Volumetric Brain Changes in the Number Processing Network Over Time in Individuals with Autism Spectrum Disorder

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Autism Spectrum Disorder (ASD) affects around one percent of people worldwide and is commonly known to impair behavior and language. Recent studies have also shown that it affects other subjects such as mathematics, a complex involving many brain processes, including number processing, number visualization, problem decomposition, and more. Many autistic individuals struggle with number processing and visualization, but no prior study has analyzed the volumetric growth and structural covariance of regions involved in the number processing network. The present study investigates how the growth of brain regions of the number processing network changes with ASD. Brain region volumes of 482 individuals with Autism and 412 individuals without Autism were estimated from MRI scans of the Autism Brain Imaging Data Exchange (ABIDE database). Regression models identified the regions of the number processing network that were the most significant predictors of mathematical capability. The identified regions all belonged to the inferior parietal lobule. After analyzing interaction models involving the identified regions, it was determined that the growth of these regions varies more in individuals with ASD than in typically developing individuals. It is known that brain structure affects function, so the variation in growth is significant because it suggests that, specifically in individuals with ASD, the regions identified are the ones that are responsible for differences in math ability. Future studies should focus on activation patterns of the inferior parietal lobule and how number visualization competency changes over time in individuals with ASD.

Introduction

Autism Spectrum Disorder (ASD) is a neurological disability that affects social interaction, behavior, and communication[1]. It is known as a "spectrum disorder" because of its heterogeneous nature; the effects of ASD and its severities vary tremendously. All races, ethnicities, and genders can be diagnosed with ASD. As a result of improvements in diagnostic technologies and our understanding of the autism spectrum, the incidence of autism has increased in the past decades as more people have been correctly diagnosed. Currently, an estimated 5,437,988 (2.21%) adults in the United States have ASD[2], and it is estimated that one in 100 children has autism worldwide[3]. With an increasing prevalence of ASD, it is important to learn more about the brains of autistic individuals to understand the differences between individuals with typical development (TD) and ASD.

Much research has been done on determining how ASD affects processes in the brain, namely those associated with communication and behavior[4,5]. Some research has also focused on analyzing how ASD affects processes related to numbers and calculations[6]. A few studies, along with anecdotal evidence, have reported cases of individuals with ASD showing mathematical giftedness - one particular study showed that children with autism and average IQs consistently demonstrated superior math skills compared with nonautistic children in the same IQ range[7].

There is, however, an equal amount of evidence proving the contrary. Some studies have reported higher word problem-solving ability and higher everyday mathematical knowledge in individuals of the TD group[8]. Thus, there is no clear consensus on how ASD affects mathematical competency. What is known, however, is that individuals with ASD have different multivariate activation patterns related to problem complexity[9]. Thus, differences in mathematical competency are likely to be explained by differences in activation patterns in the brain.

There are a vast variety of activation patterns and processes in the brain that fall under the umbrella of "math processes." They include specific networks for performing mathematical operations such as addition and subtraction[10], but additional concepts like memorization add further nuance to brain processes. These are examples of how the brain performs calculations, but another subcomponent of math processing is how the brain registers numbers (i.e. words, numbers, pictures, etc). The well-known 'triple-code' model predicts that numbers are represented in the brain in three formats: a visual code of strings of digits, an analog quantity, and a verbal code represented by words[11]. Activity in the inferior ventral occipitotemporal areas underlies visual code, activity in the inferior

parietal areas underlies analog qualities, and activity in the left perisylvian areas underlies verbal code [12]. Studies have shown that calculation skills are intact in individuals with ASD, but differences lie in conceptual understanding and number visualization, which are possibly due to deficits in listening and reading comprehension [13]. Thus, the present study focuses on the brain regions involved in number processing instead of calculation.

In addition to processes and activation patterns, it is known that the physiological structures of the brains of individuals with ASD are different. There is accelerated brain volume growth in children with ASD around the age of 2 to 4, followed by arrested growth and a possible decrease in size around the age of 10 to 15 [14]. It is also known that brain regions that are part of the same network tend to grow and shrink around the same time, a concept known as structural covariance [15]. This phenomenon follows the common neuroscientific dogma that neurons that fire together also wire together, and that neurons that are out of sync are also out of link. To my knowledge, no study has analyzed the development of brain regions belonging to the number processing network over time. The current study performs this analysis and also compares typically developing individuals to autistic individuals to explore the differences in development between the two groups.

Using brain region volume data obtained from MRI scans, the brain regions involved in the number processing network, as identified in Figure 4, were entered into a lasso regression model. The model predicted the regions of the number processing network that were most predictive of Full Intelligence Quotients (FIQ), which is used to indicate an individual's intelligence. FIQ was the study's indicator of mathematical ability, as FIQ is a proven predictor of mathematical ability (see Statistical Analysis section). The volumetric data for these regions were then entered into regression models to further analyze the development of these regions.

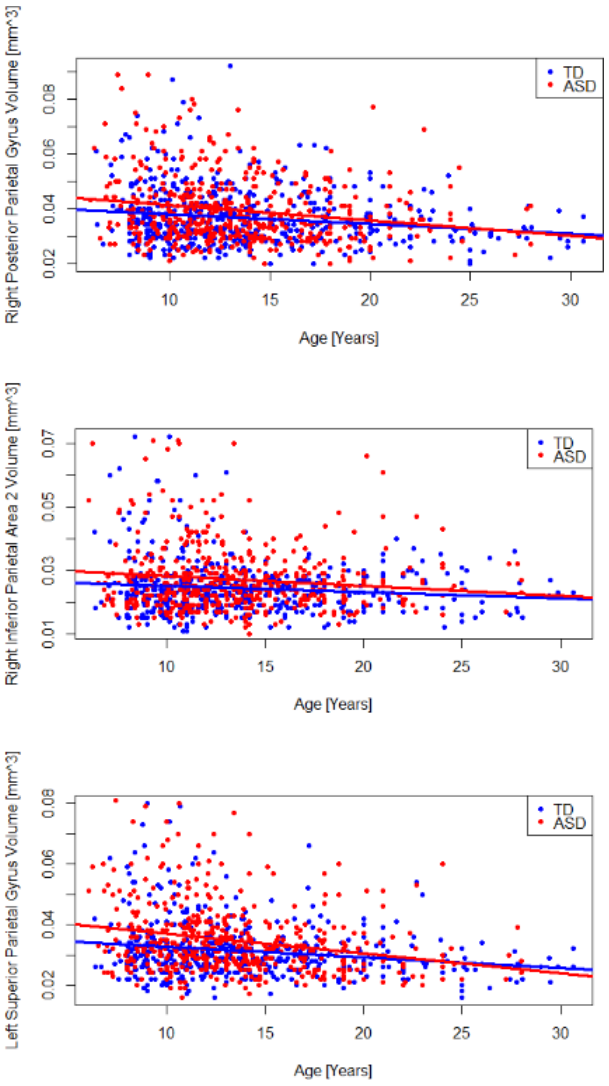

Fig. 1 The relationship between age and volume for both the TD and ASD groups. **a)**. In the Right Posterior Parietal Gyrus. **b)**. In the Right Inferior Parietal Area 2. **c)**. In the Left Inferior Parietal Gyrus.

Results

There were three major findings from the analysis performed.

Regions of the Inferior Parietal Lobule are the most significant predictors of mathematical ability.

From the LASSO regression model, in typically developing individuals, FIQ was most related to individual subregions of the parietal cortex, namely the following three: Right Posterior Parietal Gyrus, Right Inferior Parietal Area 2, and the Left Superior Parietal Gyrus. These three regions were all part of the inferior parietal lobule. This suggests that differences in volumes of regions of the inferior parietal lobule are most significant in the processing of numbers.

The regions of the Inferior Parietal Lobule that are most significant for processing numbers have a negative trend with age in both groups compared with total brain volume.

The three brain regions were then entered into regression models shown in Figures 1a-c. The models looked at the relationship between age and the volume of the brain region of interest. The figures show the ASD group having a more negative slope and greater y-intercepts. This means two things:- (1) that the initial brain volume for ASD individuals in the study (minimum age was 6) was, on average, greater than that for TD individuals, and (2) that the rate at which the brain regions shrunk was greater for ASD individuals than TD individuals. This corresponds with the finding that many individuals with

ASD experience an abnormal increase in brain volume around the age of 2-4 and that some see a decrease in the total brain volume around the age of 10-15[14]. Although total brain volume has a positive trend with respect to age in the TD group, the regions of the study have a negative trend with age."

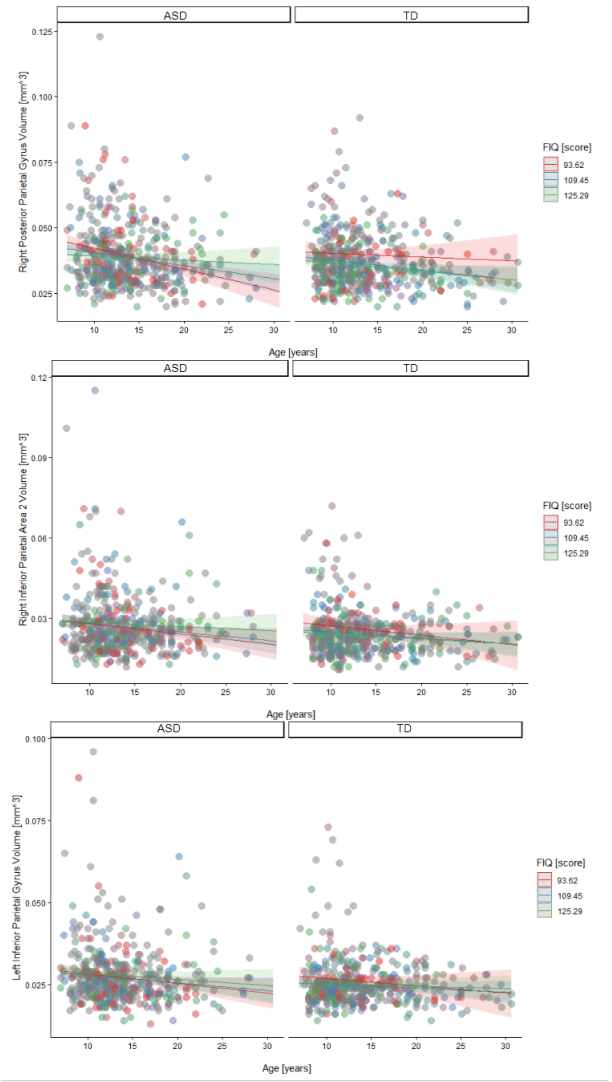

Fig. 2 For all three figures, the individuals in each group (TD and ASD) are divided into three subgroups based on FIQ scores, and the relation between age and brain region volume is shown for each subgroup. Each graph features the brain volume data for one of three regions: (top) Right Posterior Parietal Gyrus, (middle) Right Inferior Parietal Area 2, and (bottom) Left Inferior Parietal Gyrus.

Structural differences within the ASD group are more pronounced than those within the TD group.

The three regions were also entered into 3-way interaction models as shown in Figures 2a-c. From Figures 2a-c, the differences in slopes (as a result of partitioning the data based on FIQ) of the regression lines are greater in the ASD group than in the TD group, which suggests that structural differences within the ASD group are more profound than those in the TD group.

Discussion

It is reasonable that the regions in the number processing network that are most predictive of FIQ are also part of the inferior parietal lobule. Other studies have proven that activity in the parietal cortex is associated with a number of mental arithmetic tasks, and that some impaired arithmetic abilities (such as acalculia) often result from lesions to the parietal cortex[16].

As shown in Figures 1a-c, it is interesting that on average, the brain regions decrease in volume. It has been stated that the volumes of brain regions do not necessarily increase and decrease with the total brain volume[17], and the present study shows an example of this. There also appears to be structural covariance, as the three regions have similar negative trends in Figures 1a-c.

One limitation of the study is that although FIQ is a predictor of math capability, using math capability itself as the dependent variable of the study would yield better results. This data was not available as per the ABIDE database. Another limitation is sampling bias, which is common in databases like ABIDE because the studies are done on a volunteer basis. For this reason, it may be more unlikely that the data includes an adequate proportion of the more extreme cases of autism.

Further studies can analyze brain activation patterns of ASD patients while paying special attention to the inferior parietal lobule. Despite the heterogeneity of ASD, it is possible for humans to improve number processing and intelligence in autistic individuals down the line by stimulating specific regions at specific ages. An example of this is Transcranial Magnetic Stimulation (TMI), which is currently an effective treatment in treating depression by stimulating certain nerve cells[18]. Improving number processing in individuals with ASD would result in greater math capabilities and better job prospects.

Methods

Materials

MRI scans were acquired from the Autism Brain Imaging Data Exchange (ABIDE), a multisite open-access data repository with scans from individuals with TD and ASD. Data was collected across 17 testing sites, including: Barrow Neurological Institute, ETH Zürich, Georgetown University, Indiana University, Institut Pasteur and Robert Debré Hospital, Kennedy Krieger Institute, Olin Neuropsychiatry Research Center, Oregon Health and Science Univer-

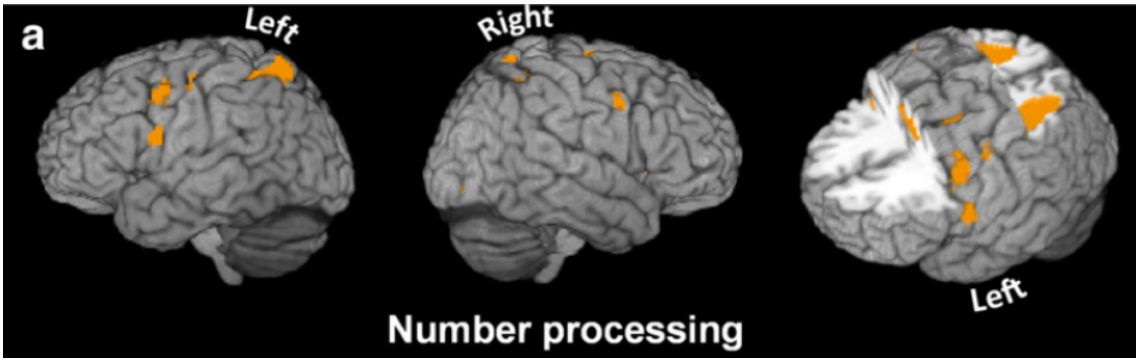

Fig. 3 The regions most involved in number-processing tasks are highlighted in orange. Taken from Arsalidou and Taylor (2011).

sity, San Diego State University, Stanford University, Trinity Center for Health Sciences, University of Miami, University of California Davis, University of California Los Angeles, University of Michigan, University of Pittsburgh School of Medicine, and Yale Child Study Center (*http* : *//fcon*$_1$*000.projects.nitrc.org/indi/abide/abide*$_I$*I.html*).

Participants and Behavioral Measures

A total of 994 participants were included in the present study. Of the 994 participants, 482 were diagnosed with ASD (mean age: 13 years, minimum: 6 years, maximum: 30 years). A diagnosis of ASD was given upon review of the Autism Diagnostic Interview[19] and the Autism Diagnosis Observation Scale[20] by a trained clinician at each testing site. Full Intelligence Quotients (FIQ) were calculated as per the Wechsler Abbreviated Scale of Intelligence[21] or the Differential Ability Scale-II[22] depending on the age and school year of the individual. FIQ is a score derived from a group of tests that is used to determine a person's relative intelligence.

MRI Acquisition and Processing

Magnetic resonance imaging (MRI) scans were acquired within 3 months of behavioral testing. FreeSurfer Software version 7.3.2 was used for processing and visualizing (*https* : *//surfer.nmr.mgh.harvard.edu/*) First, the skull and the dura were removed to only include the cortical surface of the brain. Next, the brains were registered onto a common coordinate space to allow brain-to-brain comparisons. Then, the brains were segmented into white matter, gray matter, and cerebral spinal fluid. The gray matter was further parcellated into individual brain regions as per the Human Connectome Project Multimodal Parcellation Atlas scheme (HCP-MMP). Every brain cortical mask in the 994 sample was checked and manually corrected as needed. The volumetric size (mm^3) was estimated for every brain region.

To identify the brain regions of interest, I used a meta-analysis paper from Arsalidou and Taylor[8], which looked at the neural correlates of number processing. Coordinates with the highest activation likelihood estimation (ALE) values were identified in Figure 4. Reported coordinates are represented as Talairach coordinates and the location of these coordinates on the human brain is depicted in Figure 3. To identify the brain region each coordinate belonged to as per the HCP-MMP, the coordinates were converted from Tailarch to Montreal Neurological Institute (MNI) coordinates. The coordinates were then projected onto an "HCP-MMP converted to MNI" space atlas, and the regions that the coordinates belonged to were recorded. The present study performed analyses using the volumetric sizes of these specific brain regions.

Data Validation Tests

All statistical analyses and plots were performed using R version 4.2.1. Brain region volumetric data was subsetted into two groups based on whether the individual belonged to the TD or ASD group.

Three tests were done to confirm the accuracy of the data. The first test was to identify if a correlation between 'FIQ' and 'Total Estimated Intracranial Volume' exists. A linear regression model and its line of best fit were used to determine this correlation (Figure 5a). From previous studies, there exists a correlation between FIQ and total brain volume[23]. From Figure 5a, there exists a significant positive correlation (p = 0.4933) between FIQ and brain volume, which is consistent with previous studies.

The second test was to identify a correlation between 'Total Estimated Intracranial Volume' and 'Age.' A linear regression model and its line of best fit were used to determine this correlation (Figure 5b). From previous studies, there exists a correlation between total brain volume and age before shrinking occurs around the age of 40[24]. Thus, since the maximum age of participants in the data is 30 years, a successful test

Concordant areas for number tasks.

Hem.	Brain area	BA	x	y	z	ALE	Vol./mm^3
L	Inferior parietal lobule	40	−34	−48	40	0.029	10,952
L	Superior parietal lobule	7	−26	−56	42	0.024	
L	Superior parietal lobule	7	−30	−64	54	0.016	
R	Inferior parietal lobule	40	36	−46	46	0.027	10,464
R	Superior parietal lobule	7	26	−58	42	0.023	
R	Inferior parietal lobule	40	44	−32	46	0.019	
R	Superior parietal lobule	7	32	−56	60	0.010	
R	Superior parietal lobule	7	28	−56	58	0.010	
R	Superior frontal gyrus	6	2	10	48	0.016	3264
L	Cingulate gyrus	24	−8	8	46	0.016	
L	Medial frontal gyrus	6	0	−2	60	0.012	
L	Middle frontal gyrus	6	−50	0	40	0.014	2096
L	Precentral gyrus	6	−42	−2	42	0.014	
L	Precentral gyrus	6	−48	0	32	0.013	
R	Insula	13	34	16	12	0.016	2024
R	Claustrum		28	20	0	0.014	
R	Precentral gyrus	6	48	0	36	0.016	1672
R	Inferior frontal gyrus	9	50	4	28	0.012	
L	Insula	13	−32	12	8	0.015	1336
R	Precentral gyrus	6	28	−14	56	0.019	1328
R	Cerebellum/anterior lobe		24	−56	−28	0.019	1160
L	Middle frontal gyrus	6	−26	−10	54	0.017	1080
R	Middle frontal gyrus	6	28	−4	42	0.013	736
R	Middle frontal gyrus	6	26	0	48	0.012	
R	Cingulate gyrus	32	8	24	40	0.012	640
R	Cingulate gyrus	32	12	18	34	0.011	
L	Fusiform gyrus	37	−38	−56	−10	0.013	520
L	Precentral Gyrus	6	−58	2	20	0.014	504
R	Supramarginal gyrus	40	54	−42	32	0.013	336
L	Lentiform nucleus/putamen		−20	6	14	0.012	272
L	Postcentral gyrus	3	−48	−18	44	0.010	256
L	Postcentral gyrus	3	−50	−18	52	0.008	
L	Cerebellum/pyramis		−26	−64	−28	0.012	184
R	Middle occipital gyrus	18	40	−80	−10	0.012	184
L	Cingulate gyrus	23	0	−20	30	0.012	168

Coordinates (x, y, z) are reported in Talairach convention; Hem., Hemisphere; L, Left; R, Right; BA, Brodmann area; ALE, Activation likelihood estimate; Vol., volume.

Fig. 4 The Talairach coordinates of neural correlates most involved in number-processing tasks are shown above. Taken from Arsalidou and Taylor (2011) [12].

should yield a positive correlation between brain volume and age. From Figure 5b, since there exists a significant positive correlation (p = 1.38*10-5), the result is consistent with previous studies.

The third test was to identify a significant difference between the average FIQ value of ASD and TD individuals. A scatterplot of FIQ values was created, where the independent variable was the group to which the individual belonged (Figure 5c). The average FIQ for each group was also calculated and plotted (ASD average FIQ: 105.9, TD average FIQ: 112.9). An independent two-sample t-test was done on the FIQ data to prove that the difference in the FIQ means was statistically significant (t = 6.622, df = 799.09, p-value = 6.499 * 10-11). One of the characteristics defining intellectual disability is having an FIQ value around 70-75 [25]. Intellectual disability only affects about 1% of the population [25], whereas it affects 31% of children with autism [26]. Thus, the data is consistent with other statistics.

The accuracy of the data was verified by the three tests and was thus used for the analysis of the study.

Statistical Analysis

All brain regions of the number processing network were entered into a LASSO regression model predicting FIQ in typically developing individuals. This was done to assess which regions within the number processing network relate most to FIQ, which was our indicator of mathematical ability. FIQ has been proven to be a positive predictor of mathematical ability [27]. Thus, a higher FIQ score indicates a better chance of high mathematical ability, and a lower FIQ score indicates a lesser chance of high mathematical ability.

The regions that were the most significant predictors of FIQ (and hence, mathematics performance) were then used in linear regression models which assessed the relationship between age and the volume of the brain region. This was done for both

the TD group and the ASD group. Scatterplots of the age by brain region volume graph were created for each brain region (Figures 1a-c). The line of best fit of the model was plotted for both the TD group and the ASD group.

Lastly, three-way interaction models were created for each region to formally test the development of these regions with respect to IQ ($BrainRegionVolume \sim Age \times FIQ \times Diagnosis$). The slopes of the resulting graphs were analyzed (Figures 2a-c).

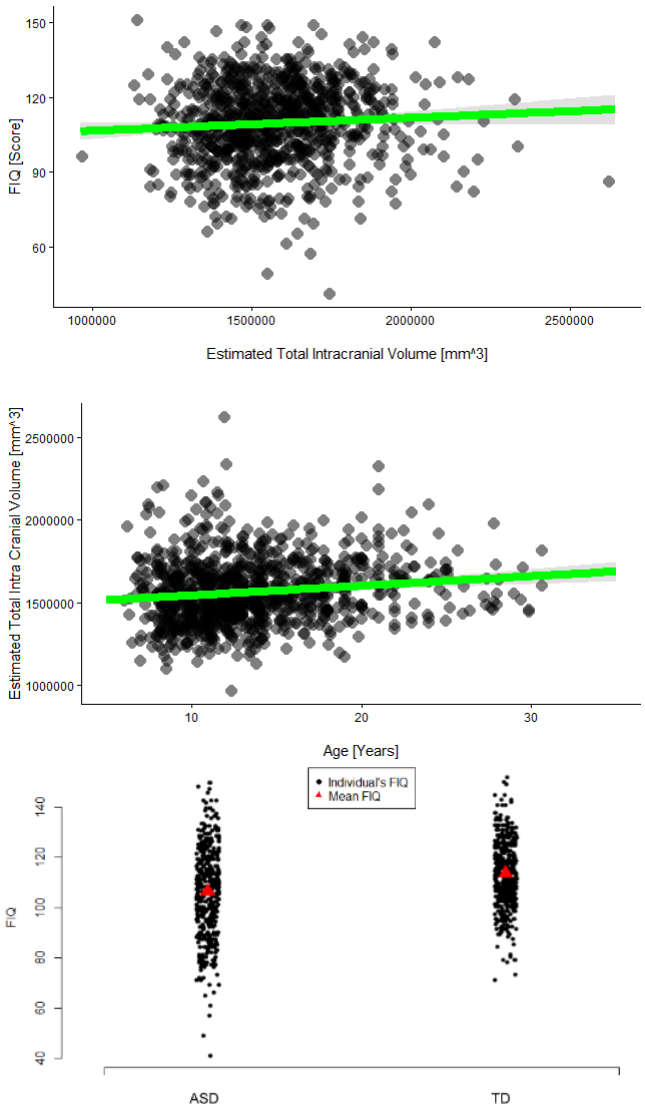

Fig. 5 (Top) The relationship between brain volume and FIQ. (Middle) The relationship between age and brain volume. (Bottom) shows the spread of FIQ values, as well as the mean FIQ value, for both the TD and ASD groups.

Conclusion

The results of the study confirmed the hypothesis that the growth of regions involved in the number processing network would vary in individuals with ASD. In individuals with ASD, brain growth varies more depending on the FIQ (which was used as the indicator of math ability) compared to typically developing individuals. Neuroscientists have long determined that brain structure affects function, which means that the variation in growth is significant because it suggests that the regions identified are the ones that are responsible for differences in math ability. Given that the three regions most predictive of IQ belong to the inferior parietal lobule, future studies can analyze how activation patterns of the inferior parietal lobule differ in individuals with ASD. Understanding the differences in the mathematical brain function of autistic individuals is the first step toward helping them become more competitive in the work environment.

References

1 A. S. Disorder, *National Institute of Mental Health (NIMH*, `https://www.nimh.nih.gov/health/topics/autism-spectrum-disorders-asd`.

2 C.D.C., *Centers for Disease Control and Prevention*.

3 *Autism*.

4 D. Llaneza, S. DeLuke, M. Batista, J. Crawley, K. Christodulu and C. Frye, *Physiology Behavior*, **100**, 268–276.

5 R. Kuenssberg, K. McKenzie and J. Jones, *Research in Developmental Disabilities*, **32**, 2183–2192.

6 A. Hiniker, M. Rosenberg-Lee and V. Menon, *Journal of Autism and Developmental Disorders*, **46**, 1268–1281.

7 T. Iuculano, M. Rosenberg-Lee, K. Supekar, C. Lynch, A. Khouzam, J. Phillips, L. Uddin and V. Menon, *Biological Psychiatry*, **75**, 223–230.

8 Y. Bae, H.-M. Chiang and L. Hickson, *Journal of Autism and Developmental Disorders*, **45**, 2200–2208.

9 T. Iuculano, M. Rosenberg-Lee, K. Supekar, C. Lynch, A. Khouzam, J. Phillips, L. Uddin and V. Menon, *Biological Psychiatry*, **75**, 223–230.

10 A. Abd Hamid, A. Yusoff, S.-M. Mukari and M. Mohamad, *The Malaysian Journal of Medical Sciences: MJMS*, **18**, 3–15.

11 S. Dehaene and L. Cohen, *Cortex*, **33**, 219–250.

12 M. Arsalidou and M. Taylor, *NeuroImage*, **54**, 2382–2393.

13 M. Klaren, B. Pepin and M. Thurlings, *Autism and mathematics education. CERME*, **10**, year.

14 S. Ha, I.-J. Sohn, N. Kim, H. Sim and K.-A. Cheon, *Experimental Neurobiology*, **24**, 273–284.

15 A. Alexander-Bloch, A. Raznahan, E. Bullmore and J. Giedd, *Journal of Neuroscience*, **33**, 2889–2899.

16 S. Rivera, A. Reiss, M. Eckert and V. Menon, *Cerebral Cortex*, **15**, 1779–1790.

17 R. Peters, *Postgraduate Medical Journal*, **82**, 84–88.

18 *Transcranial magnetic stimulation*, `https://www.mayoclinic.org/tests-procedures/transcranial-magnetic-stimulation/about/pac-20384625`, n.d.). Mayo Clinic.

19 A. Le Couteur, G. Haden, D. Hammal and H. McConachie, *Journal of Autism and Developmental Disorders*, **38**, 362–372.

20 R. Luyster, K. Gotham, W. Guthrie, M. Coffing, R. Petrak, K. Pierce,

S. Bishop, A. Esler, V. Hus, R. Oti, J. Richler, S. Risi and C. Lord, *Journal of Autism and Developmental Disorders*, **39**, 1305–1320.

21 *Wechsler Abbreviated Scale of Intelligence*, https://psycnet.apa.org/doiLanding?doi=10.1037%2Ft15170-000.

22 T. Beran and D., *Canadian Journal of School Psychology*, **22**, 128–132.

23 J. Lee, M. McGue, W. Iacono, A. Michael and C. Chabris, *Intelligence*, **75**, 48–58.

24 A. Tierney and C. Nelson, *Zero to Three*, **30**, 9–13.

25 *What is intellectual disability?*, https://www.psychiatry.org/patients-families/intellectual-disability/what-is-intellectual-disability#:~:text=While%20a%20specific%20full%2Dscale,significant%20limitation%20in%20intellectual%20functioning.

26 *Autism statistics and facts*, https://www.autismspeaks.org/autism-statistics-asd, Retrieved August 30, 2022, from.

27 M. Moenikia and A. Zahed-Babelan, *Procedia - Social and Behavioral Sciences*, **2**, 1537–1542.