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FUNCTIONAL CONNECTIVITY OF THE INFERIOR FRONTAL GYRUS IN AUTISM SPECTRUM DISORDERS

by
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A thesis submitted to the faculty of the University of Mississippi in partial fulfillment of the requirements of the Sally McDonnel Barksdale Honors College

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ABSTRACT

The American Speech-Language-Hearing Association defines Autism Spectrum Disorder (ASD) as a "neurodevelopmental disorder characterized by deficits in social communication and social interaction" which is heavily impacts language abilities. There is an abundance of research on the neurological aspects of the disorder, which appear to have major differences of activation and functionality when compared to typically developing peers. Specifically, in the left inferior frontal gyrus (IFG), a key language region of the brain, functional connectivity levels tend to be significantly less in ASD groups. This study recognizes these trends and aims to expand the research by locating specific functional connections and relationships between the three regions of the left IFG (pars opercularis, pars triangularis, and pars orbitalis) and other locations of the brain that could impact language. By using functional magnetic resonance images, we ran a voxel-wise analysis between the three regions of the left IFG and each individual voxel throughout the brain. As we expected, there was significantly less functional connectivity in the ASD groups. However, the decreased functional connectivity was only in the pars orbitalis and not the pars opercularis or pars triangularis. This information could improve the knowledge of the neurological pathways of language processes in ASD.

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LIST OF ABBREVIATIONS

ASD – Autism Spectrum Disorder

ASHA – American Speech-Language-Hearing Association

EPI – Echo planar image

FC – functional connectivity

fMRI – functional magnetic resonance image

IFG – inferior frontal gyrus

MFG – middle frontal gyrus

MNI – minimum number of individuals

PC – parietal cortex

TD – typically developed

INTRODUCTION

Autism Spectrum Disorder (ASD) is a neurological, developmental and behavioral disorder characterized by a wide range of language and social communication abilities. Language deficits are a common clinical feature in the diagnosis of an Autism Spectrum Disorder (ASD), however, there is a large range of differences in the language abilities. Some patients diagnosed with ASD have higher than average language skills, whereas, others are completely nonverbal and unable to communicate through spoken language at all. There is a substantial amount of research on the five domains of language (phonology, morphology, semantics, syntax and pragmatics) in ASD. Inability to neurologically process any of these domains can impact the social communication skills of individuals, which is a common indication of an ASD diagnosis. There are specific locations in the brain that are responsible for language abilities, however, there is a gap in the neurological aspects (i.e: activation levels and functional connectivity) of ASD that could potentially explain language deficits.

Broca's Area is known to be a region of the brain located in the left inferior frontal gyrus (IFG) found in the frontal lobe associated with communication abilities and speech production. The left IFG as a whole is well known to be involved in a multitude of language processing systems. The left IFG contains three regions: the pars opercularis, the pars triangularis and the pars orbitalis. There is a debate in literature regarding the inclusion of all three of these regions being referred to as 'Broca's area' or just the pars opercularis and pars triangularis. There are claims that the pars orbitalis should be included in the term 'Broca's area' because it is associated with language processing and located adjacent to the pars opercularis and pars triangularis (Hagoort, P., 2014.). However, others believe the term 'Broca's area' should just refer to the pars opercularis and pars triangularis. Because of the inconsistencies in terminology throughout literature, the current study uses the term ‘left IFG’ when discussing all three areas.

Research shows the left IFG is believed to be a central location in the brain responsible for language, specifically, communication abilities and speech production. However, there is little known about the functional connectivity (FC) of this area to other locations of the brain. In Dichter, G. S. (2012), FC is described as the “temporal dynamics of brain network activity” and is measured by functional magnetic resonance imaging (fMRI) (p. 324). fMRIs are a commonly used in neuroanatomical research of ASD to gain insight of any abnormal neurological activations, functions, and connections. Once these abnormalities are located, they can be compared to a typically developed (TD) control group, allowing for the potential identification of etiologies of specific characteristics of the disorder.

Several studies have used fMRIs to compare activation of linguistic regions of the brain in subjects diagnosed with ASD to a TD group. There is a common trend in the findings of these studies that include hypoactivation of the left IFG. For example, Harris et. al (2006) presented ASD and TD participants with a semantic processing language task while undergoing fMRI tests. In a similar study, using fMRI scans, the ASD and TD groups were presented with a verb generation task (Verly et. al, 2014). Both of these study’s results provide data on the major decreases in connectivity between the left IFG and other language governing structures when participants are presented with language-based tasks (Harris et. al 2006. & Verly et. al, 2014). The results of these studies share a commonality of hypoactivation and decrease of connectivity in the left IFG in ASD participants when compared to TD groups when presented with a language-based task. These findings provide additional evidence regarding the belief that the left IFG is a neurological structure that has significant involvement in language abilities.

Another study providing similar evidence of differences in activation between the left IFG and other major language regions in ASD is Gao et. al (2019). They used resting state fMRI to identify any relationships of connectivity and functionality in areas of the brain involved in language abilities. Their results showed an atypical connection between the left IFG and other locations such as the posterior cingulate cortex. Likewise, Li et al. (2020) found “decreased [degree centrality (DC)] in the left inferior frontal gyrus and increased DC in the left inferior parietal lobe in children with ASD compared to [typically developed] children”. The frontal and parietal lobes contain several parts of the brain identified with language use. The weakened functional connectivity between these areas in ASD “...might interfere with the transmission of information between critical brain regions” and play an important factor in the language abilities of a person with ASD (Li et al., 2020). These findings congruent with similar research, which provides more information on the primary neurological locations involved in language.

Although these results are beneficial to the understanding of key neurological locations of language abilities, there is limited research on the functional connectivity to other areas of the brain. This study intends to fill the gap in research and explore the possibility of significant differences in the neural connectivity in ASD groups when compared to TD groups by using neuroimaging data such as fMRI images collected from several sites. A goal of the current study is to identify other neurological regions effected by decreased FC in the left IFG. If this goal is achieved, we can then gain a better understanding of neurological differences in ASD. Using the collected data, a voxel-wise connectivity analysis was performed in an attempt to locate correlations between the three regions of the left IFG (pars opercularis, pars triangularis, and pars orbitalis). The results of the analysis were evaluated and allowed for us to locate connections between the left IFG and other areas of the brain involved in the language network of ASD. There is significant research providing evidence of both decreased connectivity and activation of the left IFG in language abilities in ASD. Because of this information, I hypothesized that the results of the voxel-wise analysis would show decreased functional connectivity in the areas of the left IFG in ASD groups when compared to a TD control group.

METHODS

Data Acquisition

The MRI images, the clinical data, and the demographic data were obtained from Autism Brain Imaging Data Exchange (ABIDE). Among image data obtained at several sites, data subset from New York University cohort was used, which consisted of 181 individuals for whom resting state and structural data were both available. Among these individuals, 76 had a diagnosis of ASD (hereafter ASD group, 14.51±6.97 years old) and 105 were age-matched individuals (control group, 15.81±6.25 years old).

Resting state echo planar image (EPI) volumes had 33 slices of 4mm 64x80 matrix with 4mm thickness (voxel size = 3x3x4mm), with repetition time (TR) of 2000ms and echo time (TE) of 15ms. A total of 180 volumes (6 minutes) were used in the analysis. High-resolution structural T1 (MPRGE) volumes were acquired as 128 sagittal slices of 256mm x 256mm with 1mm thickness (voxel size = 1.3x1x1.3mm, TR=2530ms and TE=3.25ms).

Data Processing

Data preprocessing and statistical analyses were conducted using 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. First four EPI volumes were removed. Transient signal spikes were removed by de-spiking interpolation. To correct head motion, the volumes were linearly registered to the then first volume, through which six motion parameters and displacement distance 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. After smoothing with a 6mm FWHM Gaussian kernel, the volumes were resampled and then spatially transformed and aligned to the MNI 2mm standard brain space. Through this registration, 12 affine parameters were created between rs-fMRI volume and MNI152 2mm space, so that a seed ROI can later be registered to each individual rs-fMRI 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 (Power et al., 2015; Power et al., 2012). Volumes whose displacement distance exceeded the threshold (0.3mm) were removed (i.e., *scrubbed*) from further statistical analyses (Siegel et al., 2014).

To conduct voxelwise functional connectivity analysis of the left pars triangularis, pars opercularis and pars orbitalis were defined using the *Freesurfer* conducted on MNI 1mm brain. The mean EPI signal within each of the ROIs was first estimated for each volume.

Voxel-wise connectivity analysis was conducted from each of the three seed regions to the whole brain. The time course was spatially averaged within each region that is registered to the EPI space so that correlations can be tested between the three regions and each individual voxel across the brain. The Z-scores representing the correlations between the three regions and each voxel across the whole brain were used for group level analysis after registration to the MNI 2mm brain space.

Statistical Analysis of Functional Connectivity

The ASD and control groups were compared by *randomize* script in FSL. TFCE $p<0.05$ (FWE corrected). $K>100$

RESULTS

The voxelwise analysis of functional connectivity to/from the pars orbitalis showed significantly less connectivity to the left middle frontal gyrus (MFG) (peak MNI=[-54 -60 -18] 553 voxels; Fig 1) and left parietal cortex (peak MNI=[-20 -64 +46] 462 voxels; Fig 2) in the ASD group compare to the control group, while no regions showed greater connectivity in the ASD group. No region indicated different connectivity with the pars triangularis and pars opercularis between the ASD group and the control group.

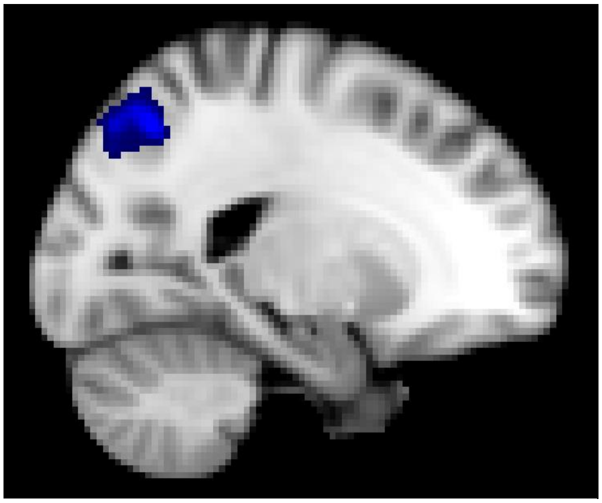

Figure 1: Sagittal view of the left parietal lobe

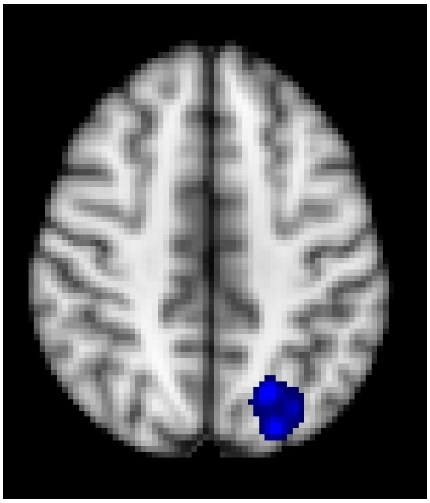

Figure 2: Axial view of the left parietal lobe

DISCUSSION

ASD is often observed as a behavioral disorder, however, several studies have proven it is a neurological disorder that can widely impact the person that is diagnosed with it. According to the Centers for Disease Control and Prevention (CDC), 1 in 59 children is diagnosed with ASD (2018). When diagnosing a person with ASD, inability to carry out age-appropriate pragmatic skills is one of the first, most prominent indicators. However, language impairments in ASD can vary from minor pragmatic issues to "extensive language deficits including syntactic, semantic and phonological domains" (Verly et. al, 2014). The study shows the left middle frontal gyrus (MFG) and the left parietal cortex (PC) have significantly less connectivity to and from the pars orbitalis in the ASD groups when compared to the control group.

The inferior frontal gyrus (IFG) of the left hemisphere of the cerebral cortex plays an essential role in language and communication; specifically, "understanding and producing syntactically complex sentences and other language functions" (Davis et. al, 2008). Broca's area is located in the IFG and is made up of smaller areas including the pars opercularis, pars triangularis and pars orbitalis. These areas play an essential role in expressive language, which can be highly impacted in people with ASD. Results of this study show the voxelwise analysis of functional activity is not significantly impacted in the pars opercularis or pars triangularis. However, the functional connectivity between the pars orbitalis to and from both the LMFG and left PC was significantly less in the ASD group when compared to the typically developed group.

The pars orbitalis is associated with language processing, with a specialization in semantics. (Rouse, M. H., 2020. p. 272). The American Speech-Language-Hearing Association

(ASHA) defines semantics as the meanings of words and combinations of words in a language; including speaking, listening, reading and writing vocabulary. The results of the study show there is significantly less functional connectivity between the pars orbitalis in ASD and other areas of the brain. Therefore, there is a possibility that the hypoconnectivity in this area could be the reasoning behind semantic impairments in the language of people with ASD. As we found in our study, the two areas with significantly less functional connectivity is the left MFG and left PC.

The left MFG is an area of the brain that is located in the prefrontal cortex. The prefrontal cortex “...is associated with cognition, personality, decision making, and social behavior” (Rouse, M. H., p. 177). The left MFG includes important, executive functions that are related to cognitive abilities such as restraint, initiative, and order. These three executive functions are defined by Blumenfeld (2010). Restraint involves the “inhibition of inappropriate behaviors” including (but not limited to): judgement, delaying gratification, inhibiting socially inappropriate responses and concentration. In contrast, initiative is defined as “motivation to pursue positive or productive activities” and include motivation, mental flexibility, curiosity and creativity. Finally, Blumenfeld (2010) describes order as “the capacity to correctly perform sequencing tasks and a variety of other cognitive operations”. A few subcomponents of order is working memory (WM), planning, abstract reasoning and organization (p.109).

Similarly, in the systematic review by Craig, et. al (2016), the “neurocognitive profiles of ASD... include several areas of [executive functions] EF such as attention, WM, and fluency” when compared to a typically developed (TD) group. Other EF with significant deficits in ASD groups is flexibility, planning, and response inhibition (Craig, et. al, 2016). Impairments in these areas of executive functions are potential characteristics of ASD. Additionally, the results of the systematic review by Craig, et. al (2016) closely resemble the definitions provided from Blumenfeld's (2010). Both Craig, et al (2016) and Blumenfeld (2010) describe executive functions of the left MFG. It is well-known that deficits in these areas are all common indicators when diagnosing a person with ASD. Therefore, the results of our study provide evidence of a potential link between the functional connectivity of the pars orbitalis and executive functions of the left MFG in ASD.

We also found that when compared to the control group, the ASD groups, had significantly less functional connectivity to and from the pars orbitalis and the left parietal cortex. Specifically, the left PC, functions consist of interpretation as well as imitation which can both be prevalent in communication abilities. The results of our study correspond with the findings of Fontana et. al (2012) which claim the decreased functional connectivity and/or damage to the PC can show impairments in an individual's abilities to imitate, understand observed actions (i.e.: *interpret*), as well as control and plan his or her own movement. Deficiencies in these areas are also commonly found in people with ASD. The inability to interpret emotions or mental states of others is a major part of the social, or pragmatic, aspects of language that most people with ASD lack. Our results provide evidence that the connectivity of the left PC and pars orbitalis impact deficiencies of interpretation aspects commonly found in ASD.

Decreased abilities to imitate others is a common indication of ASD. Our results show the left PC has significantly less connectivity in ASD groups when compared to TD groups. As previously mentioned in the discussion, imitation is a major function of the left PC, which is believed to be heavily impacted by the functioning of the mirror neuron system (MNS). Mirror neurons are believed to impact humans' ability to learn by mirroring, or *imitating,* the actions of others, which ultimately allows for us to learn new skills (Rizzolatti,G & Craighero, L, 2004; Rouse, M. H., 2020. p. 330). If there is hypoactivation of mirror neurons, a person's imitation abilities may be hindered, which could potentially cause less activation of the left PC. This could ultimately explain lack of functional connectivity of the left PC in ASD.

In a meta-analysis by Chan & Han (2020), they claim that deficiencies of imitation abilities effects communication and social skills in ASD. To defend their claim, the researchers compared MNS activation in an ASD group and a TD control group. Similar to our results, the meta-analysis concluded that individuals diagnosed with ASD have a hypoconnectivity between the IFG (which includes the pars orbitalis) and left PC when compared to the TD group. This information provides additional evidence and has significant correspondence with the results of our study.

Although there is significant evidence to support this study, there are also limitations that could have impacted the outcome. Out of the 76 participants diagnosed with ASD, we do not know the range of functionality. If majority of participants have high-functioning ASD, then the remaining participants with significantly lower functioning ASD could hinder the results and vise versa. Another potential limitation is because we do not know when these scans were taken, the ASD participants could have been evaluated with different versions of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM). Earlier versions of the DSM include Asperger's Syndrome in ASD, however, the most recent version, DSM-V, says Asperger's is not included on the Autism Spectrum. Therefore, according to the DSM-V, if any of the participants only have Asperger's but no other aspects of ASD, their scans would not be eligible to use in this study. Although these limitations exist, there is still a significant amount of information that supports the findings of the study regarding the functional connectivity in ASD.

CONCLUSION

We hypothesized that the voxel-wise analysis would show lower FC of all three regions of the left IFG (pars opercularis pars triangularis and pars orbitalis) in the ASD participants when compared to a control group. However, after the results were calculated, we found that the pars opercularis and pars triangularis did not have significant differences of functional connectivity levels. Contrastingly, the pars orbitalis did have lower FC levels to and from both the MFG and the PC. The goal of identifying specific associations and connections of the left IFG and other neural regions was achieved. In conclusion, our study successfully expands the knowledge on the left IFG connections to other locations of the brain.

FUTURE IMPLICATIONS

We learned that deficiencies in the ability to imitate others is a common indication of ASD and effects individuals' language and social communication skills. These inabilities in imitation could be due to hypoactivation of the MNS. Further research could investigate the lack of MNS activation in ASD which could provide a better understanding of why people with ASD struggle to imitate others.

LIST OF REFERENCES

American Speech-Language-Hearing Association (n.d.). *Autism* (Practice Portal). Retrieved March, 25, 2021, from www.asha.org/Practice-Portal/Clinical-Topics/Autism/.

American Speech-Language-Hearing Association. (n.d). *Language In Brief*. American Speech-Language-Hearing Association. https://www.asha.org/practice-portal/clinical-topics/spoken-language-disorders/language-in-brief/.

Andersson, M., Ystad, M., Lundervold, A., & Lundervold, A. J. (2009). Correlations between measures of executive attention and cortical thickness of left posterior middle frontal gyrus - a dichotic listening study. *Behavioral and brain functions : BBF, 5*, 41. https://doi.org/10.1186/1744-9081-5-41.

Blumenfeld, H. (2010). *Neuroanatomy through clinical cases.* Sunderland, MA: Sinauer Associates.

Cameron Davis, Jonathan T. Kleinman, Melissa Newhart, Leila Gingis, Mikolaj Pawlak, Argye E. Hillis. Speech and language functions that require a functioning Broca's area,Brain and Language,Volume 105, Issue 1, 2008, Pages 50-58, ISSN 0093-934X, https://doi.org/10.1016/j.bandl.2008.01.012.

Chan, M. M. Y., & Han, Y. M. Y. (2020). Differential mirror neuron system (MNS) activation during action observation with and without social-emotional components in autism: A meta-analysis of neuroimaging studies. *Molecular Autism, 11,* 1-18. doi:http://dx.doi.org.umiss.idm.oclc.org/10.1186/s13229-020-00374-x

Craig, F., Margari, F., Legrottaglie, A. R., Palumbi, R., de Giambattista, C., & Margari, L. (2016). A review of executive function deficits in autism spectrum disorder and attentiondeficit/hyperactivity disorder. *Neuropsychiatric Disease and Treatment, 12*, 1191-1202. doi:http://dx.doi.org.umiss.idm.oclc.org/10.2147/NDT.S104620**.**

Dichter, G. S. (2012). Functional magnetic resonance imaging of autism spectrum disorders. *Dialogues in Clinical Neuroscience*, *14*(3), 319–351.

Fontana, A. P., Kilner, J. M., Rodrigues, E. C., Joffily, M., Nighoghossian, N., Vargas, C. D., & Sirigu, A. (2012). Role of the parietal cortex in predicting incoming actions. *Neuroimage*, *59*(1), 556-564.

Hagoort, P. (2014). Nodes and networks in the neural architecture for language: Broca's region and beyond. *Current Opinion in Neurobiology*, *28*, 136–141. https://doi.org/10.1016/j.conb.2014.07.013

Lee, Y., Park, B., James, O., Kim, S., & Park, H. (2017). Autism spectrum disorder related functional connectivity changes in the language network in children, adolescents and adults. *Frontiers in Human Neuroscience, 11*. doi:10.3389/fnhum.2017.00418

Li, Y., Zhu, Y., Nguchu, B. A., Wang, Y., Wang, H., Qiu, B., & Wang, X. (2020). Dynamic functional connectivity reveals abnormal variability and Hyper-connected pattern in autism spectrum disorder. *Autism Research*, *13*(2), 230-243. doi:10.1002/aur.2212

Maenner, M. J., Shaw K. A., Baio, J., et al. Prevalence of autism spectrum disorder among children aged 8 years – Autism and Developmental Disabilities Monitoring Network, 11 sites. United States, 2016. MMWR Surveill Summ 2020;69(No. SS-4):1-12. http://dx.doi.org/10.15585/mmwr.ss6904a1external icon.

Nishitani, N., Schurmann, M., Amunts, K., & Hari, R. (2005). Broca's region: From action to language. *Physiology (Bethesda, Md.), 20*(1), 60-69. https://doi.org/10.1152/physiol.00043.2004

Rouse, M. H. (2020). In *Neuroanatomy for speech-language pathology and audiology* (Vol. 2, p. 272). Jones & Bartlett Learning.

Saffin JM, Tohid H. Walk like me, talk like me. *Neurosciences* (2016) 21(2):108–19. doi: 10.17712/nsj.2016.2.20150472

Verly, M., Verhoeven, J., Zink, I., Mantini, D., Peeters, R., Deprez, S., ... Sunaert, S. (2014). Altered functional connectivity of the language network in ASD: role of classical language areas and cerebellum. *NeuroImage: Clinical, 4*, 374-382. doi:10.1016/j.nicl.2014.01.00.

Wen J, Yu T, Liu L, Hu Z, Yan J, Li Y, Li X. Evaluating the roles of left middle frontal gyrus in word production using electrocorticography. Neurocase. 2017 Oct - Dec;23(5-6):263-269. doi: 10.1080/13554794.2017.1387275. Epub 2017 Oct 20. PubMed PMID: 29052465.