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The Functional Connectivity of the Auditory Cortex in Autism Spectrum Disorder

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THE FUNCTIONAL CONNECTIVITY OF THE AUDITORY CORTEX IN AUTISM SPECTRUM DISORDER

By

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DEDICATION

I am dedicating this thesis to my parents and friends who have answered every panicked phone call and given me guidance and encouragement throughout this year. Thank you!

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ABSTRACT

KATHERINE CONWAY WILSON: The Functional Connectivity of the Auditory Cortex in Autism Spectrum Disorder

(Under the direction of Dr. Toshikazu Ikuta)

Disturbance of the auditory cortex in Autism Spectrum Disorder (ASD) is well known as well as its influence on hearing. Functional connectivity within the brain is also known to be affected by ASD. However, functional connectivity of the auditory cortex in ASD has yet to be studied. In this study, using resting-state functional magnetic resonance imaging data from the Autism Brain Imaging Data Exchange (ABIDE), functional connectivity of the auditory cortex was examined by comparing 68 individuals with ASD and 75 individuals with ASD. Four brain regions showed smaller functional connectivity to and from the auditory cortex; the occipital cortex, motor cortex, insular cortex, and Wernicke's area. All these regions have been previously shown to be influenced by ASD. Smaller function connectivity to these regions may partly explain deficits in verbal communication of ASD.

TABLE OF CONTENTS

LIST OF FIGURES & TABLES

LIST OF ABBREVIATIONS

ABIDE	Autism Brain Imaging Data Exchange
ASD	Autism Spectrum Disorder
AQ	Autism-Spectrum Quotient
Cr	Creatine
CSF	Cerebrospinal Fluid
CWA	Children with Autism
DISCO	Diagnostic Interview for Social and Communication Disorders
EPI	Echo-planar image
FA	White Matter Fractional Anisotropy
FSL	FMRIB Software Library
MEG	Magnetoencephalography
M1	Primary Motor Region
NAA	N-acetyl-asparate
SICI	Short-Internal Intracortical Inhibition
STG	Superior Temporal Gyrus
TD	Typically Developing
TE	Echo Time
TMS	Transcranial Magnetic Stimulation
TR	Repetition time

INTRODUCTION

Autism Spectrum Disorder is a developmental condition that creates challenges for individuals in multiple facets. Autism spectrum disorder (ASD) now encompasses conditions that were once diagnosed as separate disorders. These disorders include Asperger syndrome, pervasive developmental disorder, and autistic disorder; however, nowadays, the Diagnostic and Statistical Manual of Mental Disorders considers all of them under the term ASD (5th ed.; DSM-5; American Psychiatric Association [APA], 2013). The prevalence of ASD has increased over the years and is found in approximately 1 in 54 children aged eight years old. In addition, the condition is 4.3 times more prevalent in males than females (Maenner et al., 2016). There are some questions about whether this increase relates to (1) a broader diagnostic and more apparent detection or (2) an unknown environmental risk factor (Rutter, 2005). As noted earlier, ASD is a developmental delay disorder that can impair communication, social interaction, and behavior. The spectrum attribute to ASD creates a range of effects on each individual. Although the function of hearing is not the most prevalent attribute in ASD, the connectivity of the auditory cortex can broadly impact individuals with ASD.

ASD is typically diagnosed by screening a child and determining if findings satisfy the Diagnostic and Statistical Manual of Mental Disorders (5th ed.; DSM-5; American Psychiatric Association [APA], 2013). The DSM-5 includes five criteria, including (1) persistent deficits in communication and interaction, (2) repetitive patterns of behavior, etc., (3) symptoms present in the early developmental period, (4) symptoms that cause significant impairments in social and

occupational functioning, and (5) disturbances that cannot be better explained by intellectual disability or global developmental delay (APA, 2013; Kent et al., 2013). Although there is no mention of the condition of the auditory cortex in the features required for diagnosis, the presence of unique functioning is an associated feature of ASD.

The occurrence of atypical brain function of the auditory cortex has been reported from an increase of glutamate, inferior leftward lateralization of P50m, hypothesized maturation delay, and abnormal production and maintenance of gamma oscillations (Brown et al., 2013; Edgar et al., 2015; Wilson et al., 2007; Yoshimura et al., 2013). Brown et al. (2013) discovered increased glutamate in the auditory cortex, as well as n-acetyl-aspartate (NAA) and creatine (Cr), which suggests a difference in brain energy metabolism found in individuals with ASD. A study by Yoshimura et al. (2013) suggested atypical brain function in the auditory cortex. This study used magnetoencephalography (MEG) and, while measuring the auditory evoked magnetic field, reported atypical auditory cortex behavior and less leftward lateralization of the intensity of P50m in ASD than typically developing children. Further research done by Wilson et al. (2007) found abnormal gamma band activity in the auditory cortices of participants diagnosed with ASD. It was discovered that there was significantly reduced left-hemispheric 40 Hz power from the post-stimulus onset using MEG in the contralateral hemisphere. The results from ASD participants of both production and maintenance of left-hemispheric gamma oscillations were aberrant (Wilson et al., 2007). Furthermore, Edgar et al. (2015) investigated associations between age and superior temporal gyrus (STG) auditory time-domain and time-frequency

neural activity in ASD. When conclusions were reached, researchers also hypothesized a delay in maturation of the auditory cortex (Edgar et al., 2015).

Several studies have assessed other auditory abnormalities and characteristics associated with ASD. In a study describing the sensory abnormalities in children and adults with ASD, 94% of children had sensory symptoms (Leekam et al., 2007). Although the Diagnostic Interview for Social and Communication Disorders (DISCO) showed a less significant difference in auditory symptoms in autism and non-autism groups, the DISCO did use fewer acoustic measures than similar sensory surveys and did not represent the hypo and hypersensitivity to auditory stimuli. In another study, describing the auditory characteristics of children with ASD relative to typically developing children, equivalent physiological test results were also found; however, in behavioral measures, half of the children with ASD had out-of-normal limits pure tone averages (Tharpe et al., 2006). A study, related to sensory quantitative and qualitative data, identified a positive correlation between the number of autistic traits and the frequency of atypical response to sensory stimuli (Robertson & Simmons, 2013). Roberson & Simmons (2013) used the autism-spectrum quotient (AQ) and a self-revised Glasgow Sensor Questionnaire to analyze hyper- and hyposensitivity in the following items: visual, auditory, gustatory, olfactory, tactile, vestibular, and proprioceptive. They discovered the auditory item to have the highest mean score in AQ. Thus, evidence suggests disturbance in the auditory cortex in ASD.

The perceptual and auditory processes in individuals with ASD have also been delved (Gomot et al., 2002; Whitehouse & Bishop, 2008). Whitehouse & Bishop (2008) suggest the

perceptual and early cognitive processes are impaired in children with autism in novel non-speech and speech sounds but not in familiar non-speech sounds. Gomot et al. (2002) focused on auditory processes and used an electrophysiological probe, called mismatch negativity (MMN), to record activity. The findings consisted of earlier MMN peak latency in children with Autism (CWA) and varying MMN topography for the control group and CWA, suggesting different brain mechanisms involved in the auditory stimulus-change detection (Gomot et al., 2002). Finally, Brennan et al. (2016) sought to test for abnormal phonological perception at the neural level using MEG through the use of "legal" pseudo-words like "vimp" and "illegal" non-words such as "vinp" to test the process. Evidence was found for sensitivity to "illegal" sequences in participants with ASD. They noticed the right-hemisphere response consistent with cascading effects from atypical early auditory stages, which may then impact phonological processing (Brennan et al., 2016).

Despite the fact that the auditory cortex is disturbed in ASD, functional connectivity of the auditory cortex in ASD has not been well studied. In this study, the auditory cortex's functional connectivity has been examined using the resting-state functional MRI data from Autism Brain Imaging Data Exchange (ABIDE).

METHODS

Data Acquisition

Through the use of Autism Brain Imaging Data Exchange (ABIDE) MRI images, clinical data and demographic data were obtained. In addition, data from the University of Michigan cohort was also used from the data subsets available. This image data included both resting-state and structural data of 145 individuals. Within this cohort, 68 individuals had an ASD diagnosis called the ASD group (13.13±2.41 years old), and 77 individuals were age-matched and called the control group (14.79±3.57 years old).

To acquire data, resting-state echo-planar image (EPI) volumes had 4mm 64x80 matrix with 4mm thickness with a voxel size of 3x3x4mm in 33 slices. The repetition time (TR) was 2000ms, and the echo time (TE) was 15ms. The analysis overall used 180 volumes for a total of 6 minutes. One hundred twenty-eight sagittal slices of 256mm x 256mm with 1mm thickness were acquired through high-resolution structural T1 (MPRGE) with a voxel size of 1.3x1.3mm, TR of 2530ms, TE of 3.25ms.

Data Processing

Using FMRIB Software Library (FSL) and Analysis of Functional NeuroImages (AFNI), data preprocessing and statistical analyses were completed. Each subject's skull was stripped to find the anatomical volume. The skulls were then segmented into grey matter, white matter, and cerebrospinal fluid (CSF). Finally, the subject's skulls were registered to the MNI 2mm standard

brain. The first four EPI volumes were removed, and transient signal spikes were extracted by de-spiking interpolation. They were linearly registered to the previous first volume to remedy supplementary head motion volumes, for which six motion parameters and displacement distances between two consecutive volumes were previously predicated. Each resting-state volume and the six motion parameters were regressed by CSF signal and white matter fluctuations. The volumes were resampled, spatially transformed, and aligned to the MNI 2mm standard brain space after being smoothed with a 6mm FWHM Gaussian kernel. In this enrollment, rs-fMRI volume and MN1152 2mm space created 12 affine parameters to allow a seed ROI to be later registered to each individual re-fMRI space. The root mean square deviation was calculated from motion correction parameters, using FSL's *rmsdiff* toll at an *r=40mm* spherical surface, to perform scrubbing where volumes with excess motion are removed as a displacement distance between two EPI volumes (Power et al., 2015; Power et al., 2012). When volumes exceeded the displacement distance threshold of 0.3mm, they were then *scrubbed* from any further statistical analyses (Siegel et al., 2014).

The bilateral primary auditory cortices were characterized by Heschl's gyrus's extraction, from the Harvard-Oxford atlas, to conduct voxel-wise functional connectivity analysis. The mean EPI signal, however, was first estimated for each volume within the ROI's.

Analysis of the voxel-wise connectivity was managed in the primary auditory cortices along with the whole brain. To test correlations, between the primary auditory cortex and the individual voxels across the brain, the primary auditory cortices registered to the EPI space were

spatially averaged in the time course. The Z-scores depicting the correlations within the individual voxels and the primary auditory cortices were then used for group-level analysis after being registered to the MNI 2mm brain space.

Statistical Analysis of Functional Connectivity

The ASD group and control group were studied and compared through *randomize* script in FSL. The cluster size had a threshold at $k>100$ and TFCE $p<0.05$ with FWE correction.

RESULTS

Through voxel-wise analysis of the auditory cortex's functional connectivity, results showed significantly less connection to the four clusters. This is displayed in both Table 1 and Figure 1. The four clusters were located in the occipital cortex, the visual processing center, the precentral cortex, the motor region, the parietal operculum, and the supramarginal gyrus (i.e., Wernicke's area). There was no considerable or greater connectivity found in the regions to the auditory cortex in the ASD group when compared to the controls.

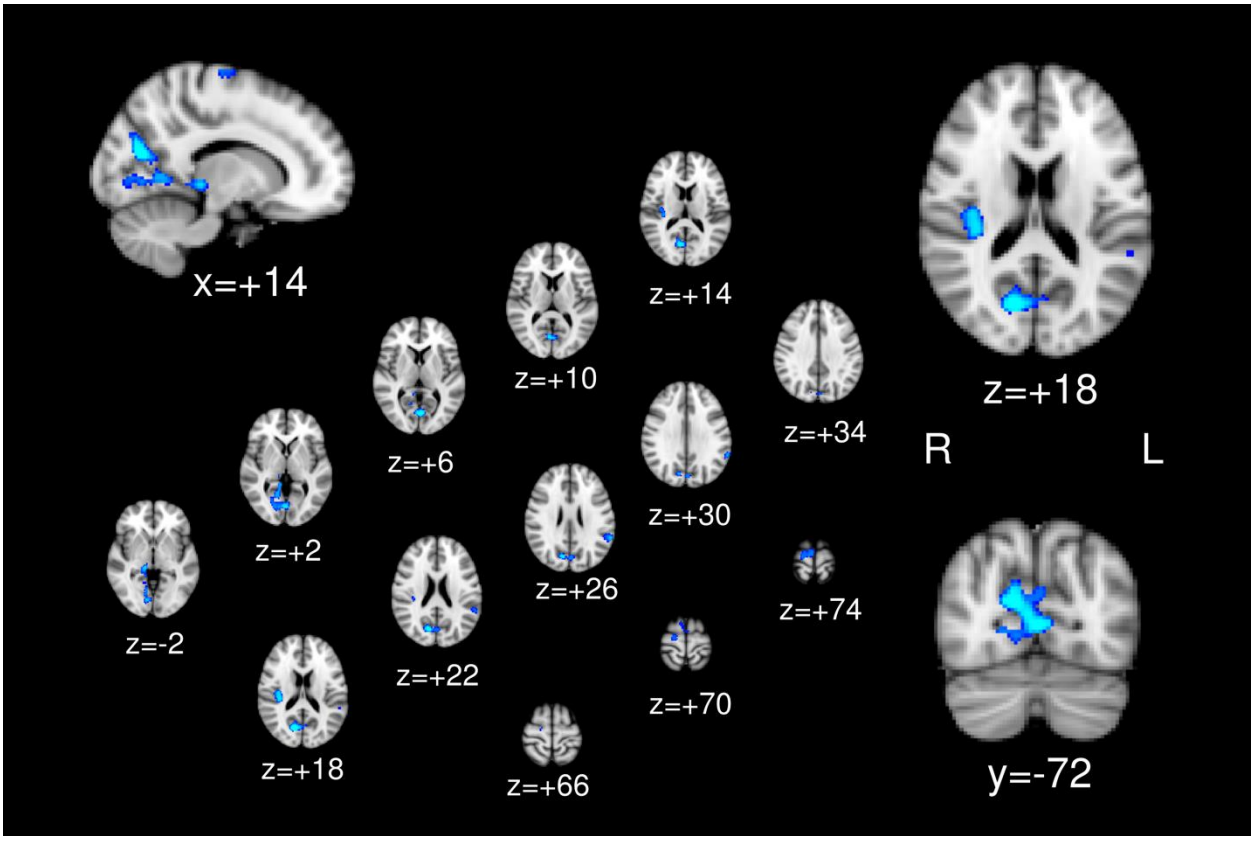

FIGURE 1: Voxel-Wise Analysis in ASD Brain

Region	Peak MNI Coordinates			Peak Voxel p (corrected)	Voxels
	x	y	z		
Intracalcarine Cortex, Cuneal Cortex	14	-72	18	0.028	1123
Precentral Gyrus	6	-14	74	0.039	180
Right Parietal Operculum	36	-26	18	0.031	179
Left Supramaginal Gyrus	-62	-46	26	0.033	158

TABLE 1: Voxel-Wise Analysis Data

DISCUSSION

This study elucidated four regions that were less connected with the auditory cortex in the ASD group than the non-autism group. These included the occipital cortex, motor cortex, insular cortex, and Wernicke's area. Previous studies reported influence of ASD to these four regions.

The occipital cortex's dysconnectivity in ASD has been seen in previous studies using brain imaging tools (Belmonte & Yurgelun-Todd, 2003; Jung et al., 2019). Jung et al., (2019) discovered significantly decreased structural connectivity, resting-state brain activity, and surface area at the occipital cortex in boys diagnosed with ASD. Another study, using functional magnetic resonance imaging during a visual-spatial attention task, discovered that modulation of activation in the ASD brain as a function of the lateral focus of spatial attention was abnormally decreased in the left ventral occipital cortex (Belmonte & Yurgelun-Todd, 2003). Further research concerning the occipital cortex in ASD also found conflicting results on white matter levels. Cheung et al., (2009), using voxel-based methods, discovered white matter fractional anisotropy (FA) in the right inferior frontal gyrus and the left occipital lobe to be significantly greater in the ASD group than in the control group. In contrast, Levitt et al., (2003) found 6.6% less white matter volume in the left occipital cortex voxel in ASD than in the matched control group. Cr plus phosphocreatine was also 16.6% lower in the right occipital cortex than controls (Levitt et al., 2003). Though these findings may not be consistent, it is manifested that ASD influences the occipital cortex. Our research found no greater connectivity in the occipital cortex with the auditory cortex in the ASD group compared to the control group.

We also observed a dysconnectivity between the motor cortex and auditory cortex in the ASD group. Literature supports this abnormal connectivity and activation of the motor cortex in the ASD population (Linke et al., 2020; Mostofsky et al., 2007). Functional connectivity was found to be significantly weaker in the ASD group than controls for the right primary motor region (M1), and impairments that were found to be affecting most motor subdomains were also accompanied by atypical functional connectivity between sensorimotor regions (Linke et al., 2020). Research has also been done to examine if the radiate white matter in the motor cortex would predict impaired motor function in children with ASD. Children with ASD showed a positive correlation between the Physical and Neurological Examination of Subtle Signs (PANESS) score and increased left hemisphere primary motor and premotor white matter volumes (Mostofsky et al., 2007). More recently, Masuda et al., (2019) conducted a systematic review on transcranial magnetic stimulation (TMS) in M1, using short-internal intracortical inhibition (SICI), which was likely to be reduced in individuals with ASD. This review also suggested that reduced GABA receptor-mediated function in neural circuits could underlie the cortical excitation/inhibition in ASD (Masuda et al., 2019). Finally, Nebel et al., (2014) discovered a gross dorsomedial to ventrolateral organization emerged within M1, which was left-right symmetric in both ASD and control groups, although there were significant differences in size and segregation of parcels, which suggest differentiation between lower limb/trunk regions and upper limb/hand regions. This finding could be due to the delay in functional specialization within the motor cortex (Nebel et al., 2014). This finding suggests that the motor control system's functional subnetworks may be altered in autism (Nebel et al., 2014), which correlates

with our dysconnectivity results in the auditory cortex and motor cortex. Hence, the findings suggest that our discovery of auditory-motor dysconnectivity is associated with the general influence of ASD on the motor cortex.

Along with our findings of reduced connectivity between the auditory cortex and the insular cortex in ASD, further research has located deficits in grey matter, connectivity, and activation in the insular cortex (Anderson et al., 2010; Francis et al., 2019; Parellada et al., 2017). For example, Parellada et al., (2017) found a grey matter deficit by comparison of the healthy control group with children with ASD and observed lack in the right anterior insula (ASD: $p=0.007$) and bilateral posterior insula (left, ASD: $p=0.011$; right, ASD: $p=0.004$). Furthermore, a voxel-based morphometry analysis discovered ASD patients had grey matter volume and thickness deficit in the left posterior insula (Parellada et al., 2017). Along with a reduction in gray matter in the insular cortex in ASD, there is also hypoactivation in high functioning autistic populations (Anderson et al., 2010). It has been shown that there are differences in insula activation between ASD and typically developing control subjects as the ASD group activation in the left posterior insula was significantly decreased (Anderson et al., 2010). Another study investigated the connectivity found in the insular cortex and observed hypoconnectivity in the anterior insula superior frontal gyrus, anterior insula-thalamus, posterior insula parietal lobe, posterior insula-fusiform gyrus, and posterior insula-lentiform nucleus/putamen (Francis et al., 2019). Further dysfunction in the insular-specific cortex was also observed in children with ASD compared to TD control subjects (Lynch et al., 2017). Lynch et al., (2017) compared a resting-state and selective attention task and found that the participation

coefficient of the frontoparietal-insular cortex decreased in children with ASD, which suggests executive impairments in ASD emerge from a failure of the frontoparietal-insula control regions. In another study, the insular cortex's functional and organization structure were examined, and alterations were found in the left insula's anterior and middle- ventral sub-regions of the right insula in the ASD brain (Yamada et al., 2016). Meta-analytic decoding showed only a single functional cluster for cognitive and sensorimotor functions in the anterior sector (Yamada et al., 2016). This information recalls the sensory information needed for hearing and relates to our study's focus, the auditory cortex's function in ASD. Our finding is consistent with other studies in that sensory regions are disconnected from the insula in ASD.

The last brain region that showed dysconnectivity to the auditory cortex in ASD was Wernicke's area. There have been reports of hypoactivity in Wernicke's area in varying ages (Lee et al., 2017; Nielsen et al., 2014). Lee et al., (2017) investigated the age-related changes in functional connectivity and degree centrality and, concerning the Wernicke's area, detected that adults with ASD had decreased degree centrality compared to the typically developing group. Concurring with this data, Nielsen et al., (2014) found that groups with ASD exhibited significantly reduced left lateralization in connections involving language regions, including Wernicke's. Nielsen et al., (2014) suggested a trend of less left lateralization in connections with the Wernicke area and posterior cingulate cortex associates with more severe autism. Further research has been done to study the changes in intrinsic connectivity in Wernicke's area once interventions are added to children with ASD (Murdaugh et al., 2015). Murdaugh et al., (2015) discovered stronger functional connectivity through analyses in Broca's and Wernicke's area

post-intervention in the experimental group of ASD children. Through the research focused on connectivity in Wernicke's area, we can infer a disconnect between this area in ASD individuals**.** Along with a disconnect found in Wernicke's area research, we also discovered research findings on an abnormal amount of connectivity within ASD groups. Just et al., (2004) studied participants using functional MRI in a sentence comprehension task and discovered that the autism group produced more activation in Wernicke's area (left lateral-superior temporal), which suggests that the neural basis of disorder language in autism entails a lower degree of information integration across the large-scale cortical network for language processing. It was also discovered in semantic processing and fMRI that there was an increase in activation in Wernicke's area for adult males with ASD (Harris et al., 2006). Our results concur that the dysconnectivity we located between the auditory cortex and Wernicke's area in the ASD population is also found in research concerning Wernicke's area activation and connectivity in the ASD brain. The lack of connectivity we discovered between Wernicke's area and the auditory cortex could lead to further difficulties and complications for those with ASD. If the auditory cortex is less connected to a vital language processing center, this could impact many facets of the individual's life, including learning and communication.

LIMITATIONS

A significant limitation in our study that needs to be addressed is the lack of hearing status in individuals for both control and ASD groups. Using the ABIDE MRI images and data from the University of Michigan cohort, we did not have access to individuals' hearing test information. This means we do not know if individuals in our study had hearing loss, and if they did, the type of loss. Our study researched the auditory cortex, which processes auditory information, so the type of hearing loss, such as a sensorineural loss, could impact the results. As we do not have access to participants' hearing status, we also do not know their personal background. This includes the social-economic status, gender, race, and ethnicity of the individuals. Without acknowledging the diversity in this study, it will be difficult to generalize our study's results. Finally, as mentioned earlier, ASD is a spectrum with wide variation, and individuals are placed in a range based on the severity of the diagnosis. Due to the lack of access, we do not know the participants' specific diagnosis of ASD, and this limitation also creates difficulties in generalizing results found.

CONCLUSION

In conclusion, through voxel-wise analysis in the ASD group, we found less connection with the auditory cortex to and from four cortices: (1) occipital cortex, (2) precentral cortex, (3) parietal operculum, (4) supramarginal gyrus. The association of weak connectivity in the auditory cortex and the mentioned cortices seems specific to ASD. In comparison, the control group had greater and more standard connectivity within the four cortices and the auditory cortex. Our results align with previous research on the functional connectivity of the auditory cortex as atypical in ASD and may suggest that many cortices functional networks may be altered in ASD (Nebel et al., 2014). Although there is research to support our findings, there is a need for further research on the auditory cortex in ASD. Future studies should collect information on the participants' (1) personal background and (2) descriptive ASD diagnoses to allow better generalization of results. Further research will be able to provide further information and knowledge for those with diagnoses of ASD, audiologists, neurologists, behavior modification counselors, and fellow health professionals that work closely with individuals diagnosed with ASD. Our findings emphasize the importance of further research on the auditory cortex's functionality within individuals diagnosed with ASD.

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