample rh_M1_thal.tck fa.mif rh_M1_fa.ascii -force
```

```
    # use tcksample to extract AD of RH M1 test track
```

```
    tcksample rh_M1_thal.tck ad.mif rh_M1_ad.ascii -force
```

```
    # use tcksample to extract RD of RH M1 test track
```

```
    tcksample rh_M1_thal.tck rd.mif rh_M1_rd.ascii -force
```

```
    # use tcksample to extract MD of RH M1 test track
```

```
    tcksample rh_M1_thal.tck md.mif rh_M1_md.ascii -force
```

```
    # use tcksample to extract FA of LH V1 test track
```

```
    tcksample lh_V1_thal.tck fa.mif lh_V1_fa.ascii
```

```
    # use tcksample to extract AD of LH V1 test track
```

```
    tcksample lh_V1_thal.tck ad.mif lh_V1_ad.ascii
```

```
    # use tcksample to extract RD of LH V1 test track
```

```
    tcksample lh_V1_thal.tck rd.mif lh_V1_rd.ascii
```

```
    # use tcksample to extract MD of LH V1 test track
```

```
    tcksample lh_V1_thal.tck md.mif lh_V1_md.ascii
```

```
    # use tcksample to extract FA of RH V1 test track
```

```
    tcksample rh_V1_thal.tck fa.mif rh_V1_fa.ascii
```

```
    # use tcksample to extract AD of RH V1 test track
```

```
    tcksample rh_V1_thal.tck ad.mif rh_V1_ad.ascii
```

```
    # use tcksample to extract RD of RH V1 test track
```

```
    tcksample rh_V1_thal.tck rd.mif rh_V1_rd.ascii
```

```
    # use tcksample to extract MD of RH V1 test track
```

```
tcksample rh_V1_thal.tck md.mif rh_V1_md.ascii
```

```
# use tcksample to extract FA of wholebrain  
tcksample sift_1mio.tck fa.mif wholebrain_fa.ascii  
# use tcksample to extract AD of wholebrain  
tcksample sift_1mio.tck ad.mif wholebrain_ad.ascii  
# use tcksample to extract RD of wholebrain  
tcksample sift_1mio.tck rd.mif wholebrain_rd.ascii  
# use tcksample to extract MD of wholebrain  
tcksample sift_1mio.tck md.mif wholebrain_md.ascii
```

```
cd
```

```
/Users/marcusmeng/Joe_lab/PD_MARCUS/PD_CohortB_Scan2_preprocessed/DESOUZA_PA  
TIENT1*_${i}/${i}_May
```

```
# use tcksample to extract FA of LH M1 test track  
tcksample lh_M1_thal.tck fa.mif lh_M1_fa.ascii  
# use tcksample to extract AD of LH M1 test track  
tcksample lh_M1_thal.tck ad.mif lh_M1_ad.ascii  
# use tcksample to extract RD of LH M1 test track  
tcksample lh_M1_thal.tck rd.mif lh_M1_rd.ascii  
# use tcksample to extract MD of LH M1 test track  
tcksample lh_M1_thal.tck md.mif lh_M1_md.ascii
```

```
# use tcksample to extract FA of RH M1 test track  
tcksample rh_M1_thal.tck fa.mif rh_M1_fa.ascii  
# use tcksample to extract AD of RH M1 test track  
tcksample rh_M1_thal.tck ad.mif rh_M1_ad.ascii  
# use tcksample to extract RD of RH M1 test track  
tcksample rh_M1_thal.tck rd.mif rh_M1_rd.ascii  
# use tcksample to extract MD of RH M1 test track  
tcksample rh_M1_thal.tck md.mif rh_M1_md.ascii
```

```
# use tcksample to extract FA of LH V1 test track  
tcksample lh_V1_thal.tck fa.mif lh_V1_fa.ascii  
# use tcksample to extract AD of LH V1 test track  
tcksample lh_V1_thal.tck ad.mif lh_V1_ad.ascii  
# use tcksample to extract RD of LH V1 test track  
tcksample lh_V1_thal.tck rd.mif lh_V1_rd.ascii  
# use tcksample to extract MD of LH V1 test track  
tcksample lh_V1_thal.tck md.mif lh_V1_md.ascii
```

```
# use tcksample to extract FA of RH V1 test track  
tcksample rh_V1_thal.tck fa.mif rh_V1_fa.ascii
```

```
# use tcksample to extract AD of RH V1 test track
tcksample rh_V1_thal.tck ad.mif rh_V1_ad.ascii
# use tcksample to extract RD of RH V1 test track
tcksample rh_V1_thal.tck rd.mif rh_V1_rd.ascii
# use tcksample to extract MD of RH V1 test track
tcksample rh_V1_thal.tck md.mif rh_V1_md.ascii

# use tcksample to extract FA of wholebrain
tcksample sift_1mio.tck fa.mif wholebrain_fa.ascii
# use tcksample to extract AD of wholebrain
tcksample sift_1mio.tck ad.mif wholebrain_ad.ascii
# use tcksample to extract RD of wholebrain
tcksample sift_1mio.tck rd.mif wholebrain_rd.ascii
# use tcksample to extract MD of wholebrain
tcksample sift_1mio.tck md.mif wholebrain_md.ascii

done
```

3.19 Subject list for 3.1 to 3.18

HC

KL

DD

MT

3.20 Transforming raw data into data frames

```
library(dplyr)
library(readr)
library(tidyr)
library(stringr)
library(vroom)

# Set the directory where your CSV files are stored
data_dir <- "/Users/marcusmeng/Documents/Joe lab/Joe_lab_stats/Raw_Data" # Update this
with the actual path

# Get a list of all CSV files in the directory
file_list <- list.files(data_dir, pattern = "\\..csv$", full.names = TRUE)

# Initialize an empty dataframe to store results
results <- data.frame()
wholebrain_results <- data.frame()

# Loop through each file and process the wholebrain data
for (file in file_list) {
  # Extract components from the filename (with optional hemisphere and region)
  file_info <- str_match(basename(file), "^((\\w+)_(\\w+)_wholebrain_(\\w+))\\.csv$")

  if (!is.na(file_info[1])) {
    subject_id <- file_info[2] # DD, MT, HC, KL
    month <- file_info[3]      # jan, may
    type <- file_info[4]       # FA, RD, MD, AD

    # Read the CSV file, skipping the first row
    data <- read_csv(file, skip = 1)

    # Convert data to numeric and clean up NAs and zeros
    numeric_data <- as.numeric(as.matrix(data))
    numeric_data_tidy <- numeric_data[!is.na(numeric_data) & numeric_data != 0]

    # Calculate the mean of the remaining numeric data
    mean_value <- mean(numeric_data_tidy, na.rm = TRUE)

    # Append the result to the results dataframe
    wholebrain_results <- bind_rows(wholebrain_results, data.frame(
      Subject = subject_id,
      Month = month,
      # Hemisphere = "wholebrain",
      Type = type,
```

```

    Mean = mean_value
  ))
}
}

# Assign a value of "wholebrain"
wholebrain_results$Hemisphere <- "wholebrain"

# Reshape the data to wide format with subjects as rows and types as columns
wholebrain_final_results <- wholebrain_results %>%
  unite("Condition", Month, Hemisphere, Type) %>%
  pivot_wider(names_from = Condition, values_from = Mean)

# Loop through each file and process the data
for (file in file_list) {
  # Extract components from the filename (with optional hemisphere and region)
  file_info <- str_match(basename(file), "^(\\w+)_(\\w+)_(\\w+)_(\\w+)_(\\w+)\\.csv$")

  if (!is.na(file_info[1])) {
    subject_id <- file_info[2] # DD, MT, HC, KL
    month <- file_info[3] # jan, may
    hemisphere <- file_info[4] # lh, rh (optional)
    region <- file_info[5] # M1, V1, wholebrain (optional)
    type <- file_info[6] # FA, RD, MD, AD

    # Read the CSV file, skipping the first row
    data <- read_csv(file, skip = 1)

    # Convert data to numeric and clean up NAs and zeros
    numeric_data <- as.numeric(as.matrix(data))
    numeric_data_tidy <- numeric_data[!is.na(numeric_data) & numeric_data != 0]

    # Calculate the mean of the remaining numeric data
    mean_value <- mean(numeric_data_tidy, na.rm = TRUE)

    # Append the result to the results dataframe
    results <- bind_rows(results, data.frame(
      Subject = subject_id,
      Month = month,
      Hemisphere = ifelse(is.na(hemisphere), "NA", hemisphere),
      Region = ifelse(is.na(region), "NA", region),
      Type = type,
      Mean = mean_value
    ))
  }
}

```

```
}  
}
```

```
# Reshape the data to wide format with subjects as rows and types as columns
```

```
final_results <- results %>%
```

```
  unite("Condition", Month, Hemisphere, Region, Type) %>%
```

```
  pivot_wider(names_from = Condition, values_from = Mean)
```

```
# Set subject IDs as row names
```

```
rownames(final_results) <- final_results$Subject
```

```
#final_results <- final_results %>% select(-Subject)
```

```
# View the final results
```

```
print(final_results)
```

```
# Append tract results with wholebrain results
```

```
full_results <- full_join(wholebrain_final_results, final_results, by = "Subject")
```

```
# Save the final dataframe
```

```
write.csv(full_results, file = "/Users/marcusmeng/Documents/Joe
```

```
lab/Joe_lab_stats/R_processing/mar13_wm_metric_real.csv")
```

3.21 T-tests and graphs for white matter data

title: "White matter data compairson and linking with behavioral data"

author: "Marcus"

date: "2025-03-13"

output: html_document

```
```{r, include = F}
```

```
library(tidyverse)
```

```
library(ggplot2)
```

```
```
```

```
```{r, include = F}
```

```
#import dataset
```

```
data <- read.csv("/Users/marcusmeng/Documents/Joe
lab/Joe_lab_stats/R_processing/mar13_wm_metric.csv")
```

```
#get rid of MT
```

```
data <- data
```

```
```
```

```
M1 lh count
```

```
```{r}
```

```
paired t-test
```

```
t.test(data$jan_lh_M1_tract_count, data$may_lh_M1_tract_count, paired = TRUE)
```

```
```
```

```
```{r}
```

```
Reshape the data to long format for ggplot
```

```
data_long_lh_M1_count <- data %>%
```

```
 pivot_longer(
```

```
 cols = c(jan_lh_M1_tract_count, may_lh_M1_tract_count),
```

```
 names_to = "Time",
```

```
 values_to = "Value"
```

```
) %>%
```

```
 mutate(Time = ifelse(Time == "jan_lh_M1_tract_count", "Jan", "May"))
```

```
Plot using ggplot
```

```
ggplot(data_long_lh_M1_count, aes(x = Time, y = Value, group = Subject, color = Subject)) +
```

```
 geom_line() +
```

```
 geom_point(size = 3) +
```

```
 labs(
```

```
 title = "Change Between Jan and May for lh M1 tract count",
```

```

 x = "Date",
 y = "Value"
) +
 theme_minimal()
 ...

M1 rh count
```{r}
# paired t-test
t.test(data$jan_rh_M1_tract_count, data$may_rh_M1_tract_count, paired = TRUE)
...

```{r}
Reshape the data to long format for ggplot
data_long_rh_M1_count <- data %>%
 pivot_longer(
 cols = c(jan_rh_M1_tract_count, may_rh_M1_tract_count),
 names_to = "Time",
 values_to = "Value"
) %>%
 mutate(Time = ifelse(Time == "jan_rh_M1_tract_count", "Jan", "May"))

Plot using ggplot
ggplot(data_long_rh_M1_count, aes(x = Time, y = Value, group = Subject, color = Subject)) +
 geom_line() +
 geom_point(size = 3) +
 labs(
 title = "Change Between Jan and May for rh M1 tract count",
 x = "Date",
 y = "Value"
) +
 theme_minimal()
...

V1 lh count
```{r}
# paired t-test
t.test(data$jan_lh_V1_tract_count, data$may_lh_V1_tract_count, paired = TRUE)
...

```{r}
Reshape the data to long format for ggplot
data_long_lh_V1_count <- data %>%
 pivot_longer(
 cols = c(jan_lh_V1_tract_count, may_lh_V1_tract_count),
 names_to = "Time",

```

```

 values_to = "Value"
) %>%
 mutate(Time = ifelse(Time == "jan_lh_V1_tract_count", "Jan", "May"))

Plot using ggplot
ggplot(data_long_lh_V1_count, aes(x = Time, y = Value, group = Subject, color = Subject)) +
 geom_line() +
 geom_point(size = 3) +
 labs(
 title = "Change Between Jan and May for lh V1 tract count",
 x = "Date",
 y = "Value"
) +
 theme_minimal()
...

V1 rh count
```{r}
# paired t-test
t.test(data$jan_rh_V1_tract_count, data$may_rh_V1_tract_count, paired = TRUE)
...

```{r}
Reshape the data to long format for ggplot
data_long_rh_V1_count <- data %>%
 pivot_longer(
 cols = c(jan_rh_V1_tract_count, may_rh_V1_tract_count),
 names_to = "Time",
 values_to = "Value"
) %>%
 mutate(Time = ifelse(Time == "jan_rh_V1_tract_count", "Jan", "May"))

Plot using ggplot
ggplot(data_long_rh_V1_count, aes(x = Time, y = Value, group = Subject, color = Subject)) +
 geom_line() +
 geom_point(size = 3) +
 labs(
 title = "Change Between Jan and May for rh V1 tract count",
 x = "Date",
 y = "Value"
) +
 theme_minimal()
...

Wholebrain AD
```{r}

```

```

# paired t-test
t.test(data$jan_wholebrain_ad, data$may_wholebrain_ad, paired = TRUE)
...

```{r}
Reshape the data to long format for ggplot
data_long_wbAD <- data %>%
 pivot_longer(
 cols = c(jan_wholebrain_ad, may_wholebrain_ad),
 names_to = "Time",
 values_to = "Value"
) %>%
 mutate(Time = ifelse(Time == "jan_wholebrain_ad", "Jan", "May"))

Plot using ggplot
ggplot(data_long_wbAD, aes(x = Time, y = Value, group = Subject, color = Subject)) +
 geom_line() +
 geom_point(size = 3) +
 labs(
 title = "Change Between Jan and May for wholebrain AD",
 x = "Date",
 y = "Value"
) +
 theme_minimal()
...

Wholebrain FA
```{r}
# paired t-test
t.test(data$jan_wholebrain_fa, data$may_wholebrain_fa, paired = TRUE)
...

Wholebrain FA
```{r}
Reshape the data to long format for ggplot
data_long_wbFA <- data %>%
 pivot_longer(
 cols = c(jan_wholebrain_fa, may_wholebrain_fa),
 names_to = "Time",
 values_to = "Value"
) %>%
 mutate(Time = ifelse(Time == "jan_wholebrain_fa", "Jan", "May"))

Plot using ggplot
ggplot(data_long_wbFA, aes(x = Time, y = Value, group = Subject, color = Subject)) +
 geom_line() +

```

```

geom_point(size = 3) +
labs(
 title = "Change Between Jan and May for wholebrain FA",
 x = "Date",
 y = "Value"
) +
theme_minimal()
...

Wholebrain RD
```{r}
# paired t-test
t.test(data$jan_wholebrain_rd, data$may_wholebrain_rd, paired = TRUE)
...

Wholebrain RD
```{r}
Reshape the data to long format for ggplot
data_long_wbRD <- data %>%
 pivot_longer(
 cols = c(jan_wholebrain_rd, may_wholebrain_rd),
 names_to = "Time",
 values_to = "Value"
) %>%
 mutate(Time = ifelse(Time == "jan_wholebrain_rd", "Jan", "May"))

Plot using ggplot
ggplot(data_long_wbRD, aes(x = Time, y = Value, group = Subject, color = Subject)) +
 geom_line() +
 geom_point(size = 3) +
 labs(
 title = "Change Between Jan and May for wholebrain RD",
 x = "Date",
 y = "Value"
) +
 theme_minimal()
...

Wholebrain MD
```{r}
# paired t-test
t.test(data$jan_wholebrain_md, data$may_wholebrain_md, paired = TRUE)
...

Wholebrain MD
```{r}
Reshape the data to long format for ggplot
data_long_wbMD <- data %>%

```

```

pivot_longer(
 cols = c(jan_wholebrain_md, may_wholebrain_md),
 names_to = "Time",
 values_to = "Value"
) %>%
mutate(Time = ifelse(Time == "jan_wholebrain_md", "Jan", "May"))

Plot using ggplot
ggplot(data_long_wbMD, aes(x = Time, y = Value, group = Subject, color = Subject)) +
 geom_line() +
 geom_point(size = 3) +
 labs(
 title = "Change Between Jan and May for wholebrain MD",
 x = "Date",
 y = "Value"
) +
 theme_minimal()
...

M1 lh AD
```{r}
# paired t-test
t.test(data$jan_lh_M1_ad, data$may_lh_M1_ad, paired = TRUE)
...

M1 lh AD
```{r}
Reshape the data to long format for ggplot
data_long_lh_AD <- data %>%
 pivot_longer(
 cols = c(jan_lh_M1_ad, may_lh_M1_ad),
 names_to = "Time",
 values_to = "Value"
) %>%
 mutate(Time = ifelse(Time == "jan_lh_M1_ad", "Jan", "May"))

Plot using ggplot
ggplot(data_long_lh_AD, aes(x = Time, y = Value, group = Subject, color = Subject)) +
 geom_line() +
 geom_point(size = 3) +
 labs(
 title = "Change Between Jan and May for lh M1 AD",
 x = "Date",
 y = "Value"
) +
 theme_minimal()

```

```

...

M1 lh FA
```{r}
# paired t-test
t.test(data$jan_lh_M1_fa, data$may_lh_M1_fa, paired = TRUE)
...

M1 lh FA
```{r}
Reshape the data to long format for ggplot
data_long_lh_FA <- data %>%
 pivot_longer(
 cols = c(jan_lh_M1_fa, may_lh_M1_fa),
 names_to = "Time",
 values_to = "Value"
) %>%
 mutate(Time = ifelse(Time == "jan_lh_M1_fa", "Jan", "May"))

Plot using ggplot
ggplot(data_long_lh_FA, aes(x = Time, y = Value, group = Subject, color = Subject)) +
 geom_line() +
 geom_point(size = 3) +
 labs(
 title = "Change Between Jan and May for lh M1 FA",
 x = "Date",
 y = "Value"
) +
 theme_minimal()
...

M1 lh RD
```{r}
# paired t-test
t.test(data$jan_lh_M1_rd, data$may_lh_M1_rd, paired = TRUE)
...

M1 lh RD
```{r}
Reshape the data to long format for ggplot
data_long_lh_RD <- data %>%
 pivot_longer(
 cols = c(jan_lh_M1_rd, may_lh_M1_rd),
 names_to = "Time",
 values_to = "Value"
) %>%
 mutate(Time = ifelse(Time == "jan_lh_M1_rd", "Jan", "May"))

```

```

Plot using ggplot
ggplot(data_long_lh_RD, aes(x = Time, y = Value, group = Subject, color = Subject)) +
 geom_line() +
 geom_point(size = 3) +
 labs(
 title = "Change Between Jan and May for lh M1 RD",
 x = "Date",
 y = "Value"
) +
 theme_minimal()
...

M1 lh MD
``{r}
paired t-test
t.test(data$jan_lh_M1_md, data$may_lh_M1_md, paired = TRUE)
...

M1 lh MD
``{r}
Reshape the data to long format for ggplot
data_long_lh_MD <- data %>%
 pivot_longer(
 cols = c(jan_lh_M1_md, may_lh_M1_md),
 names_to = "Time",
 values_to = "Value"
) %>%
 mutate(Time = ifelse(Time == "jan_lh_M1_md", "Jan", "May"))

Plot using ggplot
ggplot(data_long_lh_MD, aes(x = Time, y = Value, group = Subject, color = Subject)) +
 geom_line() +
 geom_point(size = 3) +
 labs(
 title = "Change Between Jan and May for lh M1 MD",
 x = "Date",
 y = "Value"
) +
 theme_minimal()
...

M1 rh AD
``{r}
paired t-test
t.test(data$jan_rh_M1_ad, data$may_rh_M1_ad, paired = TRUE)
...

M1 rh AD graph

```

```

```{r}
# Reshape the data to long format for ggplot
data_long_rh_AD <- data %>%
  pivot_longer(
    cols = c(jan_rh_M1_ad, may_rh_M1_ad),
    names_to = "Time",
    values_to = "Value"
  ) %>%
  mutate(Time = ifelse(Time == "jan_rh_M1_ad", "Jan", "May"))

# Plot using ggplot
ggplot(data_long_rh_AD, aes(x = Time, y = Value, group = Subject, color = Subject)) +
  geom_line() +
  geom_point(size = 3) +
  labs(
    title = "Change Between Jan and May for rh_M1_ad",
    x = "Date",
    y = "Value"
  ) +
  theme_minimal()
```

```

M1 rh FA

```

```{r}
# paired t-test
t.test(data$jan_rh_M1_fa, data$may_rh_M1_fa, paired = TRUE)
```

```

Plot for M1 rh FA

```

```{r}
# Reshape the data to long format for ggplot
data_long_rh_FA <- data %>%
  pivot_longer(
    cols = c(jan_rh_M1_fa, may_rh_M1_fa),
    names_to = "Time",
    values_to = "Value"
  ) %>%
  mutate(Time = ifelse(Time == "jan_rh_M1_fa", "Jan", "May"))

# Plot using ggplot
ggplot(data_long_rh_FA, aes(x = Time, y = Value, group = Subject, color = Subject)) +
  geom_line() +
  geom_point(size = 3) +
  labs(
    title = "Change Between Jan and May for rh_M1_fa",

```

```

    x = "Date",
    y = "Value"
  ) +
  theme_minimal()
...

M1 rh RD
```{r}
paired t-test
t.test(data$jan_rh_M1_rd, data$may_rh_M1_rd, paired = TRUE)
...

M1 rh RD graph
```{r}
# Reshape the data to long format for ggplot
data_long_rh_RD <- data %>%
  pivot_longer(
    cols = c(jan_rh_M1_rd, may_rh_M1_rd),
    names_to = "Time",
    values_to = "Value"
  ) %>%
  mutate(Time = ifelse(Time == "jan_rh_M1_rd", "Jan", "May"))

# Plot using ggplot
ggplot(data_long_rh_RD, aes(x = Time, y = Value, group = Subject, color = Subject)) +
  geom_line() +
  geom_point(size = 3) +
  labs(
    title = "Change Between Jan and May for rh_M1_rd",
    x = "Date",
    y = "Value"
  ) +
  theme_minimal()
...

M1 rh MD
```{r}
paired t-test
t.test(data$jan_rh_M1_md, data$may_rh_M1_md, paired = TRUE)
...

Plot for M1 th MD
```{r}
# Reshape the data to long format for ggplot
data_long_rh_MD <- data %>%
  pivot_longer(
    cols = c(jan_rh_M1_md, may_rh_M1_md),
    names_to = "Time",

```

```

    values_to = "Value"
  ) %>%
  mutate(Time = ifelse(Time == "jan_rh_M1_md", "Jan", "May"))

# Plot using ggplot
ggplot(data_long_rh_MD, aes(x = Time, y = Value, group = Subject, color = Subject)) +
  geom_line() +
  geom_point(size = 3) +
  labs(
    title = "Change Between Jan and May for rh_M1_md",
    x = "Date",
    y = "Value"
  ) +
  theme_minimal()
...

V1 lh AD
```{r}
paired t-test
t.test(data$jan_lh_V1_ad, data$may_lh_V1_ad, paired = TRUE)
...

V1 lh AD
```{r}
# Reshape the data to long format for ggplot
data_long_lh_AD_ctl <- data %>%
  pivot_longer(
    cols = c(jan_lh_V1_ad, may_lh_V1_ad),
    names_to = "Time",
    values_to = "Value"
  ) %>%
  mutate(Time = ifelse(Time == "jan_lh_V1_ad", "Jan", "May"))

# Plot using ggplot
ggplot(data_long_lh_AD_ctl, aes(x = Time, y = Value, group = Subject, color = Subject)) +
  geom_line() +
  geom_point(size = 3) +
  labs(
    title = "Change Between Jan and May for lh V1 AD",
    x = "Date",
    y = "Value"
  ) +
  theme_minimal()
...

V1 lh FA
```{r}

```

```

paired t-test
t.test(data$jan_lh_V1_fa, data$may_lh_V1_fa, paired = TRUE)
...

V1 lh FA
```{r}
# Reshape the data to long format for ggplot
data_long_lh_FA_ctl <- data %>%
  pivot_longer(
    cols = c(jan_lh_V1_fa, may_lh_V1_fa),
    names_to = "Time",
    values_to = "Value"
  ) %>%
  mutate(Time = ifelse(Time == "jan_lh_V1_fa", "Jan", "May"))

# Plot using ggplot
ggplot(data_long_lh_FA_ctl, aes(x = Time, y = Value, group = Subject, color = Subject)) +
  geom_line() +
  geom_point(size = 3) +
  labs(
    title = "Change Between Jan and May for lh V1 FA",
    x = "Date",
    y = "Value"
  ) +
  theme_minimal()
...

V1 lh RD
```{r}
paired t-test
t.test(data$jan_lh_V1_rd, data$may_lh_V1_rd, paired = TRUE)
...

V1 lh RD
```{r}
# Reshape the data to long format for ggplot
data_long_lh_RD_ctl <- data %>%
  pivot_longer(
    cols = c(jan_lh_V1_rd, may_lh_V1_rd),
    names_to = "Time",
    values_to = "Value"
  ) %>%
  mutate(Time = ifelse(Time == "jan_lh_V1_rd", "Jan", "May"))

# Plot using ggplot
ggplot(data_long_lh_RD_ctl, aes(x = Time, y = Value, group = Subject, color = Subject)) +
  geom_line() +

```

```

geom_point(size = 3) +
labs(
  title = "Change Between Jan and May for lh V1 RD",
  x = "Date",
  y = "Value"
) +
theme_minimal()
...

V1 lh MD
```{r}
paired t-test
t.test(data$jan_lh_V1_md, data$may_lh_V1_md, paired = TRUE)
...

V1 lh MD
```{r}
# Reshape the data to long format for ggplot
data_long_lh_MD_ctl <- data %>%
  pivot_longer(
    cols = c(jan_lh_V1_md, may_lh_V1_md),
    names_to = "Time",
    values_to = "Value"
  ) %>%
  mutate(Time = ifelse(Time == "jan_lh_V1_md", "Jan", "May"))

# Plot using ggplot
ggplot(data_long_lh_MD_ctl, aes(x = Time, y = Value, group = Subject, color = Subject)) +
  geom_line() +
  geom_point(size = 3) +
  labs(
    title = "Change Between Jan and May for lh V1 MD",
    x = "Date",
    y = "Value"
  ) +
  theme_minimal()
...

V1 rh AD
```{r}
paired t-test
t.test(data$jan_rh_V1_ad, data$may_rh_V1_ad, paired = TRUE)
...

V1 rh AD
```{r}
# Reshape the data to long format for ggplot
data_long_rh_AD_ctl <- data %>%

```

```

pivot_longer(
  cols = c(jan_rh_V1_ad, may_rh_V1_ad),
  names_to = "Time",
  values_to = "Value"
) %>%
mutate(Time = ifelse(Time == "jan_rh_V1_ad", "Jan", "May"))

# Plot using ggplot
ggplot(data_long_rh_AD_ctl, aes(x = Time, y = Value, group = Subject, color = Subject)) +
  geom_line() +
  geom_point(size = 3) +
  labs(
    title = "Change Between Jan and May for rh V1 AD",
    x = "Date",
    y = "Value"
  ) +
  theme_minimal()
...

V1 rh FA
```{r}
paired t-test
t.test(data$jan_rh_V1_fa, data$may_rh_V1_fa, paired = TRUE)
...

V1 rh FA
```{r}
# Reshape the data to long format for ggplot
data_long_rh_FA_ctl <- data %>%
  pivot_longer(
    cols = c(jan_rh_V1_fa, may_rh_V1_fa),
    names_to = "Time",
    values_to = "Value"
  ) %>%
  mutate(Time = ifelse(Time == "jan_rh_V1_fa", "Jan", "May"))

# Plot using ggplot
ggplot(data_long_rh_FA_ctl, aes(x = Time, y = Value, group = Subject, color = Subject)) +
  geom_line() +
  geom_point(size = 3) +
  labs(
    title = "Change Between Jan and May for rh V1 FA",
    x = "Date",
    y = "Value"
  ) +
  theme_minimal()

```

```

...
V1 rh RD
```{r}
paired t-test
t.test(data$jan_rh_V1_rd, data$may_rh_V1_rd, paired = TRUE)
...

V1 rh RD
```{r}
# Reshape the data to long format for ggplot
data_long_rh_RD_ctl <- data %>%
  pivot_longer(
    cols = c(jan_rh_V1_rd, may_rh_V1_rd),
    names_to = "Time",
    values_to = "Value"
  ) %>%
  mutate(Time = ifelse(Time == "jan_rh_V1_rd", "Jan", "May"))

# Plot using ggplot
ggplot(data_long_rh_RD_ctl, aes(x = Time, y = Value, group = Subject, color = Subject)) +
  geom_line() +
  geom_point(size = 3) +
  labs(
    title = "Change Between Jan and May for rh V1 RD",
    x = "Date",
    y = "Value"
  ) +
  theme_minimal()
...

V1 rh MD
```{r}
paired t-test
t.test(data$jan_rh_V1_md, data$may_rh_V1_md, paired = TRUE)
...

V1 rh MD
```{r}
# Reshape the data to long format for ggplot
data_long_rh_MD_ctl <- data %>%
  pivot_longer(
    cols = c(jan_rh_V1_md, may_rh_V1_md),
    names_to = "Time",
    values_to = "Value"
  ) %>%
  mutate(Time = ifelse(Time == "jan_rh_V1_md", "Jan", "May"))

```

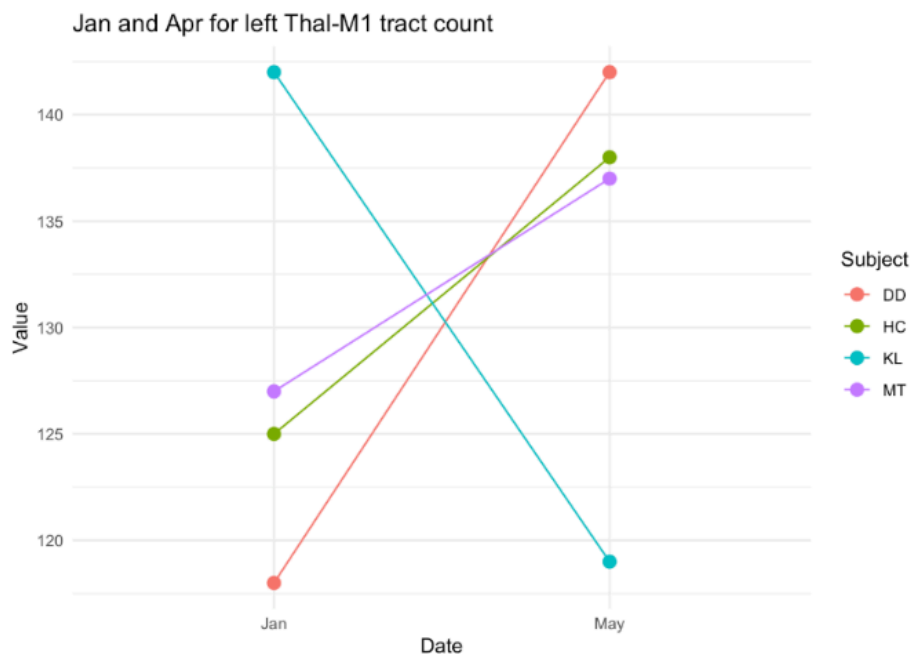
```
# Plot using ggplot
ggplot(data_long_rh_MD_ctl, aes(x = Time, y = Value, group = Subject, color = Subject)) +
  geom_line() +
  geom_point(size = 3) +
  labs(
    title = "Change Between Jan and May for rh V1 MD",
    x = "Date",
    y = "Value"
  ) +
  theme_minimal()
...

```

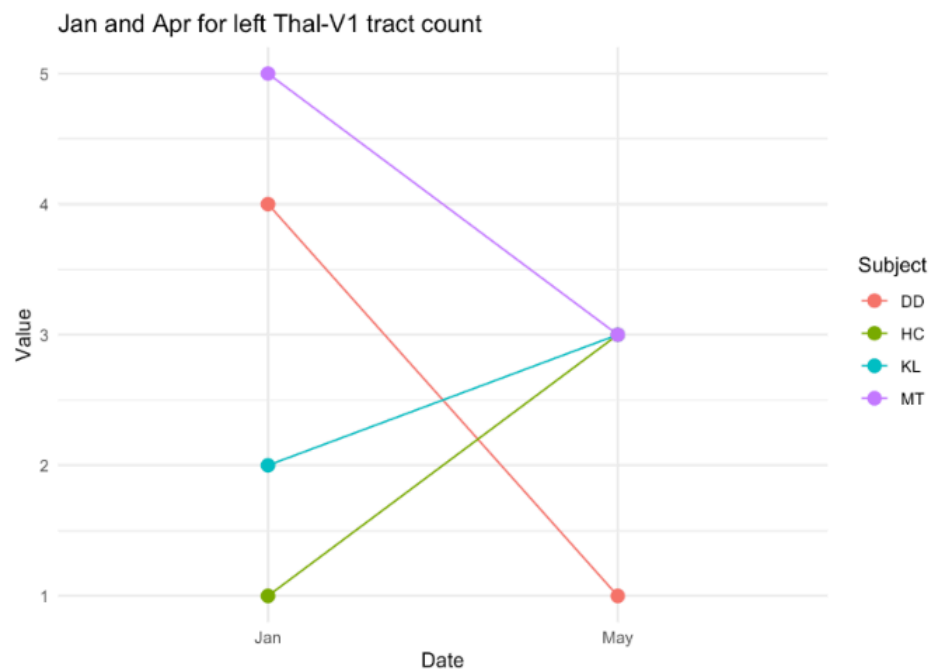
APPENDIX C - Supplemental Figures

4. Supplemental figures for white matter tractography

4.1 Left Thal-M1 tract count



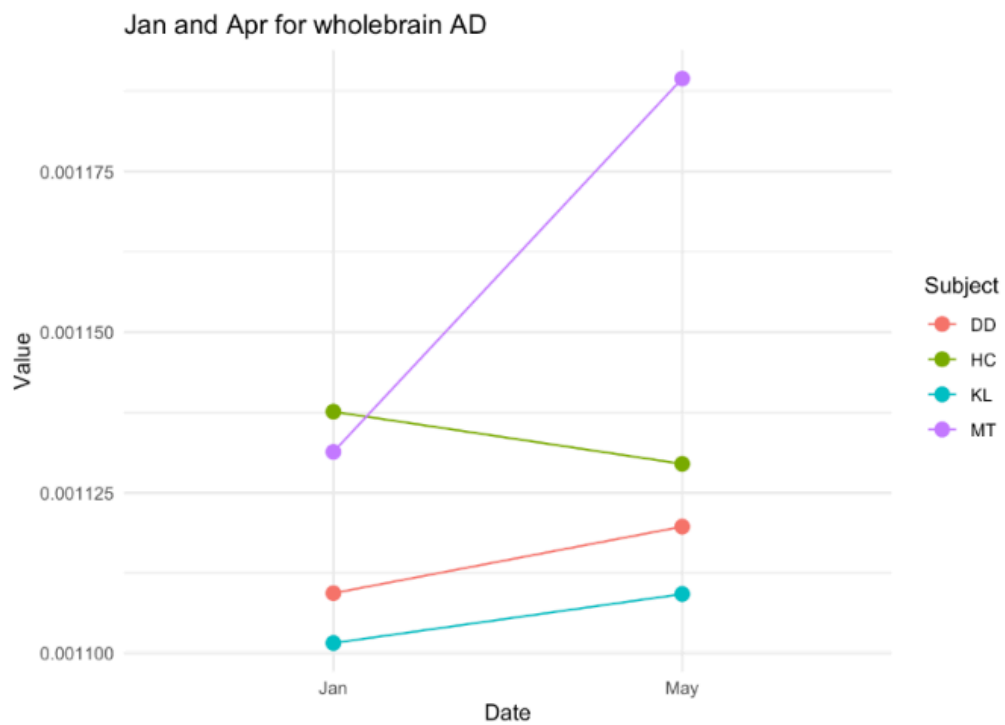
4.2 Left Thal-V1 tract count



4.3 Right Thal-V1 tract count



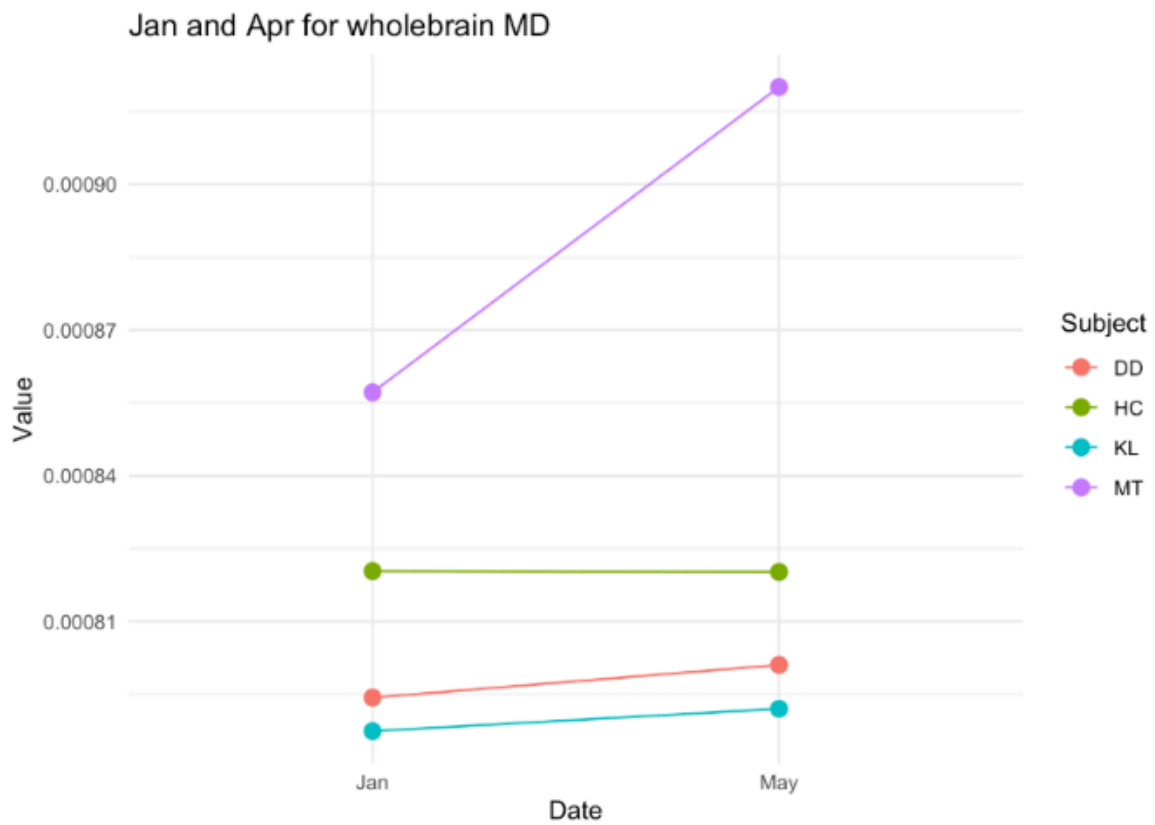
4.4 Wholebrain AD



4.5 Wholebrain RD



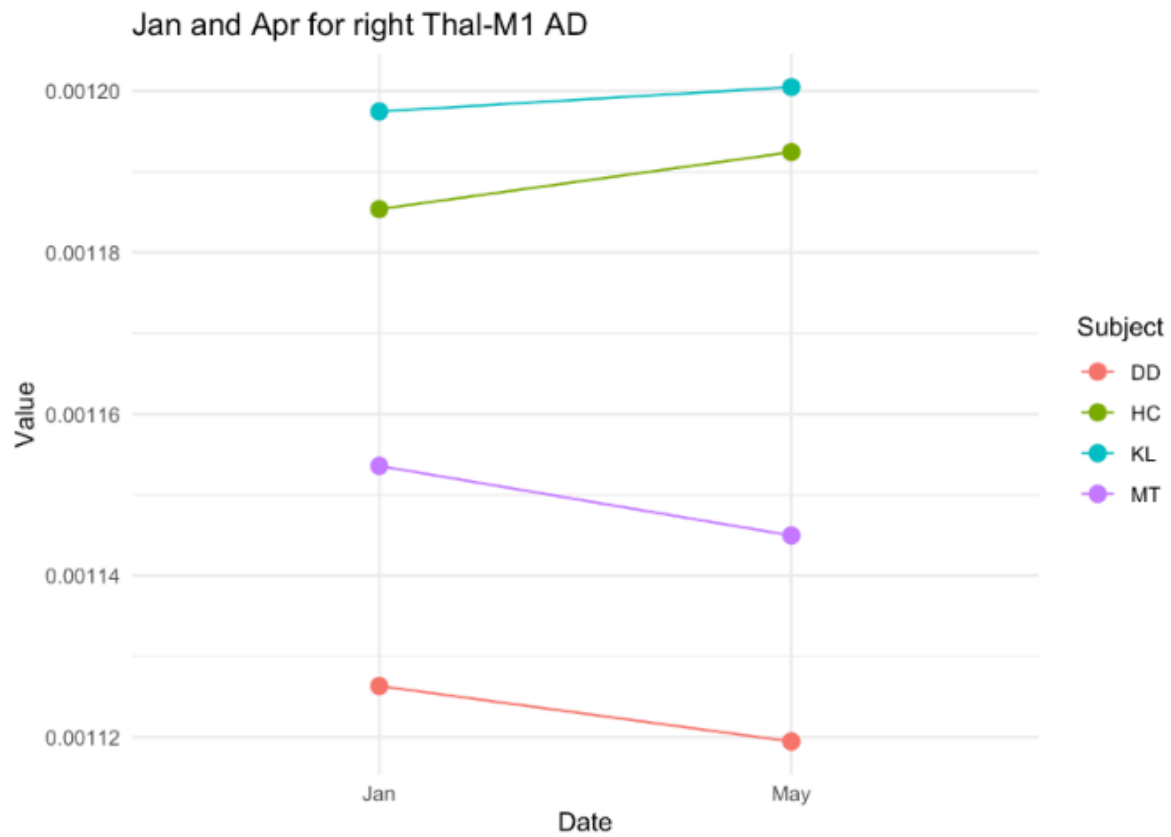
4.6 Wholebrain MD



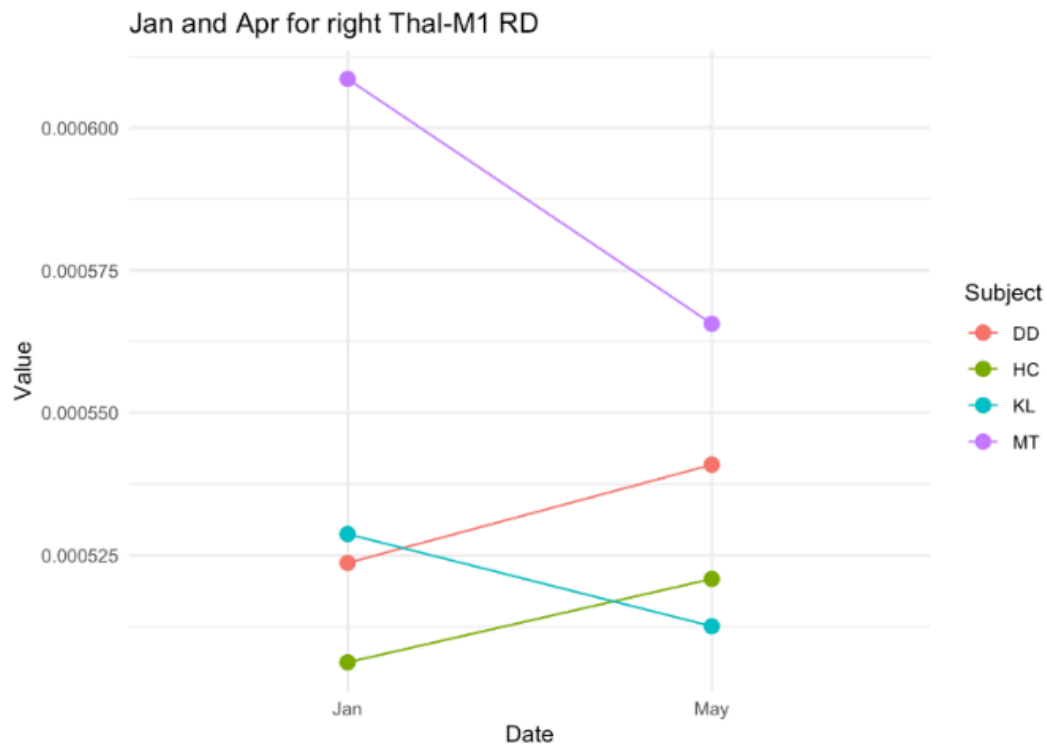
4.7 Wholebrain FA



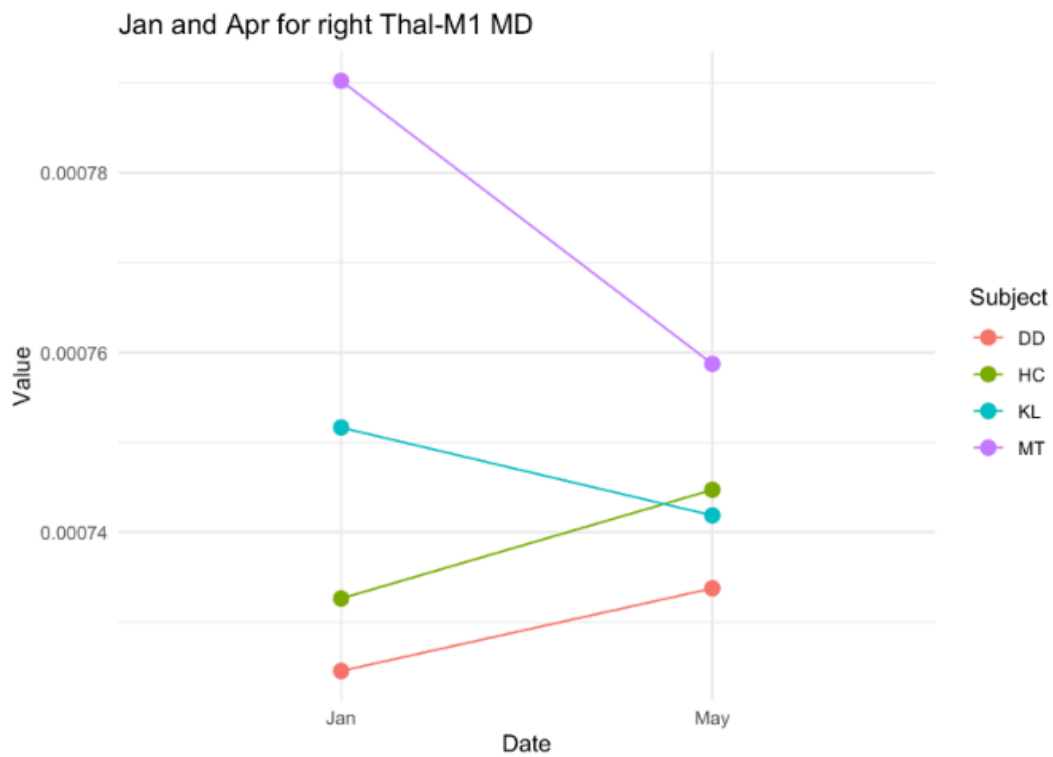
4.8 Right Thal-M1 AD



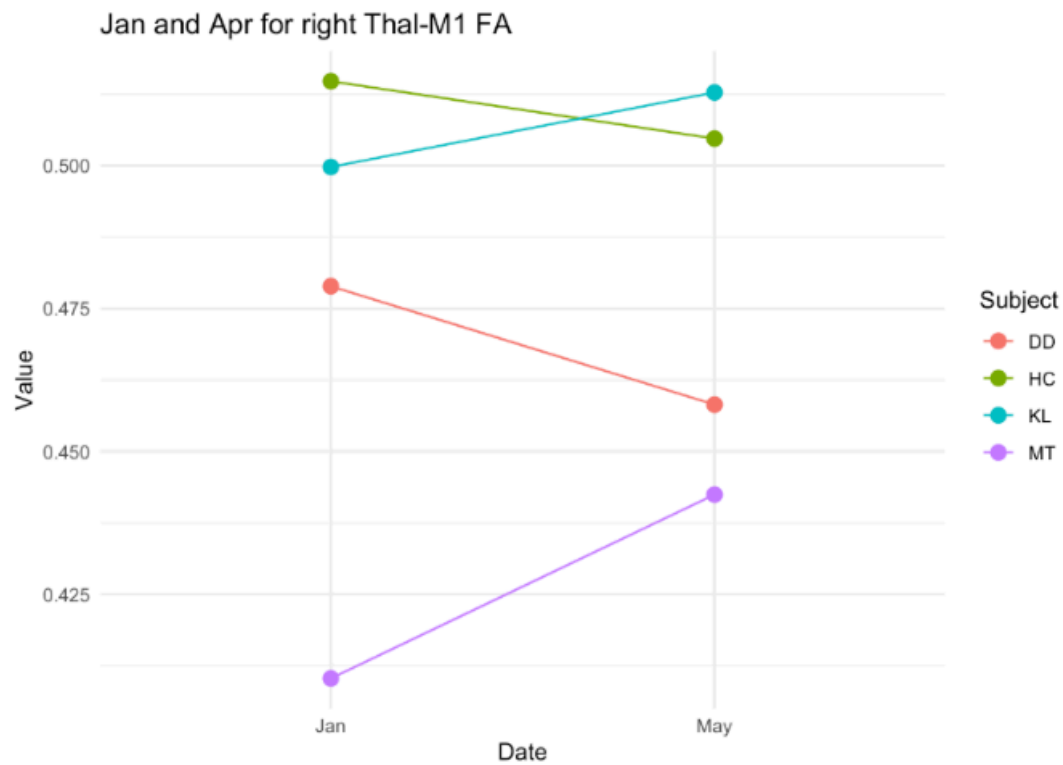
4.9 Right Thal-M1 RD



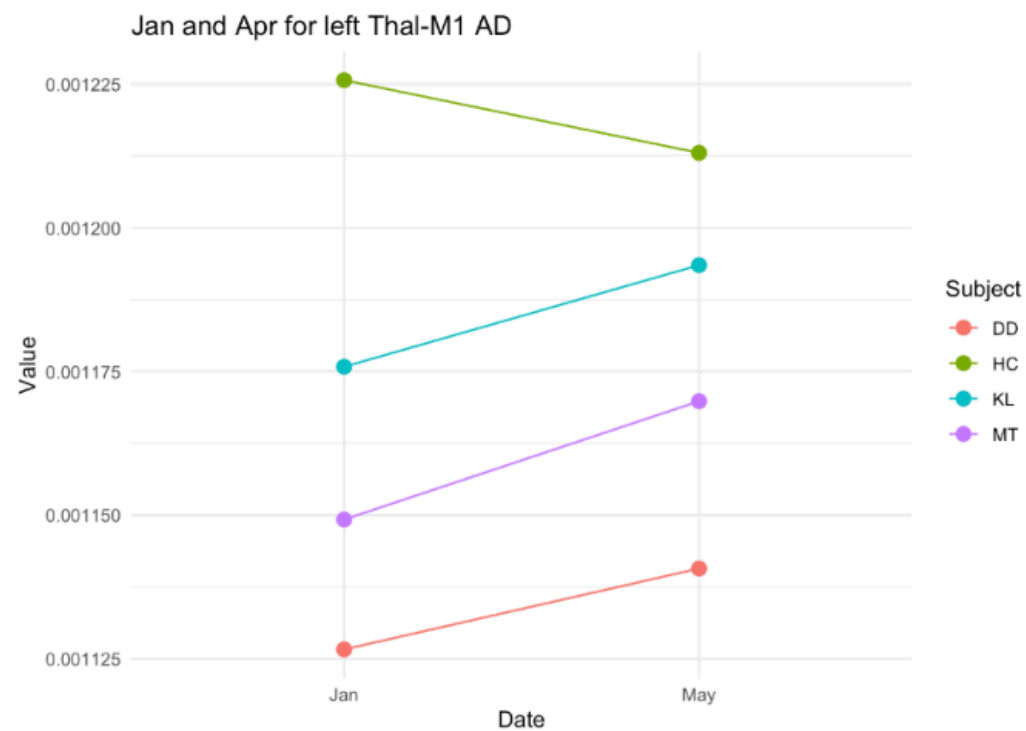
4.10 Right Thal-M1 MD



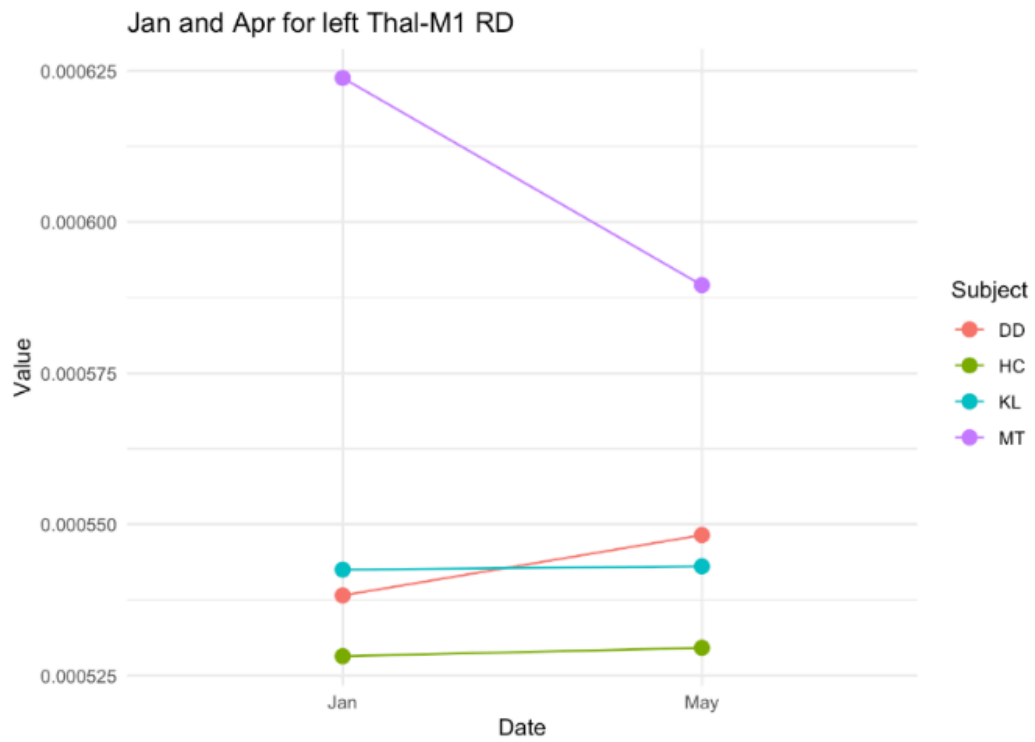
4.11 Right Thal-M1 FA



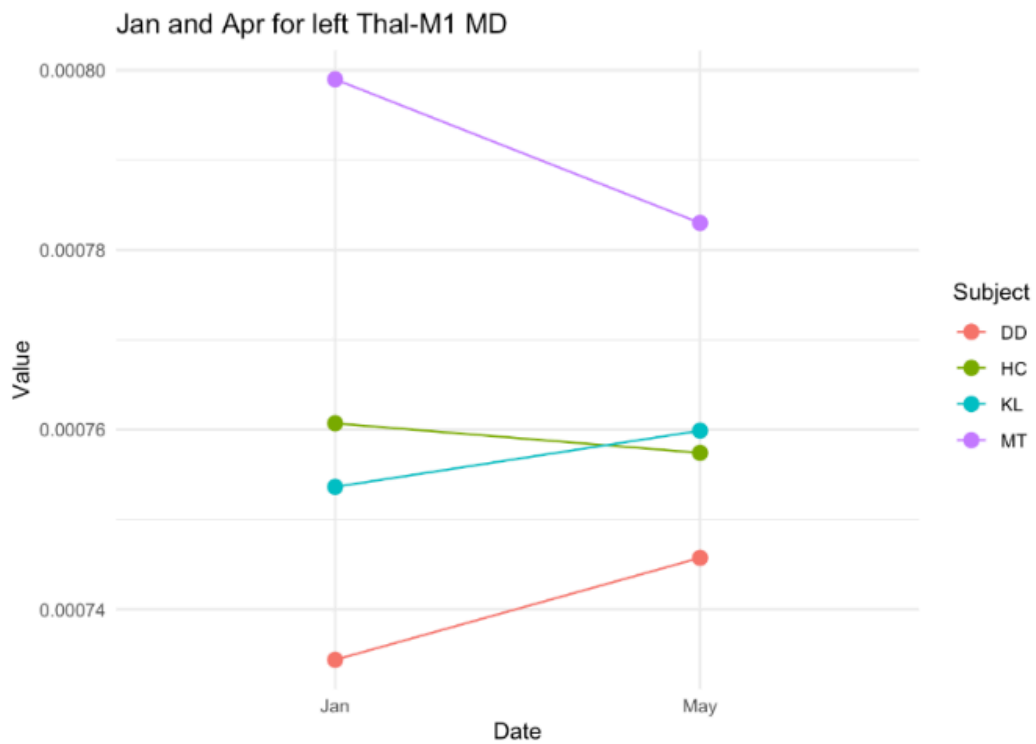
4.12 Left Thal-M1 AD



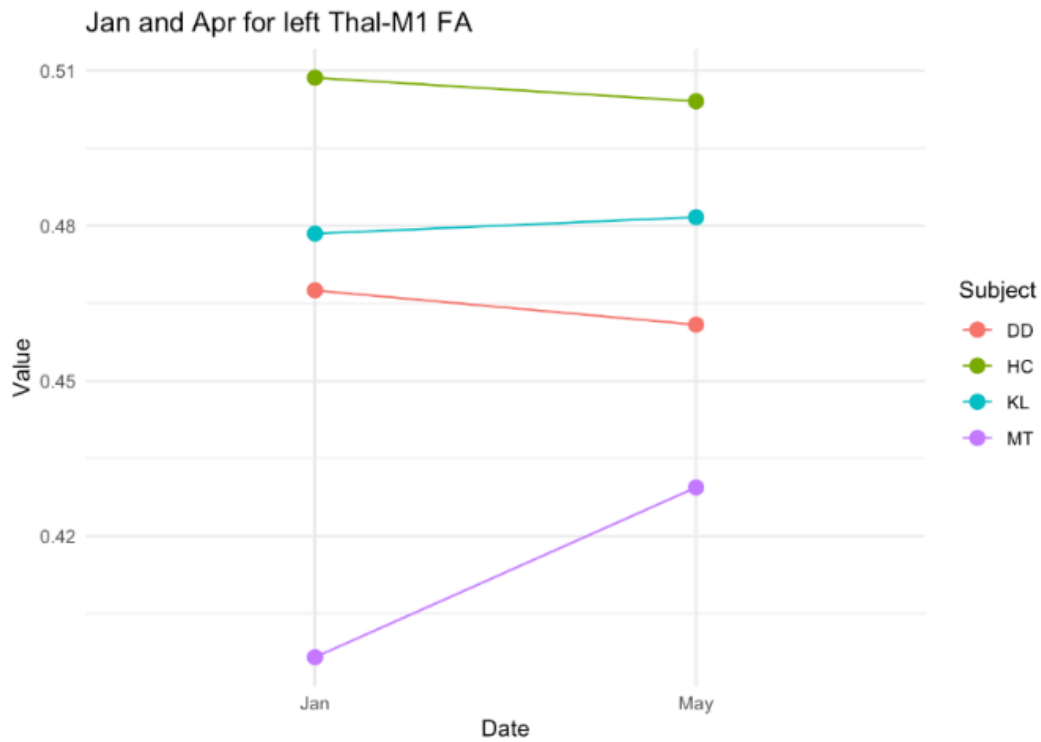
4.13 Left Thal-M1 RD



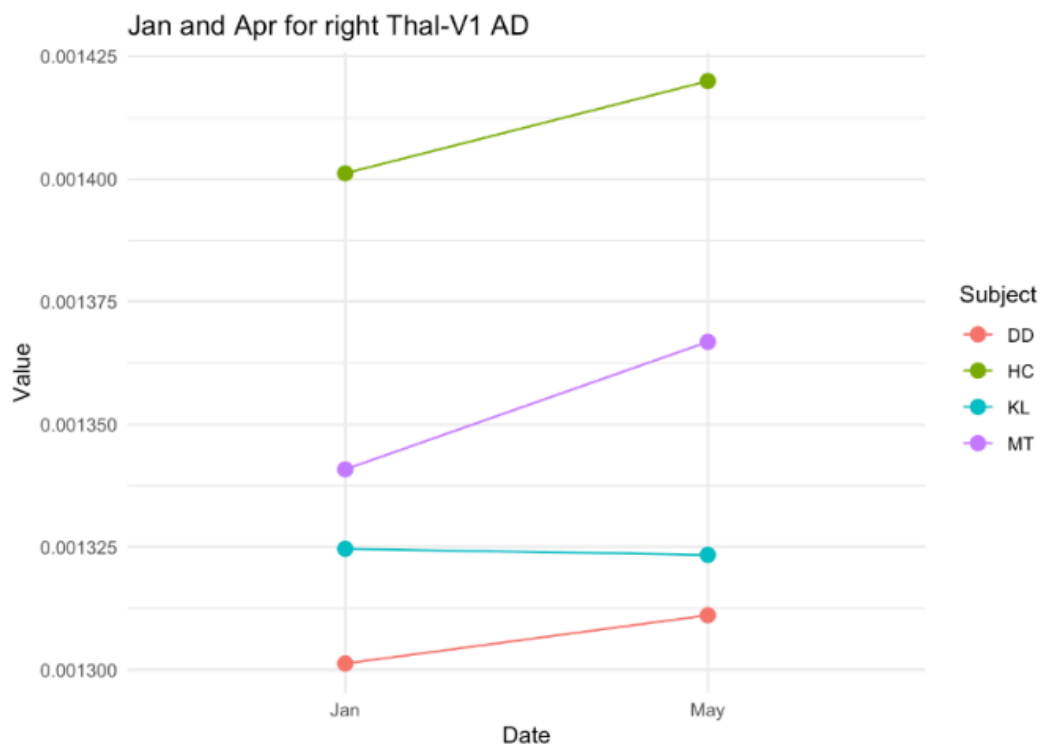
4.14 Left Thal-M1 MD



4.15 Left Thal-M1 FA



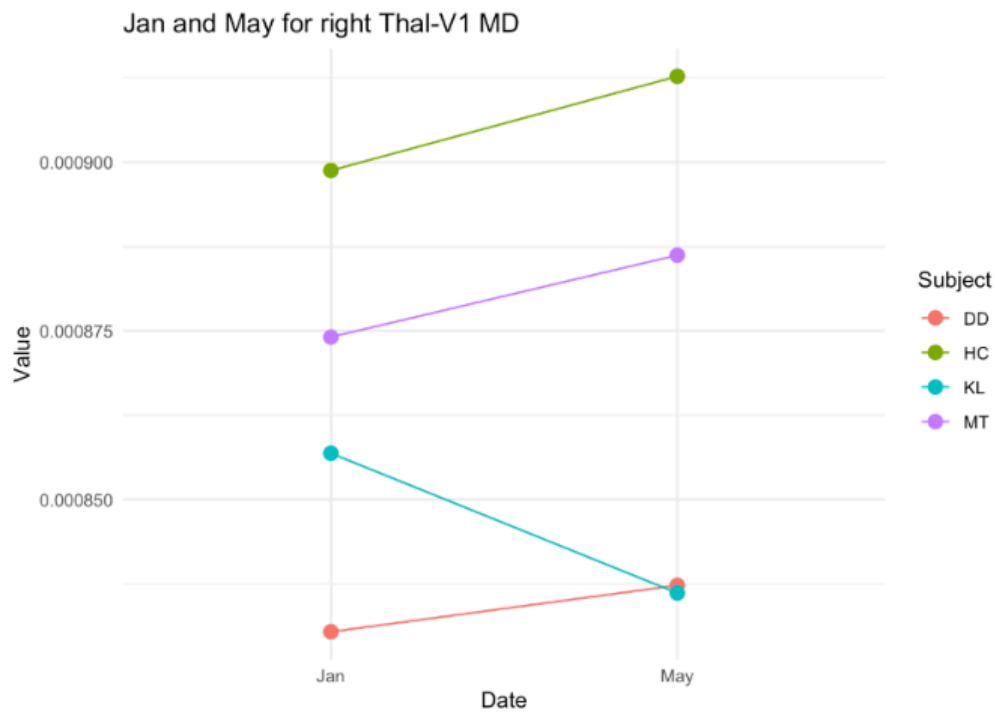
4.16 Right Thal-V1 AD



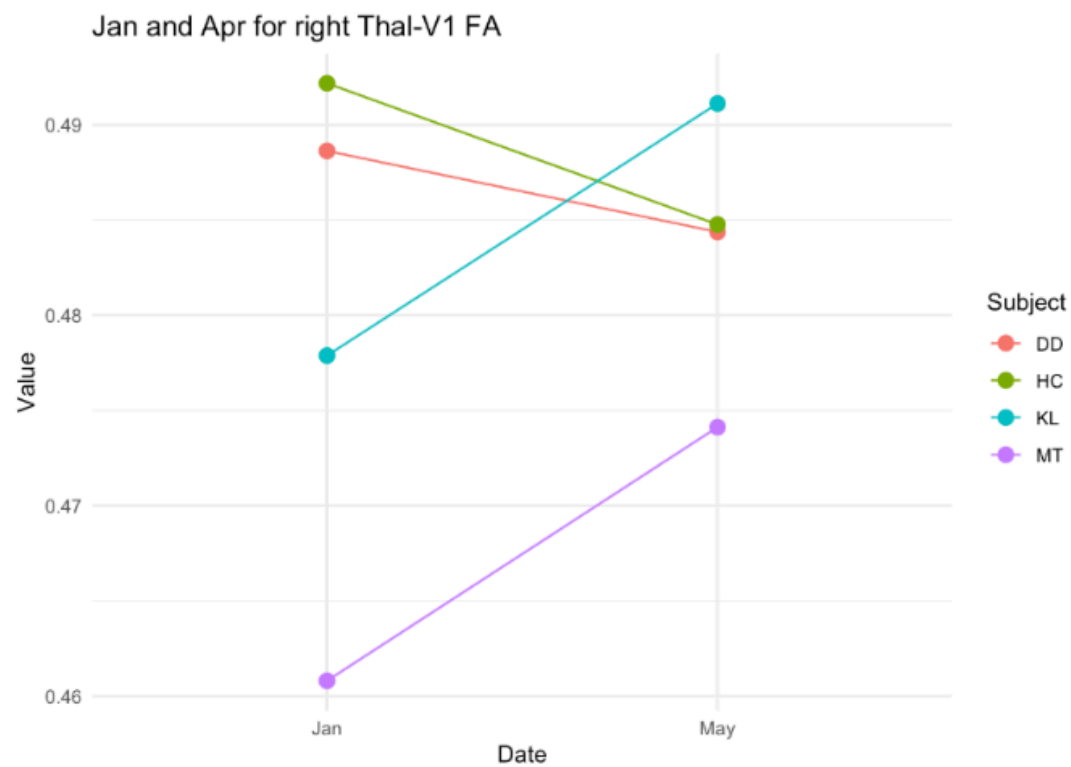
4.17 Right Thal-V1 RD



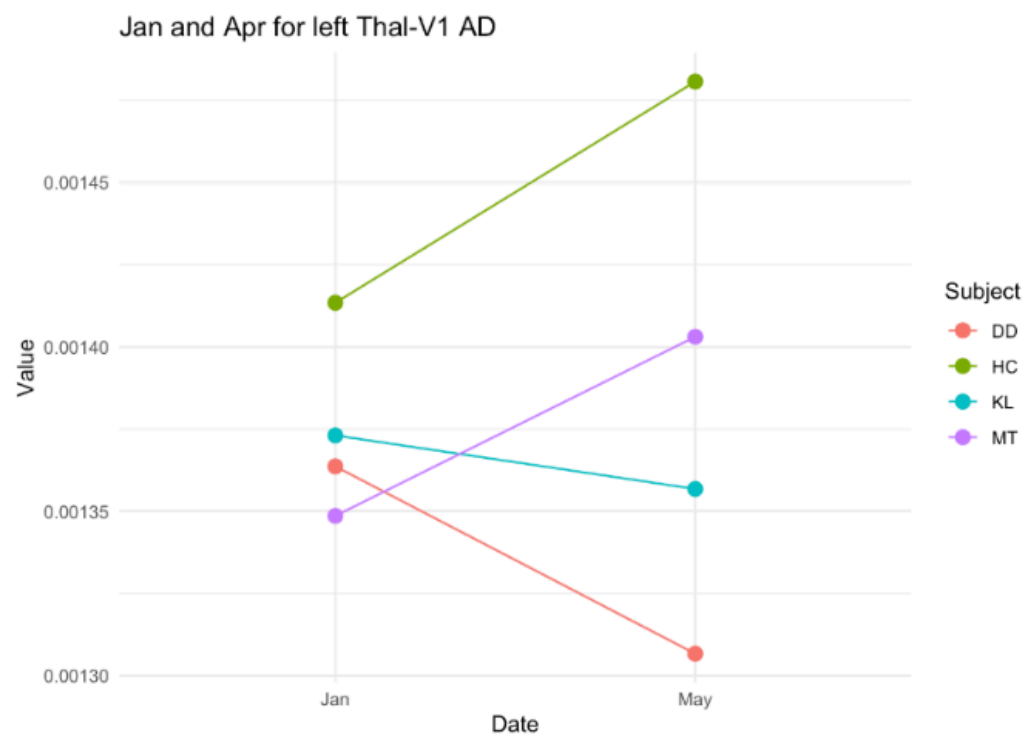
4.18 Right Thal-V1 MD



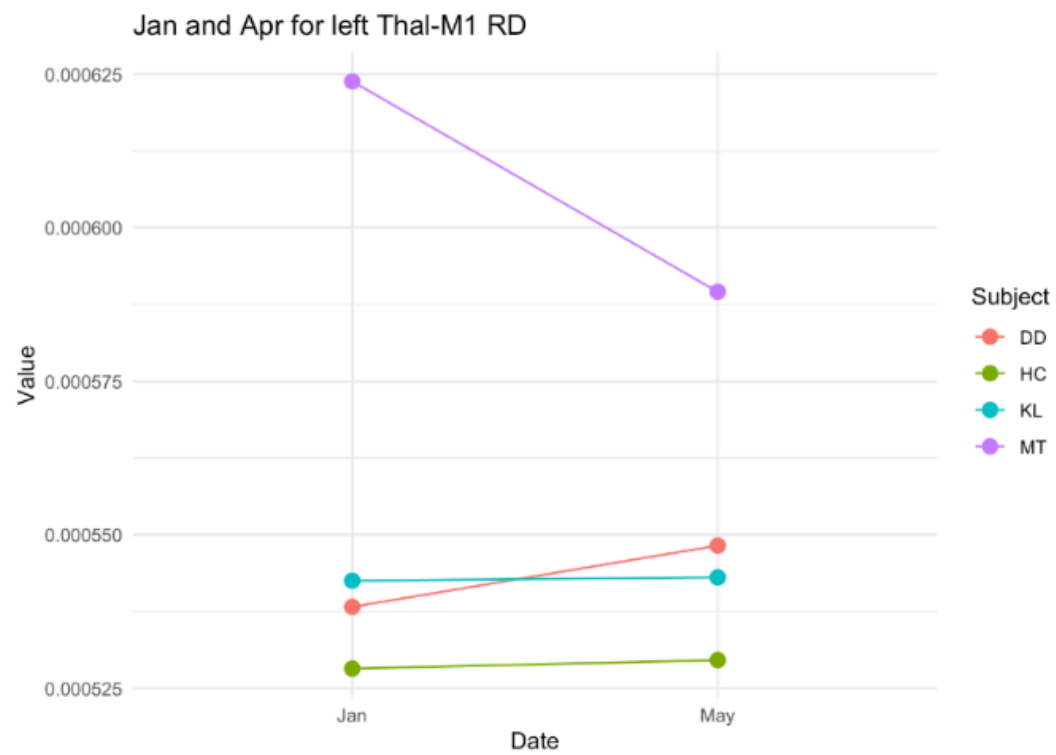
4.19 Right Thal-V1 FA



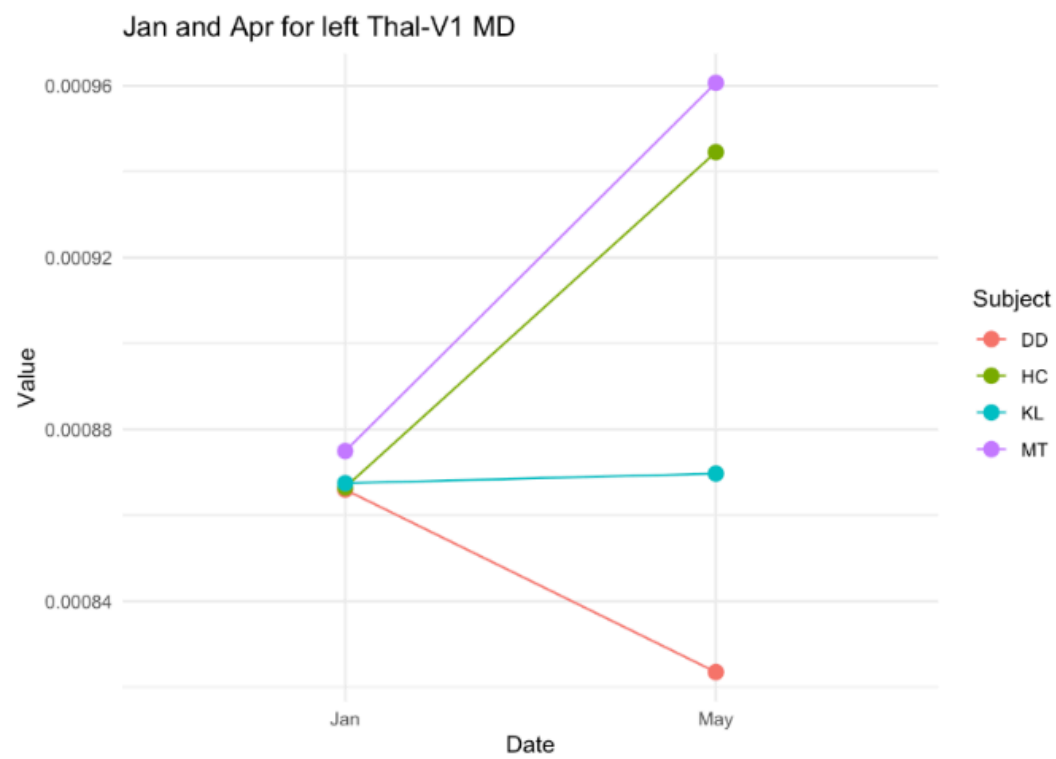
4.20 Left Thal-V1 AD



4.21 Left Thal-V1 RD



4.22 Left Thal-V1 MD



4.23 Left Thal-V1 FA

