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Intersubject Correlation (ISC) Differences Between Autism Spectrum Disorder (ASD) and Typically Developed Groups During Biological Motion Processing

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ABSTRACT

In this study, we addressed significant neurological differences between autistic and typically developed individuals, specifically when processing biological motion, using Intersubject correlation (ISC) analysis methods. ISC is a tool used to analyze functional magnetic resonance imaging (fMRI) data acquired under naturalistic stimuli. Using ISC, it is possible to pinpoint common brain responses within a group of individuals as they react to a specific stimulus. ISC is also used to highlight the different brain responses two different groups might have while experiencing the same stimulus. In this experiment, we used two subject groups, one group of autism spectrum disorder (ASD) individuals and one typically developed (TD) group of individuals. The participants in each group watched a ninety second clip of romantic ballet. A short clip of ballet dance was chosen as the stimulus because it had been used in past studies to specify brain responses associated with biological motion processing. Using a standard subject-wise permutation statistical test in the ISC Toolbox for analysis, we computed ISC difference maps between the ASD and TD groups. The findings suggested that during biological motion processing, lateralization of brain responses between the two groups differed; TD individuals had greater ISC in the right hemisphere while ASD individuals had greater ISC in the left hemisphere. Greater ISC in typically developed individuals was concentrated in the culmen of the cerebellum which is responsible for kinesthesia and coordination of movement and is also a component of the mirror neuron network that allows individuals to anticipate movement. These results were consistent with data from prior research that found that TD groups share more synchronized brain responses in the cerebellum, which characterizes higher prediction and anticipation of biological movement in TD groups than ASD groups. ISC within the autistic group was found in the temporal gyrus, which plays a neurological role in motion processing and has been seen to be activated in past comparative studies.

1. AUTISM SPECTRUM DISORDER

According to the National Institute of Public Health (2018), autism spectrum disorder (ASD) is a developmental disorder that is associated with difficulty in communication and interaction with others, restricted interests and repetitive behaviors, sensory deficits, and other problems that inhibit a person's ability to function properly in normal day areas of life. ASD affects 10 in every 1000 people, or around 1% of the general population and is more prevalent in males than in females (Salmi et al., 2013). It is considered a spectrum disorder because of its wide variety in intensity and presentation of symptoms among individuals. Typically, ASD individuals show atypical social behaviors and sensory issues, yet characteristics and phenotypes expressed vary due to differences in the environment or genetics. These sensory deficits and social impairments are a core diagnostic

features for ASD (Byrge, Dubois, Tyszka, Adolph, Kennedy, 2015).

Evidence from functional magnetic resonance imaging (fMRI) studies have indicated that autism incorporates reduced synchronization of the time course of brain activation associated with executive, memory, and visual imagery tasks (Hasson, Nir, Fuhrmann, Malach, 2004). Recent findings also reveal disruptions in the connectivity within and between cortical regions in these individuals, both during behavioral tasks and at resting state. This decreased functional connectivity and reduced synchronization of brain activation among ASD individuals is key to the functional consequences of an individual's behavior and cognition. (Hasson et al., 2009).

2. INTERSUBJECT CORRELATION

Intersubject correlation (ISC) analysis, originally introduced by Uri Hasson in 2004, allows fMRI imaging

¹ Work done in conjunction with professors at the University of Glasgow

acquired under naturalistic stimuli to be analyzed and compared. Using ISC, it is possible to pinpoint common brain responses within a group of individuals as they react to a specific stimulus (Herbec, Kauppi, Jola, Tohka, & Pollick, 2015). ISC is also used to highlight the different brain responses two different groups might have while experiencing the same stimulus (Hasson et al., 2009; Salmi et al., 2013). ISC is determined by calculating correlation coefficients between the fMRI time series of the subjects in corresponding brain locations and then averaging the coefficients (Tohka, Pollick, Pajula, & Kauppi, 2018).

When comparing common brain responses between a typically developed group and an ASD group, ISC is first found within each group to determine significant areas of shared activation among similar individuals. Those ISC results are then compared between groups to create ISC difference maps. ISC Difference maps indicate brain responses characteristic to each group compared to the other. For example, higher ISC within the TD group in a specific area of the brain would indicate that brain responses during a stimulus located in that brain region are unique to TD individuals compared to ASD individuals.

3. NATURALISTIC STIMULI

Previous studies comparing ISC between and within groups of autistic and typically developed individual have sometimes used clips from movies as stimuli (Bartles & Zeki, 2004; Salmi et al., 2013; Herbec et al., 2015). However, a study done by Herbec (2015) suggested that edited videos produce ISC maps that differ greatly from natural, unedited videos. Another study suggested that using naturalistic videos as stimuli is more efficient in eliciting reliable responses in the human brain (Salmi et al., 2013). Because of these findings, ISC must only be performed with naturalistic, unedited stimuli to produce reliable results.

4. APPROPRIATE ISC ANALYSIS METHODS

One major factor of ISC is that it can be used to locate areas of brain activation without knowing in advance a model of where contributing neuronal activation is occurring (Pajula, Kauppi, & Tohka, 2012). Non-parametric tests, or distribution free tests, analyze data without assuming the data follows a normal distribution. Since we didn't know if our data would match a certain set of parameters, we used non-parametric tests so that the threshold could be set by the data itself, not eliminating anything that wasn't considered normally distributed. Even though parametric tests have greater statistical power, non-parametric testing should be used for ISC analysis that have no prior data patterns.

One type of non-parametric statistical test, is a permutation test. Permutation tests are useful to utilize when the distribution shape of the data is unknown or doesn't follow a normal curve. Chen (2016) discusses two different permutation strategies that can be used to form a null distribution: subject-wise and element-wise permutations. Subject-wise permutation testing corresponds to the random swapping of subjects between the two groups before computing subject-pairwise ISCs, while element-

wise permutation testing corresponds to exchanging the components of the correlation matrix (Tohka et al., 2018). Chen (2016) suggested that subject-wise permutations are more reliable for non-parametric statistical testing of two groups, because element-wise permutation leads to tests with excessively liberal hypothesis tests.

5. VOXEL-NULL MODEL

A voxel is a unit of area used in brain mapping. Activation found in certain amounts of voxels over time dictates how large brain activation is in ISC maps. When using subject-wise permutation testing for ISC, two different null-models can be produced: either a null-model for each independent voxel (voxel-null model) can be used or it can be assumed that the same null model exists for all voxels (global null-model) (Tohka et al., 2018).

The ISC Toolbox (Kauppi, Jääskeläinen, Sams, & Tohka, 2010), available in matlab, produces both global-null and voxel-null model results which can be studied using comparison maps. After comparing global-null and voxel-null methods of analysis, studies found that generating null-models independently for each voxel (voxel-null model) is a better method for conducting ISC analysis since it generates more reliable results (Chen et al., 2016; Tohka et al., 2018).

In this paper, we conducted group comparisons of ISC differences, specifically between autism spectrum disorder (ASD) individuals and typically developed individuals. We created brain maps to identify where activation differed between the two groups and discussed the neurological significance between these differences in synchronization.

6. METHODS

Participants

The TD group was comprised of 10 individuals with an average age of 26.5 ± 6.9 , and the ASD group included 10 individuals with an average age of 28.4 ± 9.0 . The TD group had an average Autism Quotient (AQ) score of 12.7 ± 4.8 (N=9) and an average Intelligence Quotient (IQ) score of 118.6 ± 6.8 . The ASD group had an average AQ of 37.11 ± 7.3 (N=9) and an average IQ score of 118.3 ± 5.9 . All were right handed as assessed by the Edinburgh handedness inventory (Oldfield, 1971). Participants were recruited from the participant database at the School of Psychology, University of Glasgow. None of the participants had experience in practicing ballet dance and none regularly watched dance performances. Ethical permission for the study was obtained from the Greater Glasgow and Clyde National Health Service ethics board.

Stimuli and Procedure

The stimulus was a video (60 fps, 1280 by 720 resolution) of a Romantic ballet dance (Giselle's solo dance in *Act II of Giselle*), 90 seconds in duration (Tohka et al., 2018). To eliminate any other stimuli that might affect brain activity, the video was converted to black and white, the ballerina's face was blurred out, and there was no associated audio track. This was to only focus on the responses elicited by processing biological motion.

Stimulus presentation was controlled by Presentation® software (Neurobehavioural systems, Inc). Before beginning the experiment, participants were instructed to simply relax and enjoy watching the dances while being scanned.

fMRI Data Acquisition and Preprocessing

Data was acquired from a single functional T2*-weighted acquisition (EPI, TR 2000 ms; TE 30 ms; 32 Slices; 3[^]3mm voxel; FOV of 210, imaging matrix of 70 x70) using a 3T Tim Trio Siemens scanner. The dance presentation lasted 90 seconds. There were 8 seconds of blank at the beginning and 36 seconds at the end of the run. An anatomical scan was performed at the end of the scanning session that comprised a high-resolution T1-weighted anatomical scan using a 3D magnetization prepared rapid acquisition gradient recalled echo (ADNI-MPRAGE) T1-weighted sequence (192 slices; 1mm cube isovoxel; Sagittal Slice; TR = 1900 ms; TE = 2.52; 256 x 256 image resolution).

The fMRI data was preprocessed in Brain Voyager QX (Vers.2.6, Brain Innovation B.V., Maastricht, Netherlands). This included: 3D Motion Correction with Trilinear/sinc interpolation, slice scan-time correction, linear removal, and high-pass filtering with cutoff set to 1 cycle. Spatial smoothing with a Gaussian kernel of 6 mm FWHM was also applied. This was followed by normalization of functional scans into common Talairach space (Talairach & Tournoux, 1988), and co-registration of functional and anatomical data. Finally, the functional data were trimmed using Matlab to obtain the 45 volumes (90 seconds) for each dance, used later for Intersubject correlation (ISC) analysis.

ISC Analysis

A free MATLAB-based ISC Toolbox was used to carry our ISC analysis. A statistical map showing the ISC between subjects during the presentation of the stimulus was formed. This statistical map was converted from mat files to vmp files to visualize them in Brain Voyager. In Brain Voyager we were able to obtain significant clusters of interest, peak Talairach coordinates, and other statistical variables. The peak coordinates of each significant cluster were traced to a location in the brain using Talairach Client software. Results from the ASD control group were visualized and compared to the typically developed individuals. In this final step, we applied a standard cluster threshold of 108 mm³, and clusters smaller than this were not considered (Chen et al., 2016; Tohka et al., 2018). Because there were 20 subjects in the study, standard parametric statistical inference approaches were not valid for this test statistic due to the dependency of the correlation coefficients. Therefore, a fully nonparametric resampling test, subject-wise permutation testing, was conducted against the null hypothesis using a voxel-null model (Herbec et al., 2015; Tohka et al., 2018).

7. RESULTS

ISC maps for the group comparisons revealed that in several brain regions, synchronization differed between ASD and TD individuals (Table 1 and Figure 1). Our results ignored clusters less than 108 mm³ (p=0.01) (Chen et al., 2016; Tohka et al., 2018). Our voxel-null model yielded one cluster where ISC was greater for TD and four clusters for where ISC was greater for ASD.

The TD group had a unique ISC value in a single cluster located in the right hemisphere of the culmen in the cerebellum. The ASD group had ISC map values in four clusters. One cluster was in the cuneus of the occipital lobe, two clusters were in the middle temporal gyrus, and one in the middle frontal gyrus. The largest cluster of these four was 271 voxels and associated with Brodmann area 37.

8. DISCUSSION

Past studies have found several neural differences between autistic and control participants. It has been suggested that there are structural, functional, and developmental differences in the brains of people with autism compared to typically developed individuals (Philip et al., 2012; Cherkassky, Kana, Keller, & Just, 2006). Connectivity is a key feature that may differ in autism, commonly described as overconnectivity for short distances and underconnectivity for long distance tracts (Behrmann, Thomas, & Humphreys, 2006; Pavlova, 2012). Reduced connectivity and reduced corpus callosum volume in ASD individuals has led to the theory that lateralization deficits may contribute to symptoms of autism (Pavolva et al., 2012). In a meta-analysis it 81.5% differences in laterality were found between ASD and TD individuals (Philip et al., 2012). In terms of brain response while viewing biological motion, studies have found greater activation in the right hemisphere of typically developed individuals, in certain areas like the superior temporal sulcus and fusiform gyrus and right posterior temporal cortex (Philip et al., 2012). The right posterior temporal cortex especially is highly involved in the processing of visual information about agency, emotion, and intention of others (Grosbas). Although neural mechanisms involved in the ability to perceive biological motion have been poorly understood, many studies have suggested the major role that anatomy of the right hemisphere plays in TD people, specifically for biological motion processing. Visual biological motion processing engages a neural network in this right brain area that differs in brain response patterns from other moving stimuli. This pathway has been examined through light-point experiments and suggests that biological motion processing involves parts of the fusiform gyrus, extrastriate body area, and parietal and frontal cortices primarily on the right hemisphere (Nackaerts et al., 2012). Our results agree with the findings that TD individuals share common right brain activation while watching biological motion. The ASD group did not have any right brain activation, but instead showed synchronous responses solely located on the left side, supporting the notion in differences in lateralization between TD and ASD groups.

Our results showed a greater ISC in TD individuals in one cluster located in the right hemisphere of the culmen of the cerebellum. In a previous meta-analysis

study comparing ASD and TD brain activation, greater correlation in TD groups has been found in the right culmen when subjects engaged simple social tasks (Philip et al., 2012). The cerebellum, where the culmen is located, receives input from proprioceptors like muscles which are involved in movement (Boisgontier & Swinnen, 2014). The culmen is largely responsible for kinaesthesia, or the awareness of the parts of the body responsible for movement. Studies have suggested that the cerebellum and parts of the cerebellum associated with movement are part of a 'mirror system' of neurons, which allow individuals to make predictions about the outcomes of another individual's movements. A previous study done on motor familiarity in action observation confirmed that this mirror pathway, which included the cerebellum, was activated more when viewers watched clips of a dancer of the same sex as them performing (Calvo-Merino, Grèzes, Glaser, Passingham, & Haggard, 2006). Our results agree with the evidence of greater synchronization of in the right brain among typically developed individuals, specifically in the cerebellum which controls motion processing. ISC in this region of the brain is greater in TD individuals than ASD due to brain function associated with prediction of human motion.

Most research supports the fact that ASD individual have low-level motion processing deficits, but some studies have contradicted this theory concluding that an ASD group had no difficulty in integrating local motion signals into coherent human motion. Studies that investigated biological motion processing in ASD and the brain regions involved found that there was notable neural activity in the ASD group in superior temporal areas, especially in the superior temporal sulcus, which is a region that has been reported to be related to biological motion processing (McKay et al., 2010). Other studies have supported the importance of the superior temporal area, and Brodmann area 22, in biological motion processing, even finding greater activation in that area in ASD groups than TD groups (Philip et al., 2012). Another region of the brain which has been seen to be activated more in ASD than TD individuals during social and biological motion tasks is the fusiform gyrus (Philip et al, 2012; McKay 2010). In our present study, two clusters found unique to ASD synchronization were similarly found in the temporal region but not specifically in Brodmann area 22. Both clusters were instead found in the middle temporal gyrus. These two areas' Talairach coordinates were associated with Brodmann area's 37 and 21. According to the Cortical Functions Reference (2012), the fusiform gyrus (Brodmann area 37) and the middle temporal gyrus (Brodmann area 21) work together during tasks such as deductive reasoning, attribution of the intentions of others, and the observation of motion. These results suggest that brain patterns while watching biological motion are uniform across a group of ASD individuals, yet are distinct from the brain responses of TD individuals. More research is required to definitely say that this region of the brain is unique to autistic biological motion processing. The ability to pinpoint a unique area of the brain associated with biological motion processing in the brains of ASD individuals will help future research and treatment into social and behavioral therapy for these individuals.

9. LIMITATIONS

One limit of our study is that non-parametric testing requires a large sample size, since its statistical power isn't as strong as parametric testing. Future studies with a larger sample size will help create a stronger correlation between biological motion perception and functional anatomy of the brain.

Furthermore, all voxel clusters under 108 mm³ were not considered in our results. This voxel threshold is arbitrary, and was used per the suggestion of previous studies (Tohka et al., 2018). A standard method of setting a threshold that fits different data sets has not been created, but it could possibly eliminate clusters that may or may not be statistically significant to our findings. Hopefully in the future, a voxel threshold function will be incorporated into the Matlab's ISC Toolbox or Brain Voyager software so unique threshold can be set to any data set.

Lastly, autism spectrum disorder may be largely associated with specific structural and functional brain abnormalities, but a lack of consensus of which structures has led to many speculations and disagreements in the literature (Pavolva et al., 2012; McKay et al., 2012; Philip et al., 2012). One thing that makes ASD so hard to study is the variability within the category of the spectrum. This variance includes the severity of presented symptoms as well as structural and developmental differences between individuals (Wozniak, Leezenbaum, Northrup, West, & Iverson, 2017). The variance across the autism spectrum makes it hard to find trends and correlations that apply to all individuals with ASD, therefore another limitation to studying patterns within ASD individuals and comparing them to a typically developed population is that abnormalities might not be generalizable to the whole ASD population.

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11. FIGURES

Anatomical Region (broad, specific)	Hemisphere	Talairach-coordinate	Number of Voxels	Peak Statistic	Broadmann Area
TD>ASD					
cerebellum, anterior lobe, culmen	right	(6, -32, -20)	232	3.158559	-
ASD>TD					
cerebrum, occipital lobe	left	(-24, -76, 19)	140	3.341671	18
cerebrum, frontal lobe, middle frontal gyrus	left	(-29, 14, 52)	131	3.192400	6
cerebrum, frontal lobe, middle temporal gyrus	left	(-48, -62, 7)	271	2.885898	37
cerebrum, temporal lobe, middle temporal gyrus	left	(-62, -19, -11)	123	3.363024	21

Table 1. Results of the ISC difference maps

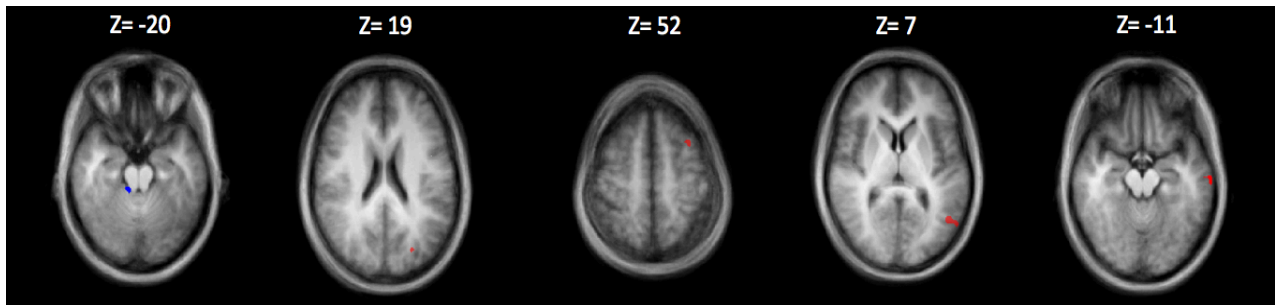


Figure 1. ISC maps using voxel-null method. TD>ASD is indicated by blue in the first image and ASD>TD is indicated by red in the next four images.