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Neha Bajaj April 08, 2025

Distinct Resting-State Functional Brain Connectivity Profiles in Healthy Aging and Parkinson's Disease-Driven Neurodegeneration

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Abstract

Distinct Resting-State Functional Brain Connectivity Profiles in Healthy Aging and Parkinson's Disease-Driven Neurodegeneration

By Neha Bajaj

Background: Parkinson's disease (PD) is the second most prevalent age-associated progressive neurodegenerative disorder. Clinically, PD is characterized by four cardinal motor signs: rigidity, tremors, bradykinesia, and postural instability. These signs define the progression and major characteristics of PD that contribute to significant motor and cognitive challenges of people with PD (PwPD). Previous studies have sought to identify the brain patterns that might underlie these impairments in PwPD versus the healthy older adult (HOA) population. In this study, we used resting-state functional Magnetic Resonance Imaging (fMRI) to compare functional connectivity patterns between PwPD and HOA and focused our analyses on brain regions previously shown to be involved in brain pathways supporting internally generated, externally generated movements, or both. Our hypothesis was that PwPD would be more affected in brain regions supporting IG movements. This study aims to shed light on the functional connectivity underlying PD using a well-powered and controlled design intended to inform PD neurobiology.

Methods: 72 PwPD and 24 neurotypical age-matched HOA underwent a 9 minute and 45 second resting-state fMRI scan via a research-dedicated 3T Siemens Trio scanner using a Siemens 12-channel head coil. Brain regions of interest were selected based on independently identified, (NeuroMark) highly reproducible components.

Results: We identified multiple pairwise combinations between brain regions that were either significantly ($p<0.05$) overconnected or under connected in PwPD, when compared to HOA. Brain areas that emerged in several significant findings were the cerebellum, postcentral gyrus, and the precuneus. Specifically, we found a preferential increase in the connectivity of these three brain areas in IG movement pathways in PwPD vs. HOA.

Discussion: Our findings agree with changes in connectivity in PwPD in the cerebellum, postcentral gyrus, and the precuneus. This could be attributed to PwPD overcompensating connectivity in these areas to support brain regions such as the basal ganglia in generating movements. Based on previous literature, the brain regions where more changes were identified in PwPD correspond to areas involved largely in IG pathways. In HOA, these areas are involved in both EG and IG, indicating different pathways supporting these movements.

Conclusions: The cerebellum, postcentral gyrus, and precuneus have all been shown to increase in functional connectivity in internally generated movement pathways in PwPD vs. HOA. These findings can inform future intervention based treatment plans for PwPD.

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Background & Introduction

Parkinson's disease (PD) is the second most prevalent age-associated progressive neurodegenerative disorder (Willis et al., 2022). Nearly 90,000 individuals are diagnosed with PD each year (Willis et al., 2022) with over 6 million living with PD in the world (Tolosa et al., 2021). The incidence of PD increases with age, with an estimated 3% of the 80+ population experiencing symptoms (Hayes et al., 2019). Pathophysiologically, PD develops due to the lack of dopamine production within the substantia nigra of the brain as dopaminergic neurons die off (Emamzadeh et al., 2018). Dopamine, a neurotransmitter, is involved in neural pathways regulating movement, motivation, memory, and other essential functions (Ramesh et al., 2023). Therefore, the loss of dopamine, along with other potential changes, leads to motor and possible cognitive deficiencies attributable to the development of PD as well as a subsequent significant decrease in the quality of life often leading to psychological distress such as depression and anxiety (Weintraub et al., 2015).

Clinically, PD is characterized by four cardinal motor symptoms: rigidity, tremors, bradykinesia, and postural instability (Bereczki et al., 2010). To gain diagnosis of PD, one must present with three of these four cardinal signs. Rigidity is present in almost 89% of all PD cases and manifests as an extreme reduction in limb mobility causing difficulty in performing basic motor movements (Ferreira-Sánchez et al., 2020). Around 80% of all people with PD (PwPD) experience limb tremors, with most of them being unilateral and occurring on the distal ends of the limbs (Jankovic et al., 2008). Bradykinesia is another very commonly recognized clinical symptom of PD associated with difficulty in planning, initiating, and executing movements (Jankovic et al., 2008). Initially, bradykinesia manifests as a significant reduction in the reaction time and the speed at which PwPD can perform daily activities. Eventually, bradykinesia progresses to include a loss of spontaneous movements such as arm swinging while walking or blinking, drooling because of impaired swallowing, speech dysarthria, and loss of facial expression (Jankovic et al., 2008). Postural instability, the fourth cardinal sign, is the most common cause of falls in PwPD and results from the loss of postural reflexes, typically seen in the later stages of PD. All these symptoms define the progression and major characteristics of PD that contribute to significant motor and cognitive challenges in PwPD.

Previous studies have sought to identify the brain patterns that might underlie these impairments in PwPD versus the healthy older adult population. One of the most prominent methods utilized to understand the neurobiology underlying these symptoms is comparing resting-

state functional connectivity patterns in people with PD (PwPD) versus healthy older adults (HOA), using functional Magnetic Resonance Imaging (fMRI). Although findings from previous studies have been informative *(see Supplementary Table 1 for a comprehensive review)*, the field is far from a consensus regarding the connectivity trends in PwPD. This lack of consensus could be due to several reasons, including a) different analytical approaches (whole brain [Vereb et al., 2022] vs. region of interest [Ragothaman et al., 2022, Müller-Oehringa et al., 2016, Rodriguez-Sabatea et al., 2019] approaches); b) different regions of interest in different levels of granularity (e.g., "dorsal attention network" [Ragothaman et al., 2022] vs. specific regions, such as the caudate and the putamen [Müller-Oehringa et al., 2016); c) different sample sizes (e.g., limited by small sample sizes in Kaut et al., 2020 and larger sample sizes in Ragothaman et al., 2022); and d) different interpretation frameworks (e.g., Rodriguez- Sabatea et al., 2019, Vereb et al., 2022). These diverse approaches and gaps in the literature have inspired this study to provide a more comprehensive analysis of resting state functional connectivity in PD and healthy aging.

In this study, resting-state fMRI was utilized to compare functional connectivity patterns between PwPD in mild-moderate stages and HOA. Building on previous evidence that supports a specialized dysfunction in the brain pathway of PwPD underlying internally generated (IG) movements, which include spontaneous reactions to stimuli such as humming, but a relatively intact brain pathway (in earlier stages) supporting externally generated (EG) movements, which include movements in response to external stimuli, such as swaying to a musical rhythm (Sen et al., 2010), this study delves into the functional connectivity of these specific pathways and assesses potential differences in PwPD vs. HOA. The dysfunction of brain pathways in PwPD involved in IG movement is further supported by behavioral evidence showing that PwPD have deficits such as bradykinesia when walking by themselves (IG) vs. when walking to the rhythm of a metronome (EG) (Ashoori et al., 2015). Our hypothesis was that PwPD would have less functional connectivity in brain regions supporting IG movements. This study aims to shed light on the functional connectivity in the brains of individuals with PD using a well-powered and controlled design intended to inform PD neurobiology. Furthermore, considering that dance training is currently being used as a powerful intervention in PwPD (Hackney et al., 2024) and such interventions can be structured to highlight more engagement in IG (e.g. leader in tango) or EG (e.g., follower in tango) movements, this study could also inform clinical practice.

Methods

Participant Screening

Seventy-two (72) PwPD and twenty-four (24) neurotypical age-matched HOA participants were recruited, through multiple pathways: the Atlanta Veterans Affairs (VA) Center for Visual and Neurocognitive Rehabilitation (CVNR) registry, the VA Informatics and Computing Infrastructure database, the Michael J. Fox finder website, the Movement Disorders unit of Emory University, PD organizations newsletters, support groups and educational events, and through word of mouth. The following selection criteria were used to screen participants. All PD participants were clinically diagnosed with PD by a movement disorders specialist. This diagnosis was based on the United Kingdom PD Society Brain Bank diagnostic criteria (Hughes et al., 1992). Participants were aged 40 years and older and could walk 3 meters or more with or without assistance. No participants had contraindications to undergo an fMRI scan. Participants could hear above the pure-tone threshold (>40dB). Participants were excluded if they scored <18 on the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005; Hoops et al., 2009). Exclusion criteria also included peripheral neuropathy, untreated major depression, history of stroke, or traumatic brain injury. The Beck Depression Inventory-II (BDI-II) assessed depression and a score of ≥30, indicating severe depression, was a cutoff for the BDI-II (Schrag et al., 2007). PwPD had unilateral onset of symptoms, displayed clear symptomatic benefit from antiparkinsonian medications, e.g., levodopa, and were in Hoehn and Yahr stages I-III (Hoehn and Yahr 1967). PwPD who had a tremor score greater than 1 on the Movement Disorders Society Unified Parkinson Disease Rating scale (MDS-UPDRS) Part III in either lower limb and/or moderate-severe head tremor were excluded. PD participants were tested in the OFF state, i.e. at more than 12 hours after their last dose of anti-parkinsonian medication.

	Parkinson's Disease (PwPD) (n=72)	Healthy Older Adults (HOA) (n=24)
M/F	41/31	6/18
Age (Years)	70.05 ± 8.5	64.08 ± 16.0
MoCA (/30)	25.49 ± 3.8	26.92 ± 2.9
Years with diagnosed PD	6.13 ± 4.5	N/A
UPDRS – Total Score	62.88 ± 20.9	N/A
UPDRS – III Score	35.61 ± 11.5	N/A

Table 1. Participant Demographics and Clinical Characteristics. This table includes data (mean ± standard deviation) for both PwPD and HOA, including the number of male and female participants, average age (years), and average MoCA scores. Additionally, for PwPD, it includes the number of years diagnosed with PD, average Unified Parkinson's Disease Rating Scale (UPDRS) Total Score, and average UPDRS-III (Motor Assessment) Scores.

Resting-State Functional Magnetic Resonance Imaging Procedure

All neuroimaging data were collected in the Center for Systems Imaging at Emory University on a research-dedicated 3T Siemens Trio scanner using a Siemens 12-channel head coil. All participants were instructed to lie awake for 9 minutes and 45 seconds with their eyes closed. Participants were told to let their minds wander. Foam padding was utilized to restrict all head motion. Immediately after the scan, participants were asked if they had fallen asleep. If yes, the fMRI scan was repeated. Resting-State blood oxygen level dependent (BOLD) fMRI scans were acquired with a conventional Echo Planar Imaging (EPI) sequence with an iPAT acceleration factor of 2. Scan sequence parameters were: 55 contiguous 3 mm slices in the axial plane, interleaved slice acquisition, repetition time (TR) = 3000 ms, echo time (TE) = 24 ms, flip angle = 90 degrees, bandwidth = 2632 Hz/pixel, field of view (FOV) = 230 mm, matrix = 76 x 76, voxel size = 3.0 x 3.0 x 3.0 mm. At the beginning of the run, the scanner acquired 3 TRs which were discarded automatically. An anatomical image was collected using a high resolution MPRAGE scan sequence with 176 contiguous slices in the sagittal plane, single-shot acquisition, TR = 2300

ms, TE = 2.89 ms, flip angle = 8 degrees, FOV = 256 mm, matrix = 256x256, bandwidth = 140 Hz/pixel, voxel size = 1.0 x 1.0 x 1.0 mm.

Resting-State Functional Magnetic Resonance Imaging Data Preprocessing

The imaging data underwent quality checks by an individual rater, as well as automatized quality control using the MRIQC (Magnetic Resonance Imaging Quality Control) software, which evaluates the quality of imaging data by computing a variety of metrics (e.g., signal-to-noise ratio, artifacts, spatial smoothness, motion-related metrics) to identify potential issues that might affect subsequent analysis which flagged scans with suboptimal quality or artifacts. In this process, one dataset (sub131-ses01) was flagged as problematic due to quality control issues and was excluded from the analysis. Slice-time correction and motion correction were performed on the functional volumes using SPM12. All physiological noise (pulse and respiration) was normalized to standard space. The first 8-10 scans were discarded to account for saturation effects. The Retrospective image correction (RETROICOR) algorithm removed physiological noise arising from main frequency peaks of cardiac and respiratory fluctuations (Glover et al., 2000). Cardiac and respiratory function were monitored with a photoplethysmography on the left index finger and a respiratory belt around the chest. BOLD signal changes arising from low frequency fluctuations of cardiac and respiratory waveforms were detrended using established methods (Bianciardi et al., 2009). The physiological noise corrected data were low pass filtered (cutoff frequency: 0.1 Hz) to isolate low frequency resting-state BOLD fluctuations (Gopinath et al., 2011). EPI images were then spatially normalized to Montreal Neurological Institiute (MNI) 3mm isotropic template using nonlinear registration and spatially smoothed with 10 mm FWHM Gaussian kernel. Signal intensities in each volume were scaled with z-transformation excluding the first six volumes from calculation of the mean and standard deviation, avoiding pre-steady-state outliers.

Regions of Interest selected within Internally Generated & Externally Generated Pathways

To further understand the regions of interest (ROIs) implicated in either internally generated (IG) or externally generated (EG) movements, a comprehensive literature review was conducted through NCBI PubMed. Keywords utilized to find relevant studies included: rhythmic, internally generated, externally generated, cued movement, fMRI, motor, movement, tapping, drawing, etc. This literature review was conducted with a focus on both studies involving PwPD and healthy individuals. Our goal was to understand potential differences in the brain regions

involved in IG/EG between these groups. Additionally, we aimed to be inclusive and impartial in the selection of brain ROIs to ensure a comprehensive analysis. Articles were selected and then analyzed to understand the specific brain regions involved in these movement pathways and the resulting increase or decrease in activity within the region.

Broader Brain Region	**Subregion** (As specified)	**Study (Population)**	**Scan Type; Study Task**	**EG or IG Movement Pathways**	**Activity: Increased or Decreased**
M1	N/A	Jäncke et al., 2000 (HA)	fMRI: Paced Finger Tapping	IG	**Increased**
		Horenstein et al., 2009 (HA)	fMRI; Finger Tapping	IG & EG	**Increased**
		Drucker et al., 2019 (PwPD/HOA)	fMRI; Foot Tapping	IG	**Decreased**
		Trinastic et al., 2010 (HA)	fMRI; Ankle Dorsiflexion or Plantarflexion	IG	**Increased**
		Ciccarelli et al., 2005 (HA)	fMRI; Ankle Dorsoplantar Flexion	IG	**Increased**
		Cunningham et al., 2013 (HA)	fMRI; Foot & Finger Movement	EG	**Increased**
		Vercruysse et al., 2014 (PwPD/HOA)	fMRI; Finger Flexion	IG	**Increased** (Right M1) **Decreased** (Left M1)
		Lewis et al., 2007 (PwPD/HA)	fMRI; Finger Tapping	IG	*Decreased*
	PreCG	Schwingenschuh et al., 2013 (PwPD/HOA)	fMRI; Ankle Movements	EG	*Increased*
		Gowen et al., 2007 (HA)	fMRI; Drawing	IG	**Increased**

PMC	*N/A*	Jäncke et al., 2000 (HA)	fMRI; Paced Finger Tapping	IG	**Increased**
		Horenstein et al., 2009 (HA)	fMRI; Finger Tapping	IG & EG	**Increased**
		Wu et al., 2011 (PwPD/HOA)	fMRI; Hand Tapping	IG	**Decreased**
		Sauvage et al., 2013 (HA)	fMRI; Hand Tapping	EG	**Increased**
		Trinastic et al., 2010 (HA)	fMRI; Ankle Dorsiflexion or Plantarflexion	EG	**Increased**
		Ciccarelli et al., 2005 (HA)	fMRI; Ankle Dorsoplantar Flexion	EG	**Increased**
		Ciccarelli et al., 2005 (HA)	fMRI; Ankle Dorsoplantar Flexion	IG	**Decreased**
		Ariani et al., 2015 (HA)	fMRI; Hand Reaching Movements	IG	**Increased**
		Eckert et al., 2006 (PwPD/HOA)	fMRI; Hand Movements	IG	**Increased**
		Elsinger et al., 2006 (HA)	fMRI; Finger Key Presses	IG	**Increased**
		Cunningham et al., 2013 (HA)	fMRI; Foot & Finger Movement	EG	**Decreased**
		Sen et al., 2010 (PwPD/HOA)	fMRI; Finger Tapping	IG	**Increased**
		Vercruysse et al., 2014 (PwPD/HOA)	fMRI; Finger Flexion	IG	**Increased** **(Right PMC)** **Decreased** **(Left PMC)**
		Debarae et al., 2003 (HA)	fMRI; Phasic Movements of Hand & Foot	EG	**Increased**
		Lewis et al., 2007 (HA/PwPD)	fMRI; Finger Tapping	EG	**Increased**

		Lewis et al., 2007 (PwPD/HA)	fMRI; Finger Tapping	IG	**Decreased**
SMA	*N/A*	Ariani et al., 2015 (HA)	fMRI; Hand Reaching Movements	IG	**Increased**
		Gowen et al., 2007 (HA)	fMRI; Drawing	IG	**Increased**
		Dobkin et al., 2004 (HOA)	fMRI; Ankle Dorsiflexion	EG & IG	**Increased**
		Cerasa et al., 2006 (PwPD/HOA)	fMRI; Rhythmic Tapping	EG & IG	**Increased**
		Eckert et al., 2006 (PwPD/HOA)	fMRI; Hand Movements	IG	**Increased**
		Elsinger et al., 2006 (HA)	fMRI; Finger Key Presses	IG	**Increased**
		Schwingenschuh et al., 2013 (PwPD/HOA)	fMRI; Ankle Movements	EG	**Increased**
		Cunningham et al., 2013 (HA)	fMRI; Foot & Finger Movement	EG	**Increased**
		Sen et al., 2010 (PwPD/HOA)	fMRI; Finger Tapping	IG	**Increased**
		Jahanshahi et al., 1985 (PwPD/HOA)	PET; Finger Flexion	IG & EG	**Increased**
		Lewis et al., 2007 (HA/PwPD)	fMRI; Finger Tapping	EG	**Increased**
		Lewis et al., 2007 (PwPD/HA)	fMRI; Finger Tapping	IG	**Decreased**
	Caudate	Dobkin et al., 2004 (HOA)	fMRI; Ankle Dorsiflexion	EG	*Increased*
		Wasson et al., 2010 (HA)	fMRI; Hand Force Production	EG	*Increased*

STR	*Putamen*	Ogawa et al., 2006 (HA)	fMRI; Finger Tapping	EG	*Increased*
		Sen et al., 2010 (PwPD/HOA)	fMRI; Finger Tapping	IG	**Increased**
		Lewis et al., 2007 (PwPD/HA)	fMRI; Finger Tapping	IG	*Decreased*
	N/A	Drucker et al., 2019 (PwPD/HOA)	fMRI; Foot Tapping	IG & EG	**Decreased**
		Trinastic et al., 2010 (HA)	fMRI; Ankle Dorsiflexion or Plantarflexion	EG	**Increased**
		Ciccarelli et al., 2005 (HA)	fMRI; Ankle Dorsoplantar Flexion	EG & IG	**Increased**
		Cerasa et al., 2006 (PwPD/HOA)	fMRI; Rhythmic Tapping	EG & IG	**Increased**
		Brown et al., 2006 (HA)	PET; Tango to Metered Beats	EG	**Increased**
		Debarae et al., 2003 (HA)	fMRI; Phasic Movements of Hand & Foot	IG	**Increased**
		Vaillancourt et al., 2003 (HA)	fMRI; Hand Force Production	IG	**Increased**
		Van Impe et al., 2009 (HOA)	fMRI; Hand and Foot Flexion	IG	**Decreased**
		Francois-Brosseau et al., 2009 (HA)	fMRI; Finger Button Press	IG & EG	**Increased**
		Jahanshahi et al., 1985 (HOA/PwPD)	PET; Finger Flexion	IG & EG	**Increased**
INS	*Insula*	Silfwerbrand et al., 2022 (HA)	fMRI; Finger Tapping	IG	**Increased**

		Sakata et al., 2017 (HA)	fMRI; hand grasping	IG	**Increased**
Thalamus	*N/A*	Dobkin et al., 2004 (HOA)	fMRI; Ankle Dorsiflexion	EG	**Increased**
		Cerasa et al., 2006 (PwPD/HOA)	fMRI; Rhythmic Tapping	IG & EG	**Increased**
		Sen et al., 2010 (PwPD/HOA)	fMRI; Finger Tapping	IG	**Increased**
		Debarae et al., 2003 (HA)	fMRI; Phasic Movements of Hand & Foot	EG	**Increased**
CB	*N/A*	Gowen et al., 2007 (HA)	fMRI; Drawing	EG	**Increased**
		Ogawa et al., 2006 (HA)	fMRI; Finger Tapping	EG	**Increased**
		Silfwerbrand et al., 2022 (HA)	fMRI; Finger Tapping	EG	**Increased**
		Jäncke et al., 2000 (HA)	fMRI: Paced Finger Tapping	IG & EG	**Increased**
		Horenstein et al., 2009 (HA)	fMRI; Finger Tapping	IG	**Increased**
		Drucker et al., 2019 (PwPD/HOA)	fMRI; Foot Tapping	IG	**Increased**
		Sauvage et al., 2013 (HOA)	fMRI; Hand Tapping	IG & EG	**Increased**
		Lewis et al., 2007 (PwPD/HA)	fMRI; Finger Tapping	IG	**Decreased** **(Baseline)** **Increased** **(Levodopa)**
		Trinastic et al., 2010 (HA)	fMRI; Ankle Dorsiflexion or Plantarflexion	EG	**Increased**
		Ciccarelli et al., 2005 (HOA)	fMRI; Ankle Dorsoplantar Flexion	IG	**Increased**
		Dobkin et al., 2004 (HOA)	fMRI; Ankle Dorsiflexion	EG	**Increased**

		Eckert et al., 2006 (PwPD/HOA)	fMRI; Hand Movements	IG	**Increased**
		Elsinger et al., 2006 (HA)	fMRI; Finger Key Presses	IG	**Increased**
		Schwingenschuh et al., 2013 (PwPD/HOA)	fMRI; Ankle Movements	EG	**Increased**
		Christensen et al., 2007 (HOA)	fMRI; Ankle Movements	IG and EG	**Increased**
		Kuper et al., 2012 (HA)	fMRI; Hand Tapping	IG	**Increased**
		Schlerf et al., 2010 (HA)	fMRI; Finger vs. Toe Flexion	IG and EG	**Increased**
		Salmi et al., 2010 (HA)	fMRI; Finger Button Press	EG	**Increased**
		Stoodley et al., 2012 (HA)	fMRI; Finger Tapping	EG	**Increased**
		Wiestler et al., 2011 (HA)	fMRI; Finger Button Press	EG	**Increased**
		Sen et al., 2010 (PwPD/HOA)	fMRI; Finger Tapping	IG	**Increased**
		Vaillancourt et al., 2007 (HA)	fMRI; Hand Force Production	EG	**Increased**
		Palmer et al., 2009 (PwPD/HOA)	fMRI; Hand Force Production	EG	**Increased**
		Debarae et al., 2003 (HA)	fMRI; Phasic Movements of Hand & Foot	IG	**Increased**
		Vaillancourt et al., 2003 (HA)	fMRI; Hand Force Production	EG	**Increased**
PCun	*N/A*	Sakata et al., 2017 (HA)	fMRI; Hand Grasping	IG	**Increased**
		Gowen et al., 2007 (HA)	fMRI; Drawing	IG	**Increased**

		Wai et al., 2020 (PwPD/HOA)	fMRI; Ankle Movements	IG	**Increased**
		Wenderoth et al., 2005 (HA)	fMRI; Unimanual & Bimanual movements	EG	**Increased**
IPL	*N/A*	Jäncke et al., 2000 (HA)	fMRI; Paced Finger Tapping	IG	**Increased**
		Wai et al., 2020 (PwPD/HOA)	fMRI; Ankle Movements	IG	**Increased**
		Cunningham et al., 2013 (HA)	fMRI; Foot & Finger Movement	EG	**Increased**
		Debarae et al., 2003 (HA)	fMRI; Phasic Movements of Hand & Foot	IG	**Increased**
DLPFC	*N/A*	Gowen et al., 2007 (HA)	fMRI; Drawing	IG	**Increased**
		Jahanshahi et al., 1985 (HOA/PwPD)	PET; Finger Flexion	IG & EG	**Increased**
DMPFC	*N/A*	Jäncke et al., 2000 (HA)	fMRI; Paced Finger Tapping	IG	**Increased**
	STG	Cerasa et al., 2006 (PwPD/HOA)	fMRI; Rhythmic Tapping	EG & IG	*Increased*
VLPFC	*IFG*	Cerasa et al., 2006 (PwPD/HOA)	fMRI; Rhythmic Tapping	EG & IG	*Increased*
VTC	Fusiform Gyrus	Gowen et al., 2007 (HA)	fMRI; Drawing	IG	**Increased**

Table 2: Literature Review of Internally and Externally Generated Movements. This table presents results from previously published literature that examines study tasks, their association with internally and externally generated movements, and whether these tasks led to an increase or decrease in functional connectivity. Column 1 shows the Broader Brain Region. Column 2 shows the specific subregion if specified in the study. Column 3 references the specific study with the population studied (PwPD = People with Parkinson's Disease; HA=Healthy Adults; HOA=Healthy Older Adults). The threshold chosen for the classification of a healthy older adult was an age greater than 55. The first group in the PwPD/HOA or HOA/PwPD within this column indicates which group experienced the increase or decrease in activation

within the brain region. Column 4 includes the scan type utilized as well as the task performed by the study participants. Column 5 indicates whether the study task and design are involved in internally or externally generated pathways. Column 6 indicates an increase or decrease in functional connectivity activity between either the broader brain region or specific subregion. Activity associated with the broader brain region is bolded while activity associated with the subregion is italicized. **Broader Brain Region Abbreviations:** M1, Primary Motor Cortex; PMC, Premotor Cortex; SMA, Supplementary Motor Cortex; STR, Striatum; INS, Insula; Di, Diencephalon, CB, Cerebellum; PCun, Precuneus; IPL, Inferior Parietal Lobe; DLPFC, Dorsolateral Prefrontal Cortex; DMPFC, Dorsomedial Prefrontal Cortex; VLPFC, Ventrolateral Prefrontal Cortex; VTC, Ventral Temporal Cortex. **Subregion Abbreviations:** PreCG, Precentral Gyrus; STG, Superior Temporal Gyrus; IFG, Inferior Frontal Gyrus.

Within this study, internally generated movements refer to those that do not require cues for an individual to produce a movement. Externally generated movements are those in which there is an external cue or signal prompting an individual to create a response (Ariani et al., 2015). In this study, tasks that were classified as IG movements include: non cued foot tapping, hand tapping, dorsoplantar flexion. EG movements include cued (via auditory or visual stimuli) foot tapping, hand tapping, tracing, paced finger tapping.

Independent Component Analysis

Based on the aforementioned identification of brain regions involved in IG and EG, we focused on these areas as our ROIs for the rest of the analysis. 27 of these brain regions appeared repeatedly in the IG and EG literature and were deemed as important brain regions involved in both movement pathways. These 27 regions were thus identified as the relevant ROIs to be included in further analyses. All selected papers in Table 2 included different activity peaks for their identified regions. As a result, this study needed to focus on brain components of these regions that would be as replicable as possible. For this purpose, we made use of the NeuroMark pipeline (Du et al., 2020). NeuroMark components represent well-established and reproducible brain networks, such as the auditory, sensorimotor and default mode network, among others. To follow this replicability, this study mapped our 27 pre-identified resting-state ROI to the brain regions derived from the NeuroMark pipeline (Du et al., 2020).

Following preprocessing, the resulting time courses were analyzed using the GIFT software package (Group ICA of fMRI Toolbox; Calhoun et al., 2001) to perform spatially constrained Independent Component (IC) Analysis. For each subject and each session, the ICA

procedure decomposed the fMRI time series into three primary outcome variables: Component Spatial Maps: Voxel-wise spatial representations of each independent component, reflecting the extent to which different regions contribute to a given network; Component Power Spectra: Frequency domain information for each independent component, characterizing the spectral power distribution of the associated time series; Between-Component Connectivity (Functional Network Connectivity, FNC): Temporal correlations between the time courses of independent components, providing insight into functional interactions between networks.

Broader Brain Region	**NeuroMark Subregion**	**NeuroMark IC ID**	**MNI Coordinate: X**	**MNI Coordinate: Y**	**MNI Coordinate: Z**
M1	ParaCL	IC 54	−18.5	−9.5	56.5
	ParaCL	IC 2	0.5	–22.5	65.5
	PreCG	IC 66	−42.5	−7.5	46.5
PMC	PoCG	IC 3	56.5	−4.5	28.5
		IC 72	−47.5	−27.5	−43.5
	R PoCG	IC 11	38.5	−19.5	55.5
	L PoCG	IC 9	−38.5	–22.5	56.5
SMA	SMA	IC 84	−6.5	13.5	64.5
STR	Caudate	IC 69	6.5	10.5	5.5
		IC 99	21.5	10.5	−3.5
	Putamen	IC 98	−26.5	1.5	−0.5

INS	Insula	IC 33	−30.5	22.5	−3.5
Di	Thalamus	IC 45	−12.5	−18.5	11.5
CB	CB	IC 4	20.5	−48.5	−40.5
		IC 7	30.5	−79.5	−40.5
		IC 13	−30.5	−63.5	−37.5
		IC 18	–32.5	-54.5	−37.5
PCun	Precuneus	IC 32	−8.5	−66.5	35.5
		IC 51	−0.5	−48.5	49.5
IPL	IPL	IC 68	45.5	−61.5	43.5
DLPFC	MiFG	IC 55	−41.5	19.5	26.5
		IC 88	30.5	41.5	28.5
DMPFC	SMFG	IC 43	−0.5	50.5	29.5
	STG	IC 21	62.5	−22.5	7.5
VLPFC	IFG	IC 67	39.5	44.5	−0.5
		IC 70	−48.5	34.5	−0.5
VTC	Fusiform Gyrus	IC 93	29.5	−42.5	−12.5

Table 3: Peak MNI Coordinates of Selected NeuroMark Independent Components. This table includes the 27 selected NeuroMark Components that correspond to the ROIs identified as being involved in IG and EG neural pathways. Column 1 shows the broader brain region each NeuroMark component is located within. Column 2 shows the name of each specific subregion corresponding to a NeuroMark component. Column 3 shows the index ID of the NeuroMark IC. Columns 4, 5, and 6 indicate the MNI X, Y, and Z peak coordinates for each specified NeuroMark component used in the analyses. **Broader Brain Region Abbreviations:** M1, Primary Motor Cortex; PMC, Premotor Cortex; SMA, Supplementary Motor Cortex;

STR, Striatum; INS, Insula; Di, Diencephalon, CB, Cerebellum; PCun, Precuneus; IPL, Inferior Parietal Lobe; DLPFC, Dorsolateral Prefrontal Cortex; DMPFC, Dorsomedial Prefrontal Cortex; VLPFC, Ventrolateral Prefrontal Cortex; VTC, Ventral Temporal Cortex. **NeuroMark Subregion Abbreviations:** ParaCL, Paracentral Lobule; PreCG, Precentral Gyrus; PoCG, Postcentral Gyrus; R PoCG, Right Postcentral Gyrus; L PoCG, Left Postcentral Gyrus; SMA, Supplementary Motor Area; CB, Cerebellum; IPL, Inferior Parietal Lobe; MiFG, Middle Frontal Gyrus; SMFG, Superior Medial Frontal Gyrus; STG, Superior Temporal Gyrus; IFG, Inferior Frontal Gyrus.

Statistical Analyses

All 27 ROIs were selected and subsequent pairwise comparisons were conducted. Derived spatial maps, power spectra, and functional network connectivity (FNC) matrices were entered into the MANCOVAN software package (Multivariate Analysis of Covariance) for group-level statistical analysis. The P-value threshold of significance for this study was selected as 0.05. To identify differences between all selected NeuroMark ICs, independent t-tests for all pairwise comparisons were conducted across each brain region.

Results

To comprehensively assess the relationships among all 27 selected NeuroMark ROIs, a total of 351 pairwise comparisons were conducted. These analyses aimed to examine all the differences in functional connectivity between pairs of brain regions. Our MANCOVAN findings report 55 significant pairwise comparisons of brain regions that were implicated to have a greater functional connectivity in either: PwPD > HOA or PwPD < HOA ($P<0.05$) *(Table 4, Figure 1, Figure 2, Supplementary Figure 1, Supplementary Figure 2).* Independent t-tests further confirmed the statistical significance of the functional connectivity differences by identifying the direction of the relationship, PwPD > HOA or PwPD < HOA (*Supplementary Figure 2)*. Across the selected ROIs, certain brain regions exhibited a disproportionately high number of functional connectivity associations with other selected ROIs. For example, as shown in Table 4, the different cerebellar ICs (IC 4, IC 7, IC 13, IC 18) collectively showed 20 significant connections, altogether, the precuneus (IC 32) showed 9 connections, and collectively, the PoCG showed 8 connections. Heatmaps and other color-coding data visualization methods utilized in this paper reflect the directionality of significant functional connectivity differences, distinguishing whether PwPD > HOA vs. PwPD < HOA *(Table 4, Figure 1, Figure 2, Supplementary Figure 2).*

Across these brain regions, there were several notable trends that emerged from our findings. For example, the postcentral gyrus (IC 3) was mostly implicated with an increase in functional connectivity in PwPD vs. HOA while, on the contrary, the left postcentral gyrus (IC 9) only showed an increase in functional connectivity in HOA vs. PwPD and the right postcentral gyrus (IC 11), depending on the connected brain region, showed both an increase and decrease in functional connectivity. Furthermore, certain brain regions exhibited limited connectivity with the selected ROIs, appearing to be linked to only a single other region, including the superior medial frontal gyrus (IC 43) which has greater functional connectivity in HOA vs. PwPD. In addition, the precuneus (IC 51), paracentral lobule (IC 54), middle frontal gyrus (IC 55), inferior frontal gyrus (IC 67), inferior parietal lobe (IC 68), caudate (IC 69), postcentral gyrus (IC 72) were also connected with one additional brain region and show an increase in functional connectivity in PwPD compared to HOA. Two of the four cerebellar ICs, IC 13 and IC 18, displayed extensive functional connectivity with other selected ROIs. Across these brain regions, they exhibited an even distribution with the number of brain regions involved in an increase or decrease in functional connectivity with PwPD vs. HOA. Furthermore, the superior temporal gyrus (IC 21) was mostly implicated with brain regions that led to an increase in functional connectivity in PwPD vs. HOA.

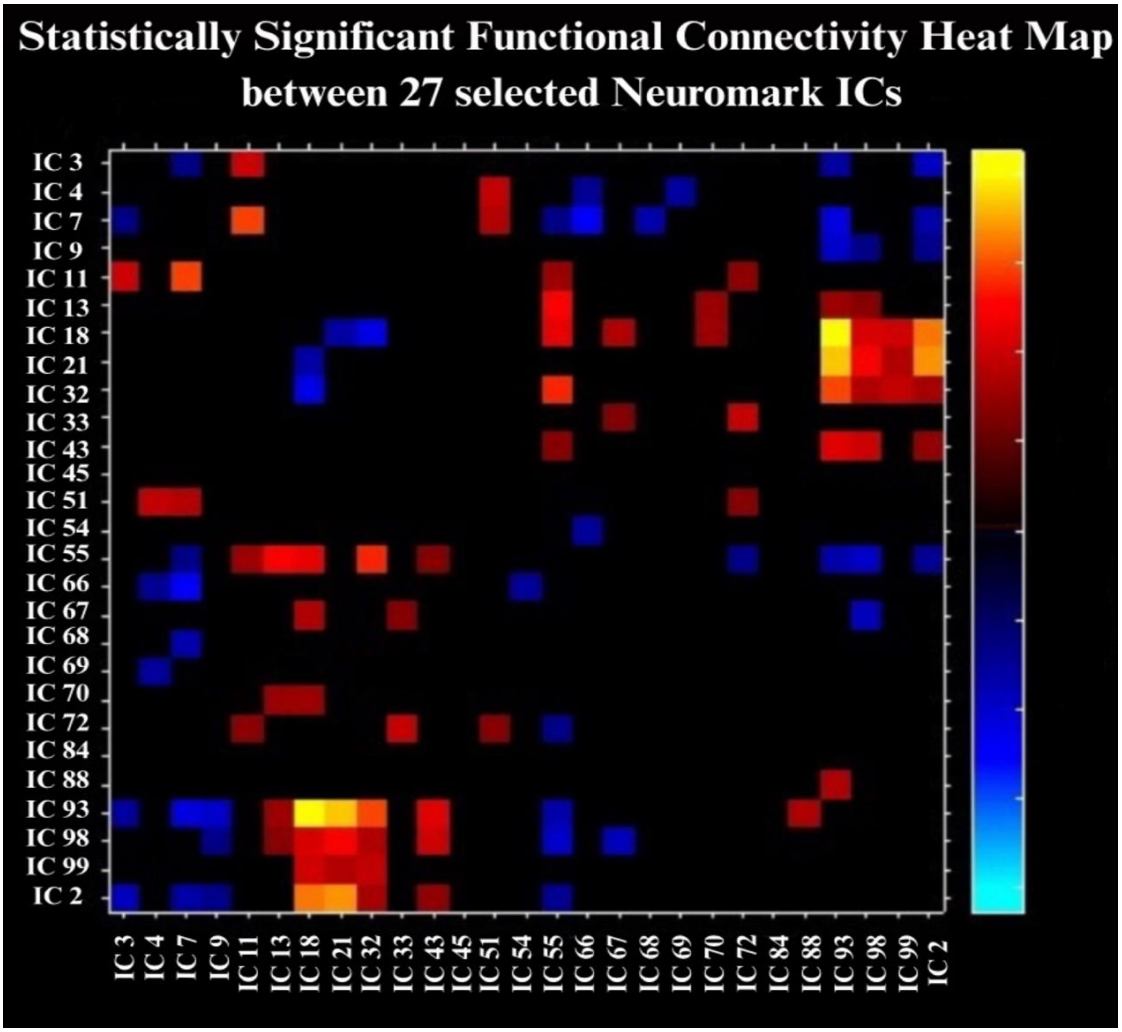

Figure 1: Statistically Significant Functional Connectivity Heat Map between 27 selected NeuroMark ICs. This figure is a 27x27 heat map representing the 55 statistically significant functional connections found between brain regions. The axes represent the index ID of the selected NeuroMark IC. Each comparison is associated with a colored grid/square on the heat map. Light blue indicates a decrease in functional connectivity in PwPD vs. HOA. As the color gradient increases, yellow colors indicate an increase in functional connectivity in PwPD vs. HOA. **IC Brain Region Key:** IC 3, Postcentral gyrus; IC 4, Cerebellum; IC 7, Cerebellum; IC 9, Left postcentral gyrus; IC 11, Right postcentral gyrus; IC 13, Cerebellum; IC 18, Cerebellum; IC 21, Superior temporal gyrus; IC 32, Precuneus; IC 33, Insula; IC 43, Superior medial frontal gyrus; IC 45, Thalamus; IC 51, Precuneus; IC 54, Paracentral lobule; IC 55, Middle frontal gyrus; IC 66, Precentral gyrus; IC 67, Inferior frontal gyrus; IC 68, Inferior parietal lobule; IC 69, Caudate; IC 70, Inferior frontal gyrus; IC 72, Postcentral gyrus; IC 84, Supplementary motor area; IC 88, Middle frontal gyrus; IC 93, Fusiform Gyrus; IC 98, Putamen; IC 99, Caudate; IC 2, Paracentral lobule.

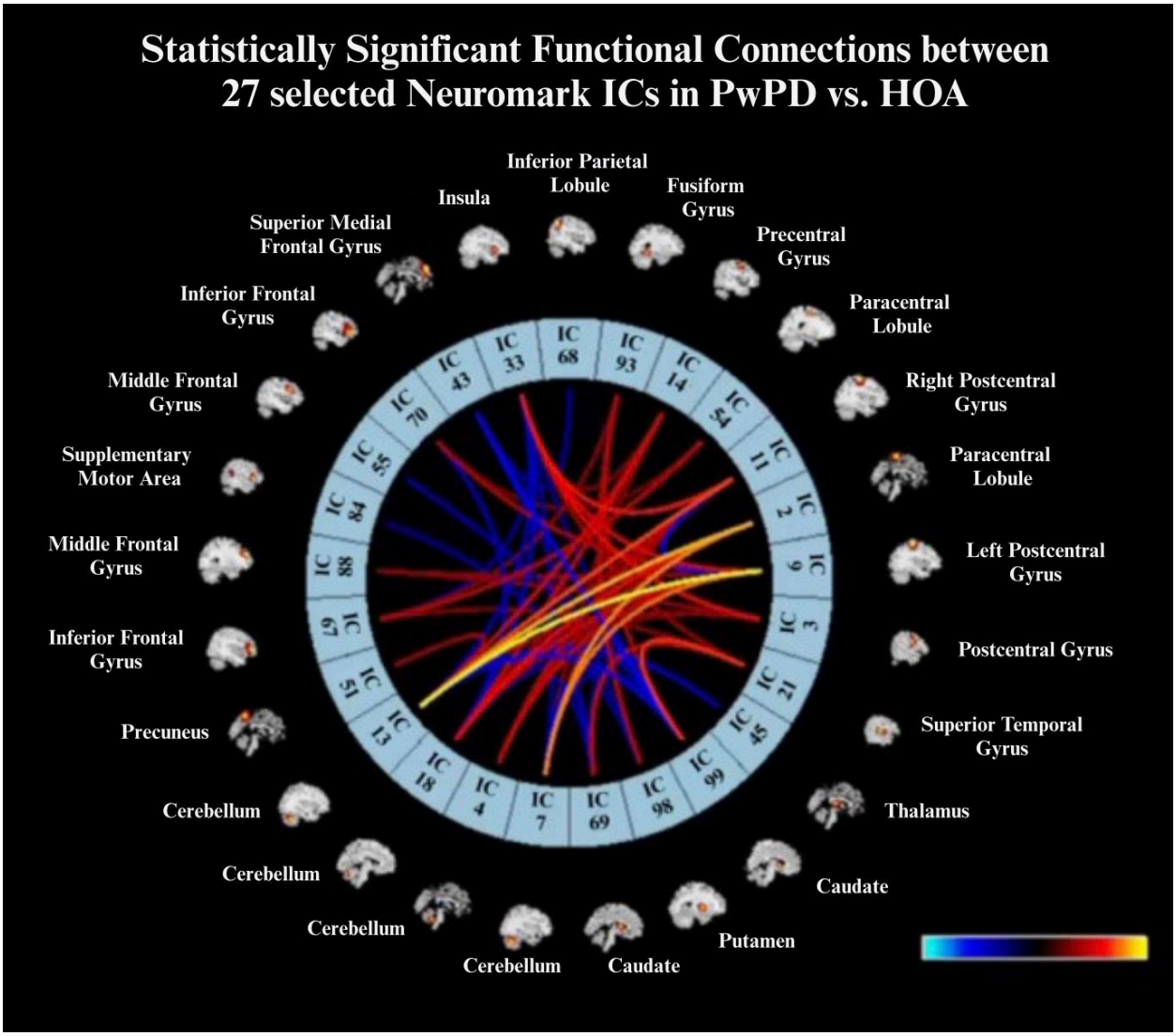

Figure 2: Statistically Significant Functional Connections between 27 Selected NeuroMark ICs in PwPD vs. HOA. This figure is a connectogram that indicates a statistically significant increase or decrease in functional connectivity between selected brain ROIs via a colored line. Each selected ROI is represented by its NeuroMark index ID. Between 2 ROIs, a light blue line indicates a decrease in functional connectivity in PwPD vs. HOA. As the color gradient increases, yellow lines indicate an increase in functional connectivity in PwPD vs. HOA.

Pairwise Comparisons between IC 3: PoCG and other ROIs

IC ID	IC NeuroMark Region	P-value
IC 7	CB	0.05
IC 9	Left PoCG	0.01
IC 33	Insula	0.01
IC 69	Caudate	0.03
IC 93	Fusiform Gyrus	0.05

Pairwise Comparisons between IC 4: CB and other ROIs

IC ID	IC NeuroMark Region	P-value
IC 21	STG	0.03
IC 68	IPL	0.03

Pairwise Comparisons between IC 7: CB and other ROIs

IC ID	IC NeuroMark Region	P-value
IC 66	PreCG	0.05
IC 68	IPL	0.05
IC 98	Putamen	0.04

Pairwise Comparisons between IC 9: L PoCG and other ROIs

IC ID	IC NeuroMark Region	P-value
IC 33	Insula	0.04
IC 55	MiFG	0.01
IC 99	Caudate	0.01

Pairwise Comparisons between IC 11: R PoCG and other ROIs

IC ID	IC NeuroMark Region	P-value
IC 21	STG	0.01
IC 55	MiFG	0.04
IC 69	Caudate	0.00
IC 72	PoCG	0.00

Pairwise Comparisons between IC 13: CB and other ROIs

IC ID	IC NeuroMark Region	P-value
IC 45	Thalamus	0.02
IC 51	Precuneus	0.01
IC 68	IPL	0.02
IC 69	Caudate	0.01

IC 70	IFG	0.00
IC 72	PoCG	0.02
IC 98	Putamen	0.02

Pairwise Comparisons between IC 18: CB and other ROIs

IC ID	IC NeuroMark Region	P-value
IC 33	Insula	0.03
IC 55	MiFG	0.04
IC 68	IPL	0.01
IC 69	Caudate	0.01
IC 70	IFG	0.00
IC 72	PoCG	0.01
IC 98	Putamen	0.01

Pairwise Comparisons between IC 21: STG and other ROIs

IC ID	IC NeuroMark Region	P-value
IC 43	SMFG	0.00
IC 45	Thalamus	0.04
IC 69	Caudate	0.00
IC 70	IFG	0.02
IC 72	PoCG	0.02

Pairwise Comparisons between IC 32: Precuneus and other ROIs

IC ID	IC NeuroMark Region	P-value
IC 45	Thalamus	0.00
IC 51	Precuneus	0.02
IC 66	PreCG	0.04
IC 67	IFG	0.00
IC 70	IFG	0.00
IC 84	SMA	0.04
IC 93	Fusiform Gyrus	0.03
IC 98	Putamen	0.03

Pairwise Comparison between IC 43: SMFG and other ROIs

IC ID	IC NeuroMark Region	P-value
IC 45	Thalamus	0.02

Pairwise Comparison between IC 51: Precuneus and other ROIs

IC ID	IC NeuroMark Region	P-value

IC 68	IPL	0.01

Pairwise Comparison between IC 54: ParaCL and other ROIs

IC ID	IC NeuroMark Region	P-value
IC 67	IFG	0.03

Pairwise Comparisons between IC 55: MiFG and other ROIs

IC ID	IC NeuroMark Region	P-value
IC 68	IPL	0.02
IC 70	IFG	0.00
IC 72	PoCG	0.05

Pairwise Comparison between IC 67: IFG and other ROIs

IC ID	IC NeuroMark Region	P-value
IC 2	ParaCL	0.02

Pairwise Comparison between IC 68: IPL and other ROIs

IC ID	IC NeuroMark Region	P-value
IC 84	SMA	0.01

Pairwise Comparisons between IC 69: Caudate and other ROIs

IC ID	IC NeuroMark Region	P-value
IC 72	PoCG	0.01
IC 84	SMA	0.01

Pairwise Comparison between IC 72: PoCG and other ROIs

IC ID	IC NeuroMark Region	P-value
IC 84	SMA	0.04

Table 4: P-values of Significant Pairwise Comparisons between 27 selected NeuroMark Independent Components. This table includes the significant P-values obtained by conducting pairwise comparisons between the 27 selected NeuroMark Components. 55 significant P-values were obtained. Column 1 contains the IC ID. Column 2 indicates the name of each NeuroMark Brain Region represented by the IC. Column 3 shows the significant P-value in either yellow or blue. A yellow highlight indicates an increase in functional connectivity in PwPD vs. HOA. A blue highlight indicates a decrease in functional connectivity in PwPD vs. HOA and an increase in functional connectivity in HOA vs. PwPD. **IC NeuroMark Region Abbreviations:** CB, Cerebellum; PoCG, Postcentral Gyrus; L PoCG, Left Postcentral Gyrus; STG, Superior Temporal Gyrus; IPL, Inferior Parietal Lobe; PreCG, Precentral Gyrus; MiFG, Middle Frontal

Gyrus; R PoCG, Right Postcentral Gyrus; IFG, Inferior Frontal Gyrus; SMFG, Superior Medial Frontal Gyrus; SMA, Supplementary Motor Area; ParaCL, Paracentral Lobule.

Discussion

In this study, we aimed to understand the brain regions associated with a greater or less effect in functional connectivity in PwPD vs. HOA. The findings from this analysis report 55 significant functional connectivity differences across the 27 selected NeuroMark ICs.

Across the selected ROIs, some brain regions exhibited a high number of functional connectivity associations with other selected ROIs, including the different cerebellar ICs (IC 4, IC 7, IC 13, IC 18), the precuneus (IC 32), and the Post Central Gyrus (IC 3). Our comprehensive literature review *(Table 2)* allows for nuanced interpretations of these results. The cerebellum shows increased BOLD in both IG and EG movements in HA (Jäncke et al., 2000, Sauvage et al., 2013, Christensen et al., 2007, Schlerf et al., 2010), though it is more strongly involved in IG movements in PwPD (Drucker et al., 2019, Lewis et al., 2007, Eckert et al., 2006, Schwingenschuh et al., 2013, Sen et al., 2010), with only one study showing increased activity in EG movements (Palmer et al., 2009). Importantly, one of the ICs that showed an increased connectivity in PwPD was with the PoCG, a brain region showing increased activation in both IG and EG in HA, but a preferential increase only in IG in PwPD (Eckert et al., 2006, Sen et al., 2010, Vercruysse et al., 2014, Lewis et al., 2007). These results suggest that the increased functional connectivity observed between the different cerebellar components and postcentral gyrus, in PwPD, may point towards a compensatory mechanism specifically regarding IG movements. Given that IG movements are typically more impaired in PwPD due to dysfunction of circuits involving the basal ganglia, the increased connectivity between the cerebellum and the postcentral gyrus could indicate that these brain regions are being co-activated to supplement motor processes that are typically controlled by basal ganglia-centered circuits (Blandini et al., 2000). The cerebellum, a brain region that plays a key role in regulating motor coordination, error correction and balance, we hypothesize will be supplementing the basal ganglia by providing additional sensorimotor integration to execute movements. (Fang et al., 2017, Caligiore et al., 2016, Lewis et al., 2013, Wu & Hallett, 2013). Similarly, the postcentral gyrus, home to the sensorimotor cortex, we hypothesize will also be involved in sensory processing and sensorimotor integration, for IG movements in PwPD. However, previous literature is limited in understanding this relationship of the compensatory mechanism

of the postcentral gyrus. Additionally, many of the previous studies *(Table 2)* reporting PoCG activation in IG/EG movement used tasks that correspond to specific muscle movements, specifically hand and leg movements. The specific NeuroMark ICs that we used to assay PoCG connectivity in our study largely matches the PoCG activation area reported for both upper limb and hand movements in other studies in HA (Meier et al., 2008, Yousry et al., 1997, Lotze et al., 2000). Thus, this increased connectivity between the cerebellum and PoCG in PwPD relative to that seen in HOA might differentially underlie these regions' involvement in specific types of movements (IG) and/or specific types of muscles (hand and leg movements).

Furthermore, the precuneus (IC 32), which our study highlights for its numerous significant functional connectivity associations, has also been identified in previous studies as playing a crucial role in various types of movement *(Table 2)*. Specifically, activation in the precuneus increases in both IG and EG movements in HA, but only in IG movements in PwPD (Sakata et al., 2017, Gowen et al., 2007, Gordon et al., 2023, Wenderoth et al., 2005). In our study, it specifically showed increased connectivity with key regions of the motor pathways, such as the PreCG in M1 and the thalamus. Both these regions are involved in both IG and EG movements in HA, but PwPD seem to rely more on their increased activity in IG movements (Cerasa et al., 2006, Sen et al., 2010). The ROI of the PreCG we tested in this study falls under the broader brain area of the M1 which have independently been shown to control hand and laryngeal movements (Simonyan & Jürgens, 2016, Eichert et al., 2020, Lotze et al., 2000), so our results could point to different control of these specific muscles, although we acknowledge the variation of the motor topography across individuals. These results also indicate a possible compensatory mechanism of the PreCG, potentially more focused on IG movements in PwPD.

As previously mentioned, many chosen brain ROIs have been involved in research published by numerous other studies *(Supplementary Table 1)*. Although this research does not refer to the NeuroMark ICs as included throughout this paper, the body of literature included in Supplementary Table 1 showcases additional resting-state fMRI studies between PwPD and HOA and the results obtained for an increase or decrease in functional connectivity between selected ROIs. For example, the cerebellum, a brain region that is heavily implicated in PD functional connectivity, was shown to have greater connectivity in PwPD vs. HOA in resting-state fMRI studies (Kaut et al., 2020, Wu et al., 2009, Fang et al., 2017, Hacker et al., 2012). In addition, the precuneus also demonstrated an increase in functional connectivity in PwPD vs.

HOA (de Schipper et al., 2018) while the postcentral gyrus showed a decrease in functional connectivity in PwPD vs. HOA (Tuovinen et al., 2018).

In addition, the findings from this study are obtained from resting-state fMRI scans. However, the comparisons made to internally and externally generated movement pathways are derived from literature in which participants and controls were asked to perform certain tasks. Therefore, the results from this study can be understood and extrapolated with the understanding that these results provide a comprehensive view of the functional connections present, at rest, in PwPD and HOA. While these results focus on the baseline, resting-state functional connectivity, they also offer valuable context for interpreting how brain networks may respond during active motor tasks. By linking resting-state findings with existing task-based studies, we gain deeper insights into the functional alterations that may underlie movement disorders and how these changes manifest during motor activity.

Furthermore, we hypothesize that the increase in functional connectivity across ROIs including the cerebellum, postcentral gyrus, and precuneus could serve as brain regions involved in compensatory mechanisms in PD. As aforementioned, tremors are a cardinal sign of PD (Bereczki et al., 2010). The generation of tremors in PwPD involves the cerebello-thalamo-cortical circuit, which becomes engaged following activity in the basal ganglia. Altered functional connectivity in the cerebellum has been observed in PwPD, highlighting its role in compensatory adjustments (Helmich et al., 2013). In addition, the postcentral gyrus also exhibits alerted connectivity in PwPD. With its primary purpose to process and integrate sensory information, functional connectivity between the primary motor cortex and postcentral gyrus is decreased in PwPD negatively impacting motor control and contributing to major symptoms such as balance and tremors (Wu et al., 2011). Additionally, the precuneus plays a major role in the development of PD symptoms such as memory loss and an impaired ability to plan and coordinate motor movements. Dopaminergic treatment has been shown to enhance activation in the precuneus, implying its involvement in compensatory mechanisms for motor dysfunctions in PwPD (Nagano-Saito et al., 2014). Collectively, these three brain ROIs coordinate to mitigate the effects of PD on balance and tremor. The complexity of PD underscores the intricacies involved in the compensatory strategies employed to preserve motor function in neurodegeneration.

Furthermore, the findings from this study can inform the design of targeted interventions for alleviating PD symptoms. Our results indicate that IG movement pathways are typically more

impaired in PwPD. Therefore, therapies that rely more heavily on EG movement pathways, such as tango interventions, rhythmic cueing, and tai chi can be implemented to compensate for these impairments (McKee & Hackney, 2013, Ghai et al., 2018, Deuel & Seeberger et al., 2020). For example, studies have shown that Argentine tango interventions are improve mobility, gait speed, and motor-cognitive function in PwPD compared to control groups that did not receive tango-based interventions (Hackney et al., 2015). These findings highlight the potential of movement-based therapies to reduce the impairments caused by PD and increase overall quality of life.

Anthropological Implications

By examining brain regions involved in internally (IG) and externally generated movements (EG) in PwPD and HOA, this study suggests a broad scope of anthropological implications. Medical anthropology is a subfield of anthropology that studies how health, illness, and medical treatments intersect within the context of cultural, social, and biological factors (Brown & Closser 2016). From this perspective, therein lies a difference between the social stigmas and subsequent methods by which PwPD and HOA are treated within their societies. For example, in a systematic review conducted by Karacan et al in 2023, researchers investigated the stigma associated with a wide range of PD symptoms across the world. Results found that in the US, there was no significant link between the PD symptoms of tremors and postural instability and stigma. In Asia, there was a positive association between stigma and UPDRS-II (daily life activities) scores in females. Studies from Spain and Croatia found a positive association between UPDRS-III (motor symptoms) scores and stigma while there was no significant relationship in studies from the USA and Brazil. Due to these stigmas, individuals in societies may experience differential access to care, emotional and psychological stressors, social isolation, etc., that demonstrates the impact of cultural perceptions and societal norms on the treatment of illness (Dahodwala et al., 2009). The functional connectivity differences implicated in this study suggest that internally and externally generated movement pathways engage distinct brain ROIs. With the notion that stigma can shape an individual's social determinants of health and access to healthcare, understanding the neural basis of movement provides insight into why distinct rehabilitative strategies utilized around the world may be more effective for PwPD within certain cultural contexts. For example, in societies where external cues such as therapies or utilizing assistive devices are more socially accepted, PwPD may experience greater success

with participating in externally driven rehabilitation techniques. Conversely, in environments where self-directed movement is encouraged and non-stigmatized, rehabilitative interventions targeting IG pathways would prove more effective. Overall, this highlights the need for catering treatment for PwPD to be culturally sensitive and holistic, accounting for all personal and societal factors.

Biological anthropology is a subfield of anthropology that delves into the biological mechanisms that drive the evolution and origin of humans and non-human primates (Banwell et al, 2013). Our findings to understand the brain regions involved in IG and EG movement pathways between PwPD vs. HOA ties into biological anthropology by highlighting the intersection of PD, neural function, and population genetics. Across the world, different populations show genetic variations in Parkinson's risk factors such as mutations in the LRKK2 and GBA genes, which are more pronounced in certain ethnic groups (Smith et al., 2022). For example, LRRK2 mutations are seen to be more prevalent in shkenazi Jewish and North African Berber populations resulting in an increased risk in developing PD (Kmiecik et al., 2024). Developing an understanding of how brain function varies across different genetic backgrounds can shed light on why certain populations may confer higher or lower prevalence of movement impairments. Additionally, this perspective raises questions about the broader significance of movement control in humans. If PwPD individuals rely more on external cues, this could suggest an adaptive shift toward a more socially driven movement strategy rather than one based on internal motor planning. Understanding the balance between internally and externally generated movements can provide insights into the evolution of human motor and social control. Overall, this study has the potential to influence Parkinson's Disease research along with the mannerisms by which communities approach aging, disability, and rehabilitation in numerous cultural contexts.

Limitations

This study has several potential limitations. The interpretation/hypothesis framework adopted for this study is based on previous literature *(Supplementary Table 1)* identifying specific brain regions associated with internally generated, externally generated, or both movement pathways. Consequently, this study focuses on predefined ROIs rather than conducting a whole-brain analysis. As a result, these findings are limited to the functional connectivity patterns observed within the selected NeuroMark ICs and might not encompass all

possible brain regions involved in IG, EG, or combined movement pathways. Although the use of the NeuroMark components itself has important strengths, such as offering a standardized and replicable approach to identifying ICs across studies, the predefined components might not fully capture all relevant dynamics related to EG and IG movement. In addition, previous literature suggests that brain regions do not fall exclusively within a single movement pathway – IG or EG only. Instead, the movement pathways involved are highly dependent on the specific task being performed by participants, with some regions contributing to both IG and EG movements. This variability serves as another limitation as this study's framework relies on categorizations that might not fully capture the complexity of the relationship between brain regions and IG/EG movement pathways. Since this study's approach expands upon prior research, the findings are inherently heavily influenced by the validity, rigor, and methodology used in those studies. Any inconsistencies or limitations in this previous work could impact the conclusions drawn in this study. Although our approach might not have been able to holistically represent all connectivity patterns, we are confident that those identified reflect real connectivity differences between PwPD and HOA in brain regions involved in EG and IG pathways.

Conclusion

Overall, our study reports several brain regions with distinct functional connectivity patterns indicating either an increase or decrease in functional connectivity in PwPD vs. HOA when associated with internally and externally generated movement pathways. We find that the cerebellum, postcentral gyrus, and the precuneus are heavily involved in IG movement pathways in PwPD. These findings can inform future intervention-based treatment plans for PwPD.

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