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Wernicke's Area in Autism: rsfMRI study

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By
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ABSTRACT

SYDNEY CLAIRE OSBARN: Wernicke's Area in Autism: rsfMRI study
(Under the direction of Dr. Tossi Ikuta)

We investigated the functional connectivity of Wernicke's Area and its right homologue (Planum Temporale) in individuals with Autism Spectrum Disorder (ASD) and typically developing individuals. We used resting state functional magnetic resonance imaging to analyze these areas in 145 participants from The University of Michigan via ABIDE. As a retest sample, we also used data from a University of Pittsburgh cohort. There is weakened functional connectivity between Wernicke's Area and Planum Temporale in individuals with ASD as opposed to typically developing individuals. Participants with ASD did not have greater connectivity in other regions compared to the control group. Pragmatics, nonverbalism, speech perception, and receptive language could possibly be affected in individuals with ASD because of the poor functional connectivity in Wernicke's Area.

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INTRODUCTION

Autism Spectrum Disorder (ASD) is characterized by social communication deficits, as well as repetitive and restricted movements and behaviors (Tager-Flusberg, H. 2015; Simmons, E., Paul, R., Volkmar, F. 2014; Pang, E. et al. 2016). ASD is also etiologically and clinically heterogeneous, also containing a genetic component (Miles, J. 2011). There is a timeline when children should begin to reach certain milestones, and by 12 months, language and gestural communication is delayed in those with autism. There also can be some delayed motor development as well (Groen, W. et al. 2008). Communication deficits are one of the key characteristics of ASD.

There are clinical features, as well as language and speech impairments, in ASD. Communication can be difficult for individuals with autism, and this starts with not being able to formulate one and two-word combinations at a very young age. Impairments in language include expressive and receptive language barriers that keep individuals with ASD from being effective communicators. Sometimes, they will not be able to understand what is being asked of them, and in turn, will not be able to respond in the appropriate way. Studies also show that individuals with autism may refer to themselves in 2nd or 3rd person or use 1st person to the one being addressed, and this is known as pronominal reversal. Pronominal reversal is the act of switching pronouns when referring to oneself or another person (Sterponi, L. & Kirby, K. 2015). Within autism, the domain of pragmatics is a category that is most often impaired. The pragmatic uses of language that individuals with autism may have deficits includes tendencies of taking everything literally, having trouble with accepting synonyms, and using irrelevant speech within a conversation.

There are four main areas that were tested by Simmons, E. et al. (2014), and they are discourse management, conversational repair, presupposition, and communicative functions. Individuals with high functioning autism had issues with background information, topic maintenance, and requesting information within discourse management. Multiple cues had to be used with conversational repair skills, and they found that these individuals have many errors with ambiguous pronouns. All of those areas that were tested are pragmatic language skills. It is also understood for these individuals to have difficulty in acquiring grammar and sign, and they often have a reduced mean utterance length and are inconsistent with verb tense markers and articles. There can also be issues with prosody (Groen, W. et al. 2008). Speech perception is a symptom of ASD (Tager-Flusberg, H. 2015), and this is impactful knowledge based on this current study of the functional connectivity of Wernicke's Area in Autism.

There are a limited number of previous studies of Wernicke's Area in Autism Spectrum Disorder (ASD). In this study, we aimed to examine functional connectivity of the central part of Wernicke's area, the left planum temporale, using resting state functional MRI (rsfMRI) data. We hypothesized that there is hyper and/or hypo connectivity to some other part of the brain in the ASD group, compared to the typically developing group.

Interventional effort for ASD has been found to alter Wernicke's area. A reading comprehension intervention resulted in greater connectivity in Broca and Wernicke's area compared to the ASD control group who did not receive the intervention. The activation in the experimental group was increased specifically between LIFG and LMTG and bilateral cerebellum (Murdaugh, D. et al. 2015).

It has not been clear why there are contradictions in over- and under- connectivity in different studies with using ASD as their basis of functional connectivity in different parts of the brain.

Classically, Wernicke's Area had previously been defined as the posterior superior temporal gyrus (Geschwind, 1970), but more recently, it is understood to include the adjacent supramarginal gyrus as well (Binder, J. 2017). Tremblay, P. and Dick, A. (2016) describe the anatomical structure of Wernicke's Area to also be located at the posterior temporal gyrus, as well as include part of the supramarginal gyrus. Groen, W. et al. (2008) supports Wernicke's Area being located in the posterior superior temporal gyrus, but he includes the Sylvian fissure in his anatomical description. We also know that Wernicke's Area is located in the left hemisphere and is left lateralized (Binder, J. 2017; Zhu, L., et al. 2014). Understanding the functions of Wernicke's Area can help with linking our findings to what is known about the area.

Even though anatomical regions and functions are known about Wernicke's Area, there are still controversies on the function and structure of Wernicke's Area. According to Binder, J. (2017), Wernicke's area does not play a role in speech comprehension per se. In fact, a localized speech comprehension center has not been found to exist. Overall, we know Wernicke's Area to include a speech perception and receptive language component as its function.

In Wernicke's Area, the right hemisphere homologue, or the right hemisphere counterpart of the brain, is used for figurative language and possibly auditory motion perception (Zhu, L. et al. 2014). Wernicke's area is understood to be one of the language centers of the brain. It was originally thought to be responsible for the comprehension and receptiveness of language. The ability to complete language tasks are also housed in Wernicke's Area (Binder, J. 2017). According to Tremblay, P. and Dick, A. (2016), Wernicke's Area is important for language

comprehension and communication between brain regions. Language processing uses hearing and sight, and they found that Wernicke's Area is strongly anti-correlated with visual and auditory cortices (Tomasi, D. & Volkow, ND. 2012).

For speech components, phoneme perception may also be a function of Wernicke's Area. It is reported that Wernicke's area is associated with phonological representations and phonological short-term memory, which aids with sentence comprehension and providing meaning to speech sounds (Binder, J. 2017). Phonological representation refers to spontaneous speech, naming, reading aloud, repetition, etc. Damage to Wernicke's Area can cause internal mental images of phonemes to be impaired and unable to be recalled.

Functional connectivities studies indicated there is over- and under-connectivity in the brain of individuals with autism, and this depends on a couple of factors. This rapid growth in the most critical years of development may be one of the reasons why certain parts of Wernicke's area don't perform as it does in a typical individual. These areas are not able to be fully formed and organized the same as if it grew at a normal rate. The rapid growth and shrinking later in life can explain abnormalities, especially in the frontal and temporal lobe. Because the brain is changing even at older ages, this could be why with much language and speech intervention, individuals with autism can learn to speak and/or sign even after they have missed that critical period. One study showed increased activation during semantic processing in adolescents with ASD, compared to typically developing adolescents (Knaus, et al. 2008; Murdaugh, D. et al. 2015; Lee, Y. et al. 2017). Individuals with ASD showed more regions activated during semantic processing, while there was more activation in the left-brain hemisphere in both groups and hardly no activation in the right hemisphere (Knaus, T. et al. 2008). In adults with ASD, more degree centrality (DC) in Wernicke's area was found

compared to the non-ASD cohort, as well as less degree centrality (DC) in the remainder of the left STG (Lee, Y. et al. 2017). A postmortem study found increased oxidative stress markers in Wernicke's area in individuals with ASD compared to the control group (Sajdel-Sulkowska E.M. et al. 2010).

The functional connectivity of Wernicke's in ASD is unknown. Therefore, in this study, we tested the functional connectivity of Wernicke's Area to other areas in the brain and found that it is least connected to the right homologue of Wernicke's Area. We hypothesized that the functional connectivity would be different in individuals with autism as opposed to typically developing individuals. Weakened functional connectivity is found in individuals with ASD and could be the cause of some of the symptoms in ASD.

Methods

For this study, we used resting state functional magnetic resonance images(rsfMRI) to determine the difference, if any, of Wernicke's Area between individuals with ASD and typically developing individuals. All data (MRI images, clinical, and demographic) derived from Autism Brain Imaging Data Exchange (ABIDE). Our study consisted of 145 participants from a cohort at the University of Michigan. Resting state and structural data was obtained from each individual. Our participants were split into two groups: experimental and control. Sixty-eight participants had been diagnosed with ASD and 77 individuals were typically developing. Ages ranged from 10.72 to 15.54 in the experimental group with an average of 13.13. The average age in the control group was 14.79 with ages ranging from 11.22 to 18.36. As a retest sample, we also used data from a University of Pittsburgh cohort. This consisted of 83 participants. Forty-four were in the ASD experimental group (ages ranging from 13.71 to 28.89), and 39 were in the typically

developing control group (ages ranging from 14.21 to 27.77). The median age for the experimental group was 21.30 and for the control group 20.99.

Resting state echo planar imaging (EPI) was used, and those volumes had 33 slices of 4mm 64x80 matrix with 4mm thickness (voxel size=3x3x4 mm). This was done with repetition time (TR) of 2000ms, with an echo time (ET) of 15 ms. We used 180 volumes (equivalent of six minutes). Sagittal high-resolution structural T1 volumes were acquired as 128 slices of 256mm x 256mm with 1mm thickness (voxel size = 1.3x1x1.3mm, TR=2530ms and TE=3.25ms).

In order to process MRI data, FMRIB Software Library (FSL) and Analysis of Functional NeuroImages (AFNI) were used. Each participant's anatomical volume was skull stripped. The gray and white matter and CFS were segmented, and the volume was then registered to the MNI 152 2mm brain. To begin, four EPI volumes and transient signal spikes were removed. De-spiking interpolation was utilized to remove these signal spikes. To correct head motion, volumes were aligned to the first volume. From this, displacement distance and motion parameters were measured. The volumes were smoothed using a 6mm FWHM Gaussian kernel, resampled, and spatially changed. This was then matched to the MNI 2mm standard brain space. Twelve affine parameters were formed in order for EPI volumes to be paired with the MNI space. Volumes with motion were taken out in order to allow scrubbing to take place The root mean square deviation was taken from motion correction parameters assuming an r=40mm spherical surface using FSL's rmsdiff tool (Power et al. 2012, 2015). Volumes with displacement distance over .3mm were removed.

For this study, the Planum Temporale in Harvard-Oxford 2mm atlas (50% probability) was defined and used as Wernicke's Area (Fig 1). ROI, voxel-wise connectivity was analyzed.

The z scores and images between the two analyzed and estimated, respectively, based on Z>3.291. Peak voxels were conducted using vocal-wise significance estimates.

Given the findings from the primary data set, bilateral connectivity of the Planum Temporale was tested. The left and right Planum Temporale were extracted and the time course was spatially averaged within left and right Planum Temporale and the correlation between left and right was tested in each individual. Student's T-test was conducted to test the difference between the ASD and control group.

Results

In the ASD group, the functional connectivity of Wernicke's Area showed significantly lower connectivity in the right Planum Temporale (peak MNI=[+58-28 12] 1049 voxels; peak voxel's family-wise error-corrected p=0.003 Fig 2) compared to the control group. There were no regions that showed greater connectivity in the ASD group compared to the control group. Upon re-test, subjects with ASD had less connectivity in the bilateral Planum Temporale as opposed to typically developing individuals (df=81, t= -2.30, p<0.024).

Discussion

In this study, we analyzed the difference in functional connectivity of Wernicke's Area between individuals with ASD and typically developing individuals.We found that the functional connectivity to the right hemisphere homologue of Wernicke's Area (Planum Temporale) to be smaller in the ASD group than the typically developing group. In other words, the activations are less synchronized between Wernicke's area in the left hemisphere and in the right hemisphere in the ASD group.

In order to re-examine our findings, we used an independent sample from The University of Pittsburgh as our re-test group. We tested the functional connectivity between the left planum

temporale (Wernicke's area) and right planum temporale (the right hemisphere homologue of Wernicke's area). We found lesser functional connectivity between the bilateral planum temporali in individuals with ASD as opposed to typically developing individuals ($df = 81$, $t = -2.30$, $p < 0.024$), replicating our original findings from the University of Michigan cohort.

Based on our findings from our primary data set and our re-test data set, we can conclude that Wernicke's Area is not communicating fully with the right side Planum Temporale in individuals with ASD, compared to typical individuals.

As discussed in our introduction, Wernicke's Area is believed to be responsible for speech perception and providing meaning to speech sounds (Wang, J. et al. 2015). Binder, J. (2017) rejects the idea that this area is used for speech perception but does agree in the area assigning meaning to speech sounds. His research supports the understanding that this area is responsible for phoneme perception, which causes speech production and short-term memory tasks. Activation of Wernicke's Area in a study done by Groen, W. et al. (2008) supported the responsibility of this area in processing the meaning of words in individuals with ASD. Because of our findings of less functional connectivity of Wernicke's Area in ASD, this could explain these symptoms present in individuals with ASD.

Apraxia and aphasia could be conditions found in ASD that also could result, in part, from our findings. Aphasia can be caused by damage to the pSTG (classical Wernicke's Area). This is also believed to allow difficulty in assigning meaning to speech sounds (Binder, J., 2017). Phoneme perception can work in either hemisphere independently, but if the connection of Wernicke's area to the Planum Temporale is weakened in ASD, more difficulty may arise in phoneme perception. Phonological paraphasia, which is defined as impairment in speech perception, also occurs because of damage to this area. Because right Wernicke's Area is

responsible for figurative language, this could also help explain why individuals with ASD take everything literal, especially since the connection is weaker from the left and right areas (Tomasi, D. & Volkow, ND 2012; Zhu, L. et al. 2014). This deficit in understanding figurative language also falls under the pragmatic language category.

There are symptoms of ASD that we believe may be connected to our findings regarding the functional connectivity of Wernicke's Area. According to the study done by Juncos-Rabadán, O. (1992), individuals with ASD show a preference for affirmatives. Affirmatives are sentences that have a positive predicate instead of a negative one. For example, "I am happy" is a true affirmative. "I am not happy" is a true negative. When events are occurring around an individual with ASD, they have longer reaction times in general. Because negative sentences require a longer processing time, this diverts individuals with ASD to prefer affirmatives. The study mentioned above also proves our findings to be true by explaining there is a connection between Wernicke's Area and affirmatives. Left Wernicke's Area shows a connection, but right Wernicke's Area does not (Juncos-Rabadan, O. 1992). Individuals with ASD also have deficits in appreciating humor, observing politeness, maintaining relevance, and producing well-formed narrative structure. These four areas are similar to problems when individuals experience aphasia. Aphasia, relating to Wernicke's Area, is the impairment of understanding speech (Tanner, D. 2007). All of those things cannot be practiced correctly because the individual's speech perception and comprehension is impaired.

Oftentimes, individuals will exhibit nonverbal communication in Autism Spectrum Disorder (Franchini, M et al. 2018). These individuals also have a preference for nonverbal sounds (Groen, W. et al. 2008). Emergence of consistent nonverbal communication cannot be tracked until a child is at least a year old. Whether a child is verbal or nonverbal is the main

factor in determining if a diagnosis for autism is appropriate, as well as the likelihood that a sibling will have ASD. Other important nonverbal communication skills that are important for tracking development include joint attention, imitation, motor skills, and play development. Lack of these skills also point towards a diagnosis of ASD. Imitation and play development contain use of pragmatic skills which Wernicke's area plays a part in. Gestures are acquired before verbal expression in children with ASD. Motor skills are related to verbal reception development, so it would make sense that impairments to Broca's area are closer related to nonverbal communication than Wernicke's Area (Franchini, M. et al. 2018). Because of our findings, this weakness in functional connectivity of Wernicke's Area could play a part in the impairment to perceive and produce speech in ASD. If an individual cannot perceive speech, then he or she cannot produce speech. Due to a lack of functional connectivity of the speech perception center of the brain, individuals with Autism have a chance of being minimally verbal or completely nonverbal.

Wernicke's area has been known for comprehension for a long time. In fact, classical Wernicke's Area was strictly known for receptive language (Wang, J. 2015; Tomasi, D. & Volkow, ND. 2012). Now that there is more of a speech perception component added there, comprehension impairments still are involved in individuals with damage to this area. Therefore, there is more of a disconnect in the receptive language component, as opposed to expressive language. In the study done by Selassie, G. et al. (2019) , two participants underwent transcranial magnetic stimulation of Wernicke's area and it's right homologue to find that there was a delay in response in understanding sentences. The bilateral pattern that was found after testing can be used to help with language even if the left hemisphere is damaged because the research says there is a good chance the right hemisphere will compensate for the language inabilities of the

left hemisphere. Our findings of weakened functional dysconnectivity in Wernicke's Area may help prove why there are receptive language impairments in ASD.

When looking at symptoms of ASD and comparing them with our findings of Wernicke's Area, issues with discourse management, conversational repair, topic maintenance, requesting information, and background information are likely caused because of receptive language deficits. Some other symptoms of ASD include issues with prosody, presupposition, and echolalia. Processing of prosody is mainly found in the right hemisphere, but can also appear in the left, so this is likely not related to Wernicke's Area. Presupposition involves the inability to understand ambiguous pronouns (Simmons, E. et al. 2014). This lack of understanding can link to impairments in receptive langauge. For echolalia, the person is not understanding what is being said/asked, so the individual is repeating it back to the original speaker (Sterponi, L & Kirby, K. 2015). This could be related to our findings because it deals with comprehension of spoken words. Comprehensive issues in ASD may be due to dysconnectivity between bilateral Wernicke's Area. Symptoms caused as a result of our findings can have an indirect impact on social communication. Being nonverbal and exemplifying pragmatic differences can make it hard for an individual to practice socially acceptable behaviors and communication.

Pronominal reversal is a symptom of ASD (Sterponi, L. & Kirby, K. 2015). Regarding pronominal reversal, three groups, non-fluent individuals with aphasia, fluent individuals with aphasia, and healthy individuals, were presented in a study done by Khaledi, M. (2017). Present tense comprehension between all groups was found, but future tense production was only found in healthy individuals and non-fluent individuals with aphasia. Individuals with aphasia also have trouble with forming long, complex, well-formed sentences, as well as having impaired processing of tenses and objective pronouns and impairment in functional morphology usage. If

the individuals can see the story while retelling it, the individuals with aphasia can perform better overall as opposed to not being able to see the story. This could also be why visual schedules help an individual with autism. When the individual with autism is able to visually see a picture of the task they are supposed to complete, or the behavior they are supposed to exemplify, he/she is better able to perform. Reversal errors can also have an effect on empathy, a pragmatic skill (Menn, L. et al. 1997). With research showing it is a symptom of ASD and also a symptom of Wernicke's aphasia, this topic could be connected to our research. If the functional connectivity of the Planum Temporale is impaired in ASD, pronominal reversal would be affected (Khaledi, M. 2017).

Limitations:

Our study contained an experimental and control group, with the experimental group consisting of participants with ASD and the control group consisting of typically developing individuals. Some limitations of our study include that we did not actively stimulate Wernicke's Area. Both groups were retrieved from the ABIDE database, and we used 145 participants from the University of Michigan. We compared both groups based on their diagnosis of ASD. We did not compare the severity of the diagnosis and the functional connectivity of Wernicke's Area. This is an area that could be further studied in order to build on our results. Another limitation could include the fact that our participants were gathered from the same database and geographical area. We also don't have a wide range of age, which can be good for reaping results based on a certain age group, but these results may not be able to be generalized to young children or older adults. To account for the geographical area limitation, we conducted our re-test on a sample from Pittsburgh, whereas our primary data set came from Michigan.

Conclusion:

We hypothesized there would be a difference in the functional connectivity of Wernicke's Area in individuals with ASD and typical individuals. Based upon our findings, our hypothesis proves true. Upon analyzing the rsfMRI images, we found a weaker connection in Wernicke's Area in the ASD group compared with our control group in both sets of data. Functional dysconnectivity between bilateral planum temporale may account for some of the known symptoms in Wernicke's area such as pragmatic language use, non verbal-ness, pronominal reversal, and receptive language.

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