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Hippocampal Connectivity in Parkinson's Disease

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HIPPOCAMPAL CONNECTIVITY IN PARKINSON'S DISEASE

by
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This thesis is dedicated to every individual who has suffered from Parkinson's disease. My hope is that more research will allow us to better understand this disease and find a cure.

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ABSTRACT

LANDIS LLEWELYN: Hippocampal Connectivity in Parkinson's Disease
(Under the guidance of Dr. Tossi Ikuta)

BACKGROUND: This thesis was conducted in order to investigate possible connections between functional connectivity of the hippocampus in individuals who have Parkinson's disease.

METHODS: The MRI images, the clinical data, and the demographic data of 93 individuals with PD and 18 individuals without PD were obtained from the Parkinson's Progression Markers Initiative. Resting state fMRI data from a group of PD patients was compared to a control group of non-PD patients by using previously published methods with FMRIB Software Library (FSL) as well as Analysis of Functional Neuroimages (AFNI).

RESULTS: Compared to the control (non-PD) group, results bilaterally showed lesser connectivity between the paracingulate gyrus (PCG) and hippocampi in the PD group.

CONCLUSIONS: Results suggest a decline of dopaminergic innervation decreases synchrony of the hippocampi and paracingulate gyri (PCG). It is inferred that PD patients who also experience dementia may have a more severe loss of connectivity because of the underlying dopaminergic deficits that cause the onset of dementia.

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LIST OF ABBREVIATIONS

AC	anterior cingulate
AFNI	Analysis of Functional Neuroimages
CA	cornu Ammonis
CG	cingulate gyrus
CS	cingulate sulcus
CS	conditioned stimuli
CSF	cerebrospinal fluid
CT	cortical thickness
EPI	echo planar image
FC	functional connectivity
fMRI	functional Magnetic Resonance Imaging
FSL	FMRIB Software Library
FWHM	full width at half maximum
HATA	hippocampal-amygdaloid transition region
LPT	long-term potentiation
MD	mean diffusivity
MNI	Montreal Neurological Institute
MRI	Magnetic Resonance Imaging
PD	Parkinson's disease
PCG	paracingulate gyrus
PCS	paracingulate sulcus
RLS	restless legs syndrome
rs-FMRI	resting state Functional Magnetic Resonance Imaging
TE	echo time
TR	repetition time
US	unconditioned stimuli

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Introduction

Parkinson's Disease

Parkinson's disease (PD) is a neurological disorder that extensively affects the nervous system, including a variety of neurotransmitters and protein aggregates such as Lewy bodies (Kalia & Lang, 2015). The exact cause of PD is not clearly known at this time, but it is understood that it results from a combination of environmental and genetic factors affecting the body's cellular processes (Kalia & Lang, 2015). This uncertainty makes early diagnosis of the disease extremely hard, and unfortunately, there is not currently a definitive test for diagnosis of PD (Jankovic, 2008). Additionally, not all PD patients experience the same severity of the disease. Therefore, doctors must rely on clinical criteria including the following key symptoms:

Bradykinesia.

Bradykinesia refers to slow movement and is the most common symptom of PD. Because bradykinesia is directly related to the basal ganglia of the brain, it often causes difficulty with planning, initiating, and performing tasks (Jankovic, 2008). This sign is commonly first noted in patients having difficulty with fine motor tasks such as buttoning a shirt or eating with a utensil. The severity can progress quickly and even cause difficulty in swallowing, motor speech disorders, or even complete loss of facial expression (Jankovic, 2008).

Tremor

Resting tremor is another common characteristic and easily noticeable symptom of PD. These tremors usually occur unilaterally and are most commonly seen at the distal end of the extremity. They can also occur in places other than extremities such as the lips, chin, and jaw, which is most commonly noted in patients older than 70 (Lees, Hardy, & Revesz, 2009). According to Jankovic (2008), this type of tremor may disappear during sleep or extreme activity. Postural tremor may also occur alongside rest tremor. This type of tremor is often the most disabling and can also be the first symptom in some PD patients (Jankovic, 2008). Jankovic's (2008) study on tremors showed that more than half of PD patients have rest tremor at the onset of the disease.

Postural deformities and Instability

Rigidity may accompany a tremor and cause PD patients to have decreased range of motion. As the disease progresses, this can cause postural deformities such as poor posture, scoliosis, and flexed neck and extremities (Jankovic, 2008). According to Lees, Hardy, and Revesz (2009), catalepsy or fixed posturing of a hand may be present after motor activities. Additionally, postural instability may occur as a result of loss of reflexes. This can ultimately cause patients with PD to be more at risk from falls and hip fractures. There are several treatment options to aid with symptoms of postural instability, but

unfortunately, there is no definitive cure. Examples of treatment approaches include deep brain stimulation, pallidotomy, and dopaminergic therapy. (Jankovic, 2008).

Freezing

Freezing (motor blocks) is a type of akinesia, or loss of movement, and can also be very disabling (Jankovic, 2008). However, it is not as prominent across all PD patients and is typically reported at later stages of the disease. Jankovic's (2008) study showed that only 47% of PD patients surveyed recorded freezing as a symptom. In addition, it is more commonly seen in men than in women. An interesting concept about freezing is that there are five different subtypes — start hesitation, turn hesitation, tight quarters hesitation, open space hesitation, and destination hesitation (Jankovic, 2008). After the PD patient experiences one of these motor blocks, they most often move in a continuous shuffle to recover from the attack (Lees, Hardy, & Revesz, 2009). Over time and with the help of therapy, patients with PD who suffer from freezing may develop techniques to overcome these attacks (Jankovic, 2008).

PD is most commonly recognized by the motor deficits it causes, but these are not the only symptoms or characteristics of this disease. In fact, some individuals with PD have cognitive dysfunction or severe cognitive deficits that can also lead to the development of dementia. According to Murat (2003)'s article, about 40% of patients

with PD also suffer from dementia. The type of dementia seen in individuals with PD is associated with neurochemical deficits including loss of innervation in the cholinergic, dopaminergic, and noradrenergic systems (Murat, 2003). There is unfortunately not a treatment to slow down the degenerative process PD causes, and there is not much that doctors can do for management of these symptoms as the disease progresses (Kalia & Lang, 2015).

Hippocampus: Basic Anatomy

The hippocampus is a structure located deep within the medial portion of the temporal lobe. When dissected, the structure resembles a seahorse, which ultimately is what inspired the name hippocampus (Knierim, 2015). The hippocampus is considered to be a part of the limbic system, the part of the brain that deals with emotions and memory. It can also be referred to as the inferior intralimbic gyrus because it is situated within the limbic lobe and is bordered by the fimbria (Duvernoy, 2005). Additionally, the hippocampus can be divided into three different parts — "the precommissural hippocampus (prehippocampal rudiment), the supracommissural hippocampus (indusium griseum), and the retrocommissural hippocampus (the hippocampus proper)" (Duvernoy, 2005, p. 5).

In humans, the hippocampus is aligned with the progress of the lateral telencephalic vesicle, which contributes to the structure of the temporal lobe (Duvernoy, 2005). In other mammals, this structure often does not reach full development, causing

the hippocampus to be situated dorsal to the thalamus. However, in humans, this is not the case, and the hippocampus curves inferior to the thalamus (Duvernoy, 2005).

The basic structure of the hippocampus is bilaminar, meaning there are two different sections of lamina — the hippocampus proper (cornu Ammonis) and fascia denata (gyrus dentatus) (Duvernoy, 2005). This unique structure starts out as two continuous laminae but evolves during development to become two independent laminae that interlock and are separated by the hippocampal sulcus (Duvernoy, 2005). Then, the subiculum extends out of the hippocampus body, which ultimately becomes part of the parahippocampal gyrus (Duvernoy, 2005). The hippocampus proper (cornu Ammonis or CA) can then be further broken down into three main subregions — CA1, CA2, and CA3 (Dutta, 2019). Together, these subregions form a structure called the trilaminar loop, which functions as the long-term memory processing center (Dutta, 2019).

Hippocampus: Functions

Learning and Memory

The hippocampus is the part of the brain responsible for the development and storage of both short-term and long-term memory. A key component in this process is long-term potentiation (LPT), which is a type of neural plasticity involved in memory storage (Dutta, 2019). The process occurs by the utilization of two pathways to collect potential memories from the frontal lobe —

polysynaptic and direct pathways. The direct pathway is straightforward and plays a vital role in episodic memory and spatial recognition (Dutta, 2019).

As for the polysynaptic pathway, the "hippocampus receives afferent inputs via axons of the entorhinal cortex, which terminate in the dentate gyrus" (Dutta, 2019). Neurons located in the dentate gyrus then communicate with pyramidal cells in CA3 through a type of axon called mossy fibers. The neurons of the pyramidal cells are then split into two different branches (Dutta, 2019). One branch crosses to the other side of the hippocampus through the corpus callosum that separates the right and left hemispheres of the brain, and the other branch travels to CA1 via another pathway system and ultimately exits the hippocampus and returns to structures in the temporal and frontal lobes (Dutta, 2019).

The pyramidal cells in the hippocampus also play an important role in learning. The standard model is called classical eye blink conditioning in learning studies. According to Dutta (2019), "studies involving delay eye blink conditioning have revealed that pyramidal cells form a predictive paradigm of time-amplitude sequence of the learned behavioral response." Another important concept in the science behind learning is trace conditioning. This is a type of classical conditioning in which there is a short interval between the presentation of the conditioned stimuli (CS) and unconditioned stimuli (US). This causes a

neuronal plasticity to be formed in the hippocampus, which marks the beginning of the learning process (Dutta, 2019).

Spatial Navigation

The hippocampus is also involved in forming a cognitive map, "a type of mental representation related to acquisition, coding, storing, recalling, and decoding of information on relative locations within a specific environment" (Dutta, 2019). This map is formed by a type of pyramidal cell called a place cell. Activation of these place cells occurs when the person enters a place field (Dutta, 2019). This essentially means that the hippocampus is needed in order to remember the location of objects when there is a shift in location or view point (Shrager, et al., 2007). According to Brown and Chrastil's (2019) study, results indicated "a shift in the network dynamics surrounding the hippocampus as encoding demands change, reconfiguring from global integration to localized processing based on the degree of integration of environmental information." This finding ultimately confirmed that the hippocampus plays a very dynamic role in spatial memory and that "modulation after one-shot learning depends on the fidelity of prior spatial knowledge of the environment" (Brown & Chrastil, 2019).

Attention Control

Attention control is another function that the hippocampus is involved in. This function is strongly related to the functions of learning and memory because how our attention is directed plays can important role into what we eventually encode into our memory (Aly & Turk-Browne, 2017). According to Aly and Turk-Browne's (2017) study, memories produced by the hippocampus have an impact on attention gaze and eye movement. The study focused on two different types of attention — divided attention and selective attention. First, they found that "divided attention at encoding impairs memory… [and that it] does interfere with memory retrieval when the concurrent task depends on the same representations" (Aly & Turk-Browne, 2017, p. 371). Unfortunately, there has been very little research about selective attention and its relation to the formation of hippocampal memories, but researchers did find that selective attention plays an important role in what information is encoded into memory (Aly & Turk-Browne, 2017).

Lastly, an interesting fact about the study was that the methods in which research was conducted in Aly and Turk-Browne's (2017) study differed between divided and selective attention. For instance, divided attention studies includes concurrently splitting the attention between a memory task and a secondary task that is unrelated (Aly & Turk-Browne, 2017). In contrast, selective attention

research was comprised of using attention in order to choose a stimulus to use for further processing and research (Aly & Turke-Brown, 2017).

Found Relationships Between the Hippocampus and Parkinson's Disease

Memory Deficits

There have been several studies conducted that have shown there to be a connection between memory deficits associated with the hippocampus and PD. For instance, in Carlesimo, et al.'s (2012) case-control study, they used MRIs to investigate "whether the performance scores of a group of patients with Parkinson's disease (PD) without dementia on tests of declarative memory could be predicted by hippocampal volume reduction…or by the rate of microstructural alterations." They first began by taking scans of the participants' brains with both diffusion tensor and T-1 weighted imaging and also conducted neuropsychological assessments (Carlesimo, et al., 2012). They concluded that there were increased memory deficits in the hippocampus of patients with PD compared to those without PD and that there was not a visible difference in hippocampal structure. Additionally, they found that the PD patients with the greatest memory deficits also had the lowest memory scores from the neuropsychological evaluation. These results ultimately confirmed their hypothesis that "the declarative memory impairment in patients with PD without

dementia may be predicted by the rate of microstructural alterations in the hippocampal formation" (Carlesimo, et al., 2012).

Foo, et al.'s (2017) study sought to examine how the pathophysiology of cognitive impairments in PD patients are affected by hippocampal atrophy. They looked at how the cognitive progression related to hippocampal subfields atrophy and classified the participants according to whether or not they exhibited a cognitive impairment. The results showed that patients who had a cognitive impairment exhibited both lower global cognition scores and baseline volumes in the right HATA, right CA1, and left fimbria compared to patients with no cognitive impairment (Foo, et al., 2017). The participants were then revisited again in 18 months, and results showed a decline in episodic memory. This study ultimately showed that structural changes in subfields of the hippocampus could potentially aide in the early detection of cognitive impairment in PD patients (Foo, et al., 2017).

Lastly, there have been studies conducted in order to investigate an extreme form of memory deficit — dementia. For example, Murat (2003) found that the prevalence of dementia is extremely common and affects almost 40% of PD patients. Additionally, these patients are up to six times more likely to develop dementia than people who do not have PD (Murat, 2003). Dementia in PD patients is believed to be caused by neurochemical deficits including the loss of

innervation from cholinergic, dopaminergic, and noradrenergic systems (Murat, 2003). Murat also found that dementia is associated with the spread of disease to other parts of the brain, including the limbic system, cerebral cortex, and other subcortical nuclei (2003). His study ultimately led to the result of a possible treatment for PD patients with dementia — cholinesterase inhibitors (Murat, 2003).

Visual Hallucinations

According to Yao, et al.'s (2016) study, one of the most common and mentally distressing non-motor symptoms in PD are visual hallucinations. Researchers investigated MRI scans to find out whether or not visual hallucinations in PD were affected by impairments of visuospatial memory associated with the hippocampus (Yao, et al., 2016). They did this by looking at functional connectivity within the brain as well as hippocampal shape, volume, and mean diffusivity (MD) and ultimately found there to be no differences in the macrostructure; however, PD patients with visual hallucinations showed higher diffusivity in the posterior side of the hippocampus than the control groups (Yao, et. al., 2016). Additionally, they found that hippocampal functional connectivity in the visual cortices directly correlated with visuospatial memory impairments and was lower in PD patients with visual hallucinations (Yao, et. al., 2016).

Ibarretxe-Bilbao's (2008) study sought to find a connection between the hippocampus and visual hallucinations in PD patients by studying regional gray matter density. He found that PD patients with dementia and visual hallucinations had a significant amount of gray matter loss in respect to the control group. However, there was a difference in the amount and location of gray matter loss between dementia and visual hallucination PD patients. In the PD patients with dementia, the gray matter loss consisted of the entire hippocampus, whereas the PD patients with visual hallucinations only had gray matter loss in the head of the hippocampus (Ibarretxe-Bilbao, 2008). The findings of this study ultimately suggested that the process of neurodegeneration begins in the head of the hippocampus and eventually spreads down to the tail (Ibarretxe-Bilbao, 2008).

Depression

Depression is also a common symptom of PD, and Lim, Bang, and Choi's (2018) study found a connection between depression and abnormal structure of the hippocampus. Through this realization, they ultimately were able to find a possible treatment for depression — adult hippocampal neurogenesis, "a dynamic process of generating functional neurons from adult neural precursors [that] … persists throughout life in restricted brain regions," including parts of the hippocampus (Lim, Bang, & Choi, 2018, p. 944). Their study also showed evidence of a possible connection between mood disorders and impaired

hippocampal neurogenesis by recognizing that the structure of hippocampus is smaller in PD patients who experience depression (Lim, Bang, & Choi, 2018). Another major finding of Lim, Bang, and Choi's (2018) study was that "defective adult neurogenesis has been detected in the PD brain… and it is conceivable that depression in PD is related to defective hippocampal neurogenesis" (p. 947). This study ultimately proved that a connection exists between abnormal structure of the hippocampus and symptoms in PD patients.

Goal of this study

In this study, we aimed to examine functional connectivity of the hippocampus in Parkinson's disease. Resting state fMRI data from Parkinson's has previously been used to compare functional connectivity of the hippocampus between individuals with and without PD.

Materials and Methods

Data Acquisition

The MRI images, the clinical data, and the demographic data were obtained from the Parkinson's Progression Markers Initiative (Marek et al., 2011). Two sessions of resting state fMRI data were available for 93 individuals with PD (61.27±10.36 years old) and 18 individuals without PD (64.17±9.96 years old).

Resting state echo planar image (EPI) volumes had 40 slices of 4mm 68x66 matrix with 3.3mm thickness (voxel size = 3.29x3.29x3.3mm), with repetition time (TR) of 2400ms and echo time (TE) of 25ms. A total of 210 volumes (8.4 minutes) were used in the analysis. High-resolution structural T1 volumes were acquired as 176 sagittal slices of 240mm x 256mm with 1mm thickness (voxel size = 1x1x1mm, TR=2300ms and TE=2.98ms).

Data Processing

Data preprocessing and statistical analyses were conducted using previously published methods (Kiparizoska & Ikuta, 2017) with FMRIB Software Library (FSL) as well as Analysis of Functional Neuroimages (AFNI). The anatomical volume for each subject was skull stripped, segmented (gray matter, white matter and CSF), and registered to the MNI 2mm standard brain after removing the first four EPI volumes. De-spiking interpolation was used to remove transient signal spikes. To correct head motion, the volumes were linearly registered to the first volume, through which six motion

parameters and displacement distances between two consecutive volumes were estimated. Each of the resting state volumes were regressed by white matter and cerebrospinal fluid signal fluctuations as well as the six motion parameters. The volumes were resampled then spatially transformed and aligned to the MNI 2mm standard brain space, after smoothing with a 6mm FWHM Gaussian kernel. Through this registration, 12 affine parameters were created between rs-fMRI volume and MNI152 2mm space, so that the processed EPI volume can later be registered to the MNI space. To perform scrubbing where the volumes with excess motion are removed, as a displacement distance between two EPI volumes, the root mean square deviation was calculated from motion correction parameters at an *r=40mm* spherical surface using FSL's *rmsdiff* tool. Volumes whose displacement distance exceeded the threshold (0.3mm) were removed (i.e., *scrubbed*) from further statistical analyses.

To conduct voxelwise functional connectivity analysis of the hippocampus, the bilateral hippocampi were segmented by Freesurfer (Fischl, 2012) on the MNI 1mm space. Voxel-wise connectivity analysis was conducted from the bilateral hippocampus seed to the whole brain. The time course was spatially averaged within the bilateral hippocampi that is registered to the EPI space so that correlations can be tested between the hippocampi and each individual voxel across the brain. The Z-scores representing the correlations between the hippocampi and each voxel across the whole brain were used for group level analysis after registration to the MNI 2mm brain space. The time course was

spatially averaged within the cluster that showed group voxel-wise association with the hippocampi.

The PD group and control group were compared by *randomise* script in FSL by T-test fashion, adjusted for the duration between two sessions. Contrast images were estimated by the peak corrected threshold of $p<0.05$ and $k>50$.

Results

The paracingulate gyri (PCG) bilaterally showed lower connectivity to the hippocampi in the PD group, compared to the control group (Figure 1). The peak of the cluster is at the left PCG [MNI: -8 +10 +58] and the cluster extends to the ventral part of the superior frontal gyrus in the ipsilateral and contralateral side.

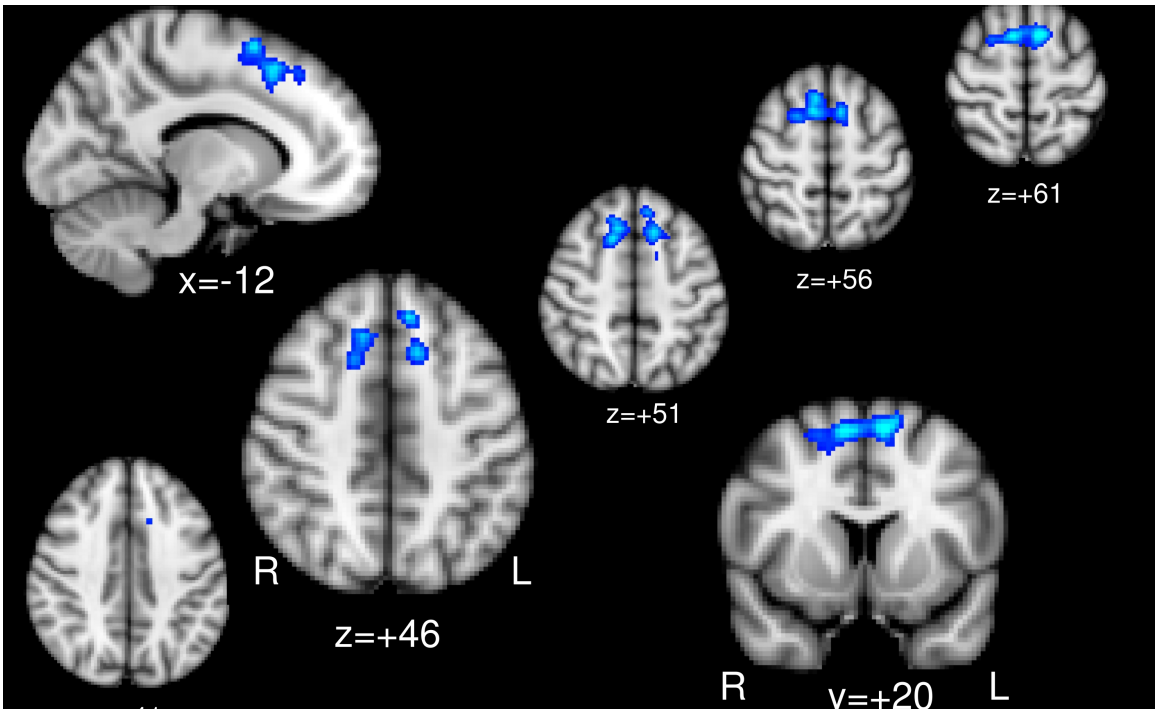

FIGURE 1: PCG CONNECTIVITY TO HIPPOCAMPI: PD-GROUP VS NON-PD (CONTROL) GROUP

Discussion

In this study, we aimed to test the functional connectivity of the hippocampus in Parkinson's disease. Functional connectivity (FC) "refers to temporal correlations (concurrent activity) of spatially remote neurophysiological events" (Segura, et al., 2013, p. 370). We chose to analyze the FC by an fMRI approach in order to obtain patterns of the entire brain. After reviewing the results of the voxelwise analysis, we found that the paracingulate gyri (PCG) showed lesser connectivity in the PD group, when compared to the non-PD control group. This finding ultimately suggests that decline of dopaminergic innervation decreases synchrony of the hippocampi and PCG.

Dopaminergic innervation in PD has previously been studied by Murat (2003). Dementia is considered to be the most prominent neurochemical impairment in PD, and it was found that "loss of cholinergic, dopaminergic, and noradrenergic innervation might be the neurochemical deficits that underlie cognitive impairment and dementia in PD" (Murat, 2003, p. 231-232). Because of this finding, we can infer that PD patients with dementia may have a more severe decline of synchrony between the hippocampus and PCG.

The PCG is not well understood compared to other brain structures, and little research has been conducted about its function and connectivity to surrounding structures. It is located dorsal to the cingulate sulcus (Wang, et al., 2007) and ventral to

the paracingulate sulcus (PCS) (Crosson, et al., 1999), and it is positioned within the medial surface of the cerebral cortex as previously seen in Figure 1.

Additionally, previous research has found that the PCG can be more prominent in some individuals compared to others. Yücel, et al.'s (2001) study sought to examine "the nature of morphometric variance in the AC of the left and right cerebral hemispheres using high-resolution structural… MRI" data. The specific function of the anterior cingulate (AC) and its subregions has remained unclear because of "interindividual variation in the cortical sulci and gyri…which makes accurate and systematic analysis of imaging data difficult" (Yücel, et al., 2001). Additionally, in some individuals, the sulci and gyri are "doubled-up," meaning that it is almost impossible to differentiate between the two. When this occurs, the superior portion is referred to as the PCG/PCS, and the inferior portion is called the cingulate gyrus/sulcus (CG/CS) (Yücel, et al., 2001). By examining the MRI scans, they found that males have a more prominent left PCS when compared to females, which suggests that there could be "hemispheric and gender differences in the underlying cytoarchitectonic size and distribution, as well as in the pattern of connectivity in the left and right hemispheres" (Yücel, et al., 2001). Additionally, when the PCG is present, it encompasses a large portion of Brodmann's area 32 (BA32) and is most commonly located on a gyral crown, and when absent, "BA32 always began in the depths of the cingulate sulcus, occupying the dorsal

wall" (Yücel, et al., 2001). This suggests that the absence of the PCS or PCG could have an impact on the architecture and connection.

Another important finding of Yücel, et al.'s (2001) study is based on Van Essen's (1997) argument that greater functional connectivity exists within gyral crowns. This raises the question that individuals who have a prominent PCG may ultimately display differences in both neuropsychological and cognitive functioning (Yücel, et al., 2001). This finding could ultimately confirm our conclusion that PD patients have lesser connectivity to the PCG because of a decline in dopaminergic innervation.

As for function, the PCG has been known to contribute to the regulation of visual attention. In Gennari, et al.'s (2018) study, they sought to study fMRI data in order to determine if cognitive load has a lasting effect on speech perception. The participants were given tasks that evaluated phoneme discrimination and visual working memory in either a low or high cognitive load. Researchers ultimately found that when performing the speech task under high load, there was "increased activity in the visual occipital cortex and … the superior parietal lobule (SPL) and the paracingulate and anterior cingulate gyrus" (Gennari, et al., 2018). Their findings suggested that the PCG also plays a key role in the allocation of "cognitive resources to concurrent auditory and visual information" (Gennari, et al., 2018).

An additional fMRI study investigated functional domains of the supracollosal medial frontal cortex during word generation (Crosson, et al., 1999). Methods included

"mapping individual subject's functional activity onto structural images of their left medial frontal cortex," and results showed a greater prominence of the paracingulate sulcus in most of the participants (Crosson, et al., 1999). After further analysis, it was understood that the majority of participants had extensively more activity in the PCS than the PCG, which was believed to be due to the fact that the PCG is so narrow. Because of these results, the study ultimately proved that "medial frontal activity during word generation reflects cognitive and motor rather than limbic system participation" (Crosson, et al., 1999).

Previously conducted studies have also shown evidence of reduced PCG connectivity in PD patients. Li, et al. (2019) sought to investigate the functional brain changes in PD patients with restless legs syndrome (RLS) using fMRI data from "14 PD-RLS+ patients, 20 Parkinson's disease without restless legs syndrome (PD-RLS-) patients, as well as 19 normal controls during restless leg syndrome-free periods." The regional homogeneity method was used for evaluating the brain activity, and results showed reduced brain activity compared to the control group in the PD patients with RLS in the "left lingual, fusiform and inferior occipital gyri, middle cingulate and paracingulate gyri, and supplement motor area" (Li, et al., 2019). Their results suggested that RLS in PD patients may be the result from "functional abnormalities in sensorimotor network [that] may disrupt the lateral pain pathway" (Li, et al., 2019).

Another study conducted by Guimarães, et al. (2017) showed gray matter atrophy located in several structures including the paracingulate gyri in groups of patients with severe PD symptoms. The study originally consisted of 66 PD patients all ages 30 and older and 40 non-PD controls, but researchers were only able to use fMRI images from 48 of the PD patients and 33 of the controls. A brain analysis with "voxel-based morphometry (VBM-SPM 8 software), cortical thickness (CT) using CIVET, and resting state fMRI using the Neuroimaging Analysis Kit software" was used to evaluate the participants (Guimarães, et al., 2017). Results ultimately indicated that the participants with mild PD symptoms "already have cortical involvement and similar regions are affected both structurally and functionally" (Guimarães, et al., 2017).

Lastly, a (2013) study conducted by Segura, et al. showed a connection between patients with PD and recognition memory network recruitment dysfunctions. Researchers sought to observe changes in the functional connectivity of 17 PD patients and 13 non-PD controls over time through cross-correlation fMRI (recognition memory paradigm) and neuropsychological assessments (Segura, et al., 2013, p. 370). They ultimately found that recruitment continued to decline in these patients over time, and results also showed a decrease of activation in the anterior paracingulate cortex as well as a "decrease of [task-related] deactivation in the anterior paracingulate gyrus" (Segura, et al., 2013, p. 370). They concluded that "progressive networks involved in recognition memory in PD

patients at early disease stages" were detected and suggested that further analyses on FC could be useful to monitor changes in these networks (Segura, et al., 2013, p. 370).

Conclusion

This study was successful in determining that a decline of hippocampal functional connectivity exists in PD patients. Our findings suggest that a decrease in dopaminergic innervation in PD patients causes less connectivity between the PCG and hippocampus, which could be more severe in PD patients with dementia. Given the argument of Van Essen's (1997) study that greater PCG connectivity occurs within gyral crowns, this promotes the possibility of PD patients having a less prominent PCG compared to non-PD patients. Yücel, et al. (2001) stated that differences in neuropsychological and cognitive functioning also exist between individuals with a prominent PCG and less prominent PCG, which could also account for the neurological deficits we see in PD patients such as dementia. However, the nature of these deficits still remains unclear because of our lack of understanding of the function of the cingulate and paracingulate cortices. In a future study, it would be interesting to examine the effects of gender on PCG prominence in patients with PD and how it affects functional connectivity.

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