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Parkinson's Disease, the Amygdala, and Non-motor Symptoms

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PARKINSON'S DISEASE, THE AMYGDALA, AND NON-MOTOR SYMPTOMS

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DEDICATION

This is for my mother; thank you for being my biggest cheerleader.

This is for my father; thank you for always believing in me.

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To my advisor, Dr. Tossi, thank you for your boundless patience, constant encouragement, and indispensable expertise.

To my readers, Dr. Park and Dr. Del Arco, thank you for your time and guidance.

ABSTRACT

This study sought to explore the relationship between Parkinson's Disease (PD), the amygdala, and the plethora of non-motor symptoms that plague individuals with PD. Previous research gave insights about the amygdala's function as the emotional center of the brain, its role in depression, and its participation in the non-motor symptoms of PD. The research proved to still be inconclusive on its own because of a variety of limitations. The methods of this study consist of the analysis of Functional Magnetic Resonance Imaging (fMRI) scans from 93 individuals with PD and 18 individuals without PD while in a resting state. The analysis showed that the amygdalae experienced decreased functional connectivity (FC) to the right posterior areas of the superior frontal gyrus (SFG). Because this depletion of FC is similar to the neurological effects of Major Depression Disorder (MDD), it is suggested that depression in PD is caused by the amygdala's inability to communicate effectively with the right posterior SFG.

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LIST OF ABBREVIATIONS

Analysis of Functional NeuroImages	AFNI
Cerebrospinal Fluid	CSF
Echo Planar Image	EPI
Echo Time	TE
FMRIB Software Library	FSL
Full Width at Half Maximum	FWHM
Functional Connectivity	FC
Functional Magnetic Resonance Imaging	fMRI
Major Depressive Disorder	MDD
Montreal Neurological Institute	MNI
Parkinson's Disease	PD
Repetition Time	TR
Superior Frontal Gyrus	SFG
Threshold-Free Cluster Enhancement	TFCE

INTRODUCTION

Parkinson's Disease (PD) is more than just a motor disorder. A myriad of non-motor symptoms plague many patients diagnosed with PD such as psychosis, sleep deprivation, and depression (Chaudhuri et. al., 2006). These are extremely serious symptoms and Chaudhuri et. al. (2006) pointed out that these symptoms could potentially be even more detrimental to a person's quality of life than the motor symptoms of PD would be. This study hopes to explore the relationship between the amygdala and the non-motor symptoms of PD.

The amygdala is a complex entity comprised of several interconnected nuclei that each have their own function, yet seamlessly transfer information to the rest of the brain. Though this might seem an impossible enigma, researchers have made great strides toward understanding the amygdala and its functions. Pessoa (2010), for example, explained how the amygdala contributes to human and non-human brains having the capacity for vigilance, arousal, attention, and decision making. Pessoa (2010) also focused on the amygdala's division of labor. Pessoa (2010) noted that the "basolateral amygdala appears to be responsible for Pavlovian learning and the representation of value". The research of Cardinal et. al. (2002) supported Pessoa's claim about the basolateral amygdala's connection to Pavlovian conditioned stimuli. This article primarily focused on how the amygdala is connected to conditioned responses. The article noted that the amygdala is the brain's emotion center (Cardinal et. al., 2002). The researchers also stated that the purpose of the amygdala's emotional response is to enhance decision making and to facilitate conditioned responses over time (Cardinal et. al., 2002). Therefore, the amygdala is not only the brain's emotional center but also the motivational center.

Koelsch and Skouras (2013) explored the initial emotional response to a stimulus and the lingering effects. The main conclusion from the results of the experiment was that the superficial amygdala is extremely central for the neural pathways for joy (Koelsch & Skouras, 2013). Although it is widely accepted that the amygdala is the brain's emotional center, Pessoa (2010) states that the amygdala is known for being the brain's center for fear-based conditioning. Therefore, the results from Koelsch and Skouras (2013) are surprising because joy elicited a much more active response not only in the superficial amygdala but in all nuclei of the amygdala.

In another article that took interest in the amygdala's relationship to PD, Tessitore et. al. (2013) hypothesized that due to the known deficiency of dopamine in PD, the amygdala would probably be affected. One of the most interesting conclusions to come out of this experiment is that comorbid depression with PD could be another symptom of PD due to its effect on the amygdala (Tessitore et. al., 2013). While this study did appear to suggest that there is a direct connection between PD and MDD , Tessitore et. al. (2013) were adamant that more research is needed in this area before that conclusion can be either confirmed or denied.

Similarly, Cardoso et. al. (2009) examined the connection between PD and depression. Although the amygdala was not the primary focus of the study, the researchers noted its reactions to the antidepressants (Cardoso et. al., 2009). They noted that typically the amygdala is the source of depression, and when treated, its volume should increase (Cardoso et. al., 2009). However, when the patients with PD were given antidepressants, the volumes of their amygdala's remained constant (Cardoso et. al., 2009). Harding et. al.'s (2002) study attempted to focus on which sector of the amygdala PD directly attacks. This study claimed to have

determined that a disordered amygdala is a consistent symptom in PD and that there is a correlation between increasing Lewy Body presence throughout the entire amygdala and mild neuronal cell loss (Harding et. al., 2002). They also found some evidence to suggest that Lewy Bodies in the amygdala could be the cause of visual hallucinations in the later stages of PD (Harding et. al., 2002). Harding et. al. (2002) noted that depression is normally linked to the disordered amygdala just as the disordered amygdala is linked to PD. The researchers noted that the general understanding of MDD is that the amygdala experiences increased activity (Harding et. al., 2002). Harding et. al. (2002) also pointed to other studies (de la Monte et al., 1989; Cordato et al., 2000) that showed that the amygdala experiences atrophy when PD is present. However, this contradicts what Hung et. al. (2015) reported in their findings. Their results showed that the amygdalae's volumes were approximately the same within each group of participants (Hung et. al., 2015). The contradiction was likely a result of the different participants' conditions. Harding et. al.'s (2002) participants were deceased, and PD likely had been present longer in these individuals, increasing the severity of the disease. Whereas participants in Hung et. al.'s (2015) study were still living and had only recently been diagnosed with PD. The contradictory results and conclusions of these studies display the need for more research.

Hung et. al. (2015) also suggested that the amygdala is more active in people with PD and experiences a significant loss in FC to areas of the brain such as the frontal lobe, temporal lobe, and basal ganglia. This result is similar to what Harding et. al. (2002) discovered about MDD.

There is also significant uncertainty about the efficacy of treatments for non-motor symptoms associated with PD. Chaudhuri et. al. (2006) noted that while there are a plethora of non-motor symptoms of PD such as depression, little research exists concerning treatment

options for these symptoms. Elefant et. al. (2012) hypothesized that music therapy could treat the depressive symptoms of PD. This hypothesis could be supported by the amygdala's connection to depression in PD and its link to expressing joy after exposure to joyful music (Koelsch and Skouras, 2013). However, the results of the study displayed improvement only in the motor-related symptoms of PD (Elefant et. al., 2012). Although the results were ineffective in treating depressive symptoms associated with PD, the ineffectiveness suggests that PD directly affects the amygdala, rendering the structure unable to process joy from music or any other source.

The combination of these findings and conclusions opens the door to new questions and considerations. It has suggested that there is possibly a connection between PD, the amygdala, and the non-motor symptoms of PD, but more research is required to solidify this connection. The research question that this study seeks to answer is this: how does PD affect the functional connectivity of the amygdala?

METHODS

Data Acquisition

The Parkinson's Progression Markers Initiative provided the MRI images, the clinical data, and the demographic data (Marek et al., 2011). Functional MRI data during the resting state was available for 93 individuals with PD (61.27±10.36 years old) and 18 individuals without PD (64.17±9.96 years old).

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

Data Processing

Previously published methods (Kiparizoska & Ikuta, 2017) with FMRIB Software Library (FSL,) as well as Analysis of Functional NeuroImages (AFNI) dictated the methods of data preprocessing and statistical analyses. The anatomical volume for each subject was skull stripped, segmented into gray matter, white matter, and cerebrospinal fluid (CSF), and registered to the MNI 2mm standard brain after removing the first four EPI volumes. To remove transient signal spikes, de-spiking interpolation was used. The volumes were linearly registered to the first volume, through which six motion parameters and displacement distance between two consecutive volumes were estimated to account for head motion. Each of the resting state volumes regressed by white matter, cerebrospinal fluid signal fluctuations, and the six motion

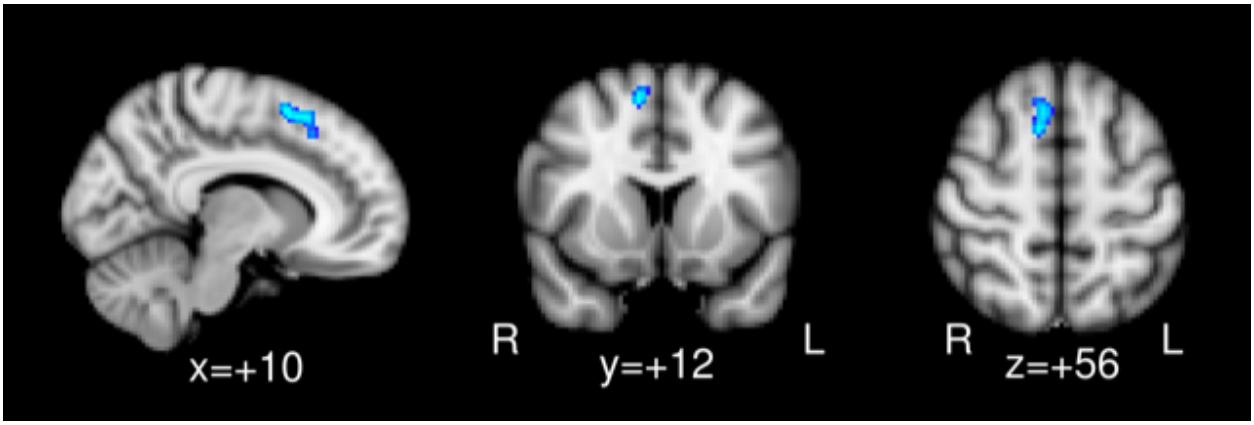
parameters. Then the volumes were resampled and spatially transformed and aligned to the MNI 2mm standard brain space, after smoothing with a 6mm full width at half maximum (FWHM) Gaussian kernel. Thus, 12 affine parameters were created between the resting-state fMRI volume and MNI152 2mm space, so that the processed EPI volume could later be registered to the MNI space. 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. This was done to perform scrubbing so that the volumes whose displacement distance exceeded the threshold (0.3mm) because of motion are removed from further statistical analyses.

The left and right amygdalae were identified in the Harvard-Oxford Subcortical atlas [12] on the MNI 2mm space. The purpose of this was to conduct voxel-wise FC analysis of the primary auditory cortices. A voxel-wise connectivity analysis was performed from the bilateral amygdala seed to the entire brain. The time course was spatially averaged within the amygdalae that is registered to the EPI space. Then, correlations could be tested between the amygdalae and each voxel across the brain. The correlations between the amygdalae and each voxel across the whole brain were represented by Z scores that 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 amygdalae.

Randomise script in FSL in paired-T test fashion adjusted for the time between two groups by comparing the two resting-state fMRI sessions. Threshold-free cluster enhancement (TFCE) of $p<0.05$ was used to estimate the contrast images.

RESULTS

The amygdalae of the PD group showed decreased FC to the right posterior medial areas of the superior frontal gyrus (SFG) [MNI: 10, 12, 56] when compared to the control group. The PD group did not display any greater connectivity within the brain in comparison to the connectivity of the control group.



DISCUSSION

The purpose of the study was to determine the role of the amygdala of non-motor symptoms associated with PD. The results of the study led to the discovery that the amygdala's effect on non-motor symptoms in PD is not necessarily dependent on its hypertrophy or hypotrophy but rather its FC to the SFG. The function of the SFG is not entirely defined in the current research. Alagapan et. al (2018) noted that previous research had not yet identified the role of the SFG, but the researchers attempted to link the left SFG's function to working memory. Their results supported their hypothesis; however, there is still much to be learned about the function of the SFG (Alagapan et. al., 2018). Cao et. al. (2020) demonstrated research that showed how the left SFG contributes to short-term memory recall and discussed how the left SFG showed a reduction in grey matter volume (GMV) during the early stages of PD and that this could account for the functional changes. Chen et. al. (2018) also concluded that GMV is decreased in the left SFG in patients with major depressive disorder (MDD). These results were compared to patients with Bipolar Disorder instead of a control group (Chen et. al., 2018).

While the previous studies listed have interesting information and theories about the function of the left SFG, the present study found the FC from the amygdala to the right posterior medial sectors of the SFG to be lacking. Falquez et. al. (2014) consider how brain-damaged individuals are able or not able to make use of self-focused reappraisal. This process allows people to detach from negative experiences they have been through and feelings of guilt. The researchers suggest that the right SFG is essential for this process to work correctly (Falquez et. al., 2014). A person's inability to detach from their negative emotions about themselves could logically contribute to a sense of depression. Liao et. al.'s (2020) research supports this

conclusion. This article reaffirms that the SFG experiences a reduction in connectivity in patients with PD (Liao et. al., 2020). It also suggests that this connection, or rather deficit in connection, is a major harbinger of depression in PD (Liao et. al., 2020).

Hernández et. al. (2018) were curious about how the natural diminishing volume and surface area of the SFG affects the cognitive functioning of individuals who have cognitive disorders such as Alzheimer's Disease over 2 years. Even though the volume and surface area of the SFG decreased over the 2 years, the results of the cognitive tests remained the same (Hernández et. al., 2018). Dipple et. al. (2017) attempted to determine the neural pathways for inhibitory control processes which allow for focus and successful, task-oriented behavior. The study determined that the SFG was likely a key component of this neural process (Dipple et. al., 2017). The qualities of inhibitory control directly oppose apathetic qualities. Alexopoulos et. al. (2012) noted that apathy is extremely common in older adults and often coincides with depression. These researchers explored how the brain's FC in older adults specifically affects apathy in Major Depressive Disorder (MDD). They discovered that apathetic depressed adults showed decreased FC in both the amygdala and SFG (Alexopoulos et. al., 2012). This finding is similar to the findings of the current study which specifies that the FC is decreased directionally from the amygdala to the right posterior SFG in individuals with PD.

The limitations of this study are that it does not monitor the participants over a long period of time to show how the participants' FC could continue to change. The study also has no knowledge of whether the participants in either the PD group or the control group have ever been diagnosed with MDD separately or in conjunction with PD. The number of participants is also too small to produce conclusive evidence, and the amygdalae's volumes are unknown. These

limitations suggest that future research should analyze fMRI scans of more participants over long periods of time with a group with PD, a group with MDD, a group with both PD and MDD, and a control group with neither. The study should also take into account the volumes of the amygdalae.

CONCLUSION

Although it could easily be assumed that depression in conjunction with PD is due to difficult circumstances caused both motor and non-motor symptoms, PD and MDD involve similar neurological components. Both disorders present with significant FC deficiencies regarding the amygdala and the SFG. Because PD and MDD share such similar neurological qualities and are often diagnosed comorbidly, it is possible that a successful treatment for one disease or disorder could also be an effective treatment for the other. This study also displays that depression in relation to PD is likely not simply a situational emotion but a serious neurological condition.

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