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Research Article

Discovery of Neurocognitive Phenotypes of Autism by Analyzing Functional Connectivity in the Default Mode Network and Dorsolateral Prefrontal Cortex

Amith Vasantha*

Department of Biotechnology, BASIS Independent Silicon Valley, San Jose, California, USA

ABSTRACT

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder usually presenting as reduced social interaction, lessened verbal communication, and repetitive behavior. Diagnosing autism spectrum disorder is extremely difficult because of its wide variety of symptoms, so it can only be diagnosed through behavioral tests and analysis of developmental history. Resting-state functional Magnetic Resonance Imaging (rs-fMRI) can help researchers discover a neural substrate for autism spectrum disorder to diagnose it earlier. One prominent fMRI database for autism spectrum disorder research is the Autism Brain Imaging Data Exchange, a large-scale collection of anonymized functional MRI scans subdivided by age, gender, handedness, and scores on behavioral assessments.

This analysis focused on two brain networks: the Default Mode Network (DMN), which is active when minds wander, and the executive network, which is active during the performance of tasks. The medial Prefrontal Cortex (mPFC), Posterior Cingulate Cortex (PCC), and angular gyrus are nodes of the default mode network, and the Dorsolateral Prefrontal Cortex (DLPFC) is the main node in the executive network. Both networks are affected by autism spectrum disorder.

This research used preprocessed resting-state fMRI data to establish neurocognitive phenotypes for autism spectrum disorder. Bivariate correlation was used to compare connectivity in the default mode network and dorsolateral prefrontal cortex between autism spectrum disorder fMRI scans and control fMRI scans, and these differences were analyzed for correlations with each patient's assessment scores. After the Benjamini-Hochberg procedure was applied to reduce the false discovery rate, analysis of these metrics revealed that in autism spectrum disorder patients there was under connectivity between the right posterior cingulate cortex and the right medial prefrontal cortex, while in control patients there was over-connectivity between the right angular gyrus and left dorsolateral prefrontal cortex. Autism spectrum disorder is extremely heritable, so phenotypic research is absolutely necessary for discovering more about the genetic causes of autism spectrum disorder, which will speed up autism spectrum disorder diagnosis and help researchers develop more targeted treatments for autism spectrum disorder.

Keywords: Joint discomfort; Knee joint; Physical activity; Mobility, Collagen

INTRODUCTION

Functional Magnetic Resonance Imaging (fMRI) is a neuroimaging method that measures changes in blood flow and blood oxygenation, which can be quantified as the Blood-Oxygen-Level-Dependent signal (BOLD). The BOLD signal measures the variance in the hemodynamic response, or the delivery of oxygen from blood vessels to surrounding neurons. Blood with varying levels of oxygenation is depicted on an MRI scan with varying levels of brightness; thus, varying levels of brightness can indicate brain activity [1]. In recent years, resting-state functional Magnetic Resonance Imaging (rs-fMRI) has been used for brain activity analysis, specifically functional connectivity analysis. Functional connectivity refers to synchronized brain activity in two brain regions that share functions, and changes in functional connectivity can indicate a change in brain circuitry [2]. Autism spectrum disorder is a "range of developmental disorders characterized by deficits in social communication and interaction and restricted and repetitive behaviors" [3]. Autism

Correspondence to: Amith Vasantha, Department of Biotechnology, BASIS Independent Silicon Valley, San Jose, California, United States, E-mail: amithvasantha0114@gmail.com

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spectrum disorder is extremely difficult to diagnose because it is extremely heterogeneous, meaning it manifests as a wide variety of behavioral and psychological symptoms. Researchers still have not definitively determined a neural substrate for autism spectrum disorder, but there are multiple theories about autism spectrum disorder's cause. One theory, the mirror neuron hypothesis, holds that autism spectrum disorder comes from dysfunction in the mirror neuron system, which activates when a person performs a task while observing another person performing the same task. Another hypothesis holds that the default mode network is affected by autism spectrum disorder; it is this hypothesis that is explored in this paper [4].

The default mode network is a brain network active during wakeful rest, when the brain is not presented with any stimuli, which makes it visible on resting-state fMRI scans. It is comprised of the medial prefrontal cortex, the posterior cingulate cortex, the precuneus, and the angular gyrus (Figure 1).

Among several things, the default mode network is responsible for our concept of the self, as well as our emotional understanding and social interaction, which relates to how autism spectrum disorder manifests.

The dorsolateral prefrontal cortex controls our executive functions, including working memory, cognitive flexibility, and planning. Executive dysfunction is a major hallmark of autism spectrum disorder [5].

It was hypothesized that there would be general under-connectivity throughout the default mode network and dorsolateral prefrontal cortex in patients with autism spectrum disorder. Thus, bivariate correlation was used to compare connectivity in the default mode network and dorsolateral prefrontal cortex between autism spectrum disorder fMRI scans and control fMRI scans to discover notable neurocognitive phenotypes of autism spectrum disorder in both brain systems.

MATERIALS AND METHODS

Abide

ABIDE, or the Autism Brain Imaging Data Exchange, is an online open-access database of resting-state fMRI scans from 1112 people collected by 17 different research groups, as of March 2022 [6]. It also includes phenotypic data for each individual, such as age, medications, gender, handedness, and scores on various assessment scores such as the Revised Autism Diagnostic Interview (ADI-R) interview and Autism Diagnostic Observation Schedule (ADOS) subscores. ABIDE also supplies data that is preprocessed through a variety of pipelines (Connectome Computation System and Neuroimaging Analysis Kit, for instance) and subdivided according to several commonly used brain atlases. In this paper, the Talairach atlas was used. The data used in this research were .1D files, 2D arrays of numbers representing the BOLD signal in each Talairach region across time. There are 42 different regions in the Talairach atlas, each corresponding to a distinct four-digit code. The regions

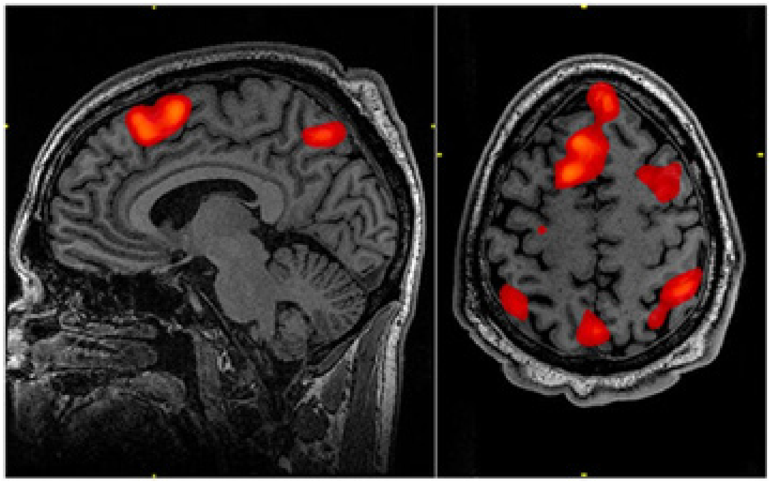

Figure 1: An MRI scan with the default mode network highlighted in red. On the sagittal scan (left), the anterior red region is the medial prefrontal cortex, and the posterior red region is the precuneus. On the axial scan (right), the lateral posterior regions in red are the left and right angular gyri [2].

Table 1: These specific regions of interests (ROIs) are extracted from the .1D files using AFNI's 1dtool.py script.

Regions of interests (ROIs)	Codes for regions in the talairach atlas
right medial prefrontal cortex	2101
left medial prefrontal cortex	2102
right angular gyrus	4101
left angular gyrus	4102
right precuneus	4501
left precuneus	4502
right dorsolateral prefrontal cortex	4701
left dorsolateral prefrontal cortex	4702
right posterior cingulate cortex	2001
left posterior cingulate cortex	2002

analyzed in this paper are as follows (Table 1).

Processing rs-fMRI data

DensParcorr, an R script for partial correlation devised by Wang et al. [7] was used to compare the BOLD signal time series for each region of interest. Partial correlation was specifically chosen because other methods of correlation, like Pearson correlation, do not consider the effect of external brain networks on the network being analyzed (Table 2).

Comparing ASD and non-ASD patients

Correlation: The correlation matrices were divided between ASD and non-ASD patients and compared using Student's t-test, and p-values were calculated for each correlation. Distinctions were made between patient's age and sex: seniors show more functional connectivity than adults under 60 and children [8], and males show more general functional connectivity than females [9]. For the purpose of this project males and females fewer than 21 were analyzed, equating to 672 unique sets of fMRI data (Tables 3 and 4).

Comparing connectivity to phenotypic data

Using Pearson correlation, each patient's correlation coefficients were compared to their assessment scores: their FIQ, VIQ, PIQ, and ADI subscores (social interaction, abnormalities in communication, and repetitive/stereotyped behaviors) [10]. The data were compared against an already established method of diagnosing autism spectrum disorder to verify that the discovered phenotypes were actually major phenotypes indicative of autism spectrum disorder. For example, Subject #51463 is a 20-year-old right-handed woman with autism. Her Full-scale IQ (FIQ), Verbal IQ (VIQ), and Performance IQ (PIQ) scores were 102, 101, and 103 respectively. She scored a 24/30 on the Autism Diagnostic Interview Social Interaction Subscore, indicating a deficit in social communication (Tables 5 and 6).

Error control

To correct for false positives, the Benjamini-Hochberg procedure was applied to the set of p-values generated for each correlation. It ranks the p-values least to greatest (1 to k) [11] and calculates the Benjamini-Hochberg critical value for each p-value according to the formula $BH=k/m \times \alpha$, where α refers to the p-value threshold (usually 0.05) and m refers to the total number of p-values [12]. Then, the greatest p-value less than its corresponding Benjamini-Hochberg critical value is found, and every p-value less than or equal to the chosen value is considered significant (Figures 2 and 3).

RESULTS

After comparing the mean correlation coefficient for each region and verifying the findings using the Benjamini-Hochberg procedure, it was found that the most notable neurocognitive phenotype of autism present in the default mode network is lower functional connectivity between the right Posterior Cingulate Cortex (PCC) and the right medial Pre-Frontal Cortex (mPFC). This manifests as a higher chance of restricted and repetitive behaviors, like repetitive hand movements or repetitive speech like echolalia. Higher functional connectivity between the right angular gyrus and left

Table 2: An example correlation matrix for Subject #51463 in the ABIDE database. Each cell represents the correlation of the BOLD signals between the two regions in the row and column. For instance, the correlation between regions 4101 and 2001 (the right angular gyrus and the right posterior cingulate cortex respectively) is 0.004033018, showing that the connectivity between the two regions is very low.

	2001	2002	2101	2102	4101	4102	4501	4701	4702
2001	1	0.3957599	0.2226107	0.1125915	0.004033018	0.1790588	-0.1237171	0.2271696	-0.07097995
2002	0.3957599	1	0.2019985	0.05579368	0.03015877	0.07724723	0.01054664	0.1431119	-0.07525002
2101	0.2226107	0.2019985	1	0.4192935	-0.04067217	0.00949765	0.001356221	-0.1782539	0.1328544
2102	0.1125915	0.05579368	0.4192935	1	0.15795	0.008793815	0.04145988	0.0488834	0.1179769
4101	0.004033018	0.03015877	-0.04007217	0.15795	1	-0.188432	-0.00784356	0.2483503	0.0260735
4102	0.1790588	0.07724723	0.00949765	0.008793815	-0.188432	1	-0.03926598	-0.0711616	0.2391627
4501	-0.1237171	0.01054664	0.001356221	0.04145988	-0.00784356	-0.03926598	1	0.4439303	0.3800334
4502	0.02950651	0.03169859	0.1101673	0.08518178	0.4199669	0.1966028	-0.2070323	-0.03079901	-0.03627
4701	0.2271696	0.1431119	-0.1782539	0.0488834	0.2483503	-0.0711616	0.4439303	1	0.00315732
4702	-0.07097995	-0.07525002	0.1328544	0.1179769	0.02607357	0.2391627	0.3800334	0.00315732	1

Table 3: The p-values for each correlation. The bold p-values, from top to bottom, are under 0.05, denoting that connectivity differs greatly in those two regions between ASD and non-ASD patients. From top to bottom, the connections are: Right Posterior Cingulate Cortex (PCC) and the right medial Pre Frontal Cortex (mPFC) (2101-2001); Right posterior cingulate cortex and the right angular gyrus (4101-2001); Left posterior cingulate cortex and the left precuneus (4502-2002); Left Dorsolateral Prefrontal Cortex (DLPFC) and the left angular gyrus (4701-4102); Right dorsolateral prefrontal cortex and the right angular gyrus (4702-4101).

	2001	2002	2101	2102	4101	4102	4501	4502	4701	4702
2001	0									
2002	0.981198	0								
2101	**0.000005**	0.391096	0							
2102	0.06	0.930402	0.966109	0						
4101	**0.022661**	0.093218	0.248312	0.264363	0					
4102	0.378092	0.602298	0.487168	0.870952	0.579585	0				
4501	0.224730	0.463425	0.156665	0.436887	0.437908	0.797496	0			
4502	0.558332	**0.010898**	0.119963	0.283832	0.21619	0.734751	0.797 123	0		
4701	0.510730	0.478064	0.486969	0.350219	0.93479	**0.033735**	1	0.1	0	
4702	0.168370	0.745725	0.871615	0.135894	**0.004571**	0.806506	1	0.6	0	0

Table 4: The corresponding t-values for each connection. Each of the bold values are negative, denoting that for each of the significant differences in connectivity, patients with autism spectrum disorder have less functional connectivity than patients without autism spectrum disorder.

	2001	2002	2101	2102	4101	4102	4501	4502	4701	4702
2001										
2002	0.02358									
2101	**-4.61805**	-0.85819								
2102	-1.8917	-0.08737	0.04250							
4101	**2.28439**	1.68106	1.15547	-1.11707						
4102	0.88200	-0.52135	-0.69520	-0.16251	-0.55426					
4501	1.21517	0.73364	1.41797	-0.77793	0.77620	-0.25669				
4502	-0.58561	**-2.55308**	1.55691	1-1.07261	1.23789	0.33895	-0.25717			
4701	0.65805	-0.70982	0.69552	-0.93482	-0.08185	**-2.12759**	-0.01444	1.95208		
4702	1.37895	0.32442	-0.16167	1.49305	**-2.84539**	-0.24503	0.08586	0.46083	0.87677	

Table 5: The Pearson correlation coefficients between each patient's connections and their assessment scores. Bold values are negative number means there is a negative relation between connectivity and the assessment scores. For instance, as connectivity between the right posterior cingulate cortex and right medial prefrontal cortex decreases in people with autism spectrum disorder (the first row of values), their full-scale IQ score, performance IQ score, and Revised Autism Diagnostic Interview Restricted and Repetitive Behaviors Subscore increase, demonstrating a higher chance of restricted and repetitive behaviors.

	FIQ	VIQ	PIQ	ADI Social	ADI Verbal	ADI RRB
2001-2101+	0.01907	0.00545	-0.0 1358	-0.03427	-0.06301	**-0.12245**
[2001-2101-	0.07753	0.06881	0.01971	NaN	NaN	NaN
2001-4101+	-0.01813	0.0424	-0.04042	0.03435	0.04066	0.0209
2001-4101-	-0.00243	0.02382	-0.007	NaN	NaN	NaN
2002-4502+	-0.03061	-0.02086	-0.06611	0.08233	0.01711	-0.00852
2002-4502-	-0.01392	-0.04721	0.02639	NaN	NaN	NaN
4102-4701+	0.06205	0.0304	-0.02981	-0.02786	0.03 101	0.00267
4102-4701-	0.0 1262	-0.00741	0.06367	NaN	NaN	NaN
4101-4702+	0.08082	0.08156	-0.0234	0.09068	0.08499	-0.02104
4101-4702-	**-0.11866**	-0.07336	**-0.10189**	NaN	NaN	NaN

Table 6: The bold text shows p-values for each correlation coefficient. This table demonstrates that connectivity between the right posterior cingulate cortex and right medial prefrontal cortex is closely related to the individual's full-scale IQ and performance IQ scores.

	FIQ	VIQ	PIQ	ADI Social	ADI Verbal	ADI RRB
2001-2101+	0.74425	0.92902	0.82457	0.5942	0.32601	**0.05561**
2001-2101-	0.15432	0.22477	0.7296	NaN	NaN	NaN
2001-4101+	0.75653	0.48784	0.50922	0.5934	0.52646	0.74478
2001-4101-	0.96444	0.67458	0.90225	NaN	NaN	NaN
2002-4502+	0.60051	0.733	0.27997	0.19999	0.78992	0.89447
2002-4502-	0.79844	0.40522	0.64345	NaN	NaN	NaN
4102-4701+	0.28816	0.619	0.62641	0.66496	0.62904	0.96686
4102-4701-	0.81686	0.89612	0.26369	NaN	NaN	NaN
4101-4702+	0.1662	0.18151	0.70246	0.15793	0.18486	0.74314
4101-4702-	**0.02893**	0.19551	**0.07324**	NaN	NaN	NaN

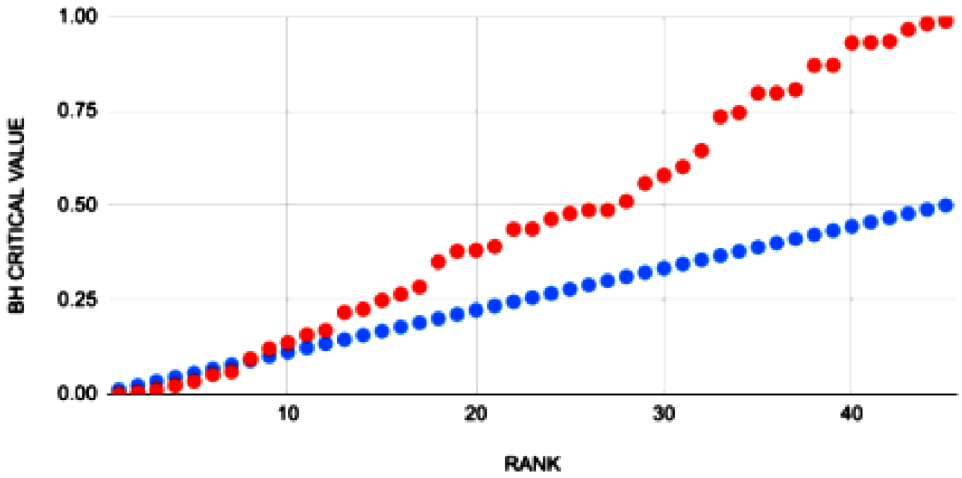

Figure 2: It shows the graph of each p-value (in red) and each Benjamini-Hochberg critical value (in blue), calculated with the inequality above. **Note:** (●) BH CRITICAL VALUE, (●) P-VALUES.

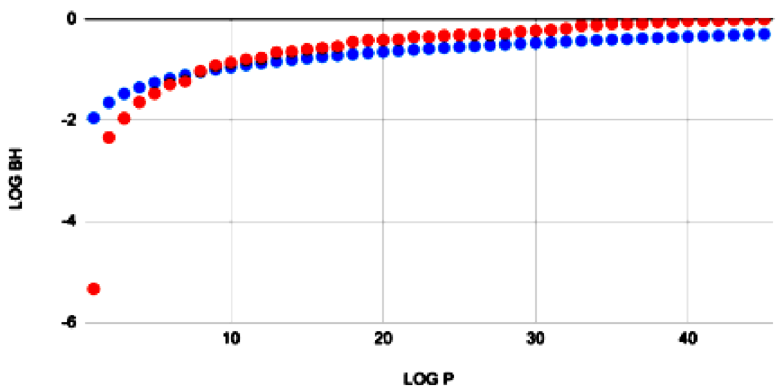

Figure 3: It shows the same values as figure 7 but on a log scale instead so the difference between p-values and Benjamini-Hochberg critical values can be more clearly seen. **Note:** (●) LOG BH, (●) LOG P.

Table 7: It indicates heatmap of differences in connectivity between ASD and non-ASD patients. A more negative number designates lower functional connectivity between two regions in autism spectrum disorder patients. The red number designates the connectivity difference between the right posterior cingulate cortex and the right medial prefrontal cortex. The blue number designates the connectivity difference between the left dorsolateral prefrontal cortex and the right angular gyrus.

	2001	2002	2101	2102	4101	4102	4501	4502	4701	4702
2001	0.00000	0.00020	-0.02508	-0.01045	0.01567	0.00577	0.00779	-0.00409	0.00408	0.00914
2002	0.00020	0.00000	-0.00535	-0.00053	0.01377	-0.00377	0.00494	-0.01852	-0.00459	0.00231
2101	-0.02508	-0.00535	0.00000	0.00028	0.00737	-0.00479	0.00913	0.00835	0.00432	-0.00107
2102	-0.01045	-0.00053	0.00028	0.00000	-0.00717	-0.00113	-0.00493	-0.00574	-0.00532	0.01040
4101	0.01567	0.01377	0.00737	-0.00717	0.00000	-0.00462	0.00670	0.00915	-0.00069	-0.02200
4102	0.00577	-0.00377	-0.00479	-0.00113	-0.00462	0.00000	-0.00198	0.00251	-0.01748	-0.00234
4501	0.00779	0.00494	0.00913	-0.00493	0.00670	-0.00198	0.00000	-0.00170	-0.00011	0.00064
4502	-0.00409	-0.01852	0.00835	0.00574	0.00915	0.00251	-0.00170	0	0.01259	0.00307
4701	0.00408	-0.00459	0.00432	-0.00532	-0.00069	-0.0175	-0.00011	0.01259	0	0.0064
4702	0.00914	0.00231	-0.0011	0.0104	-0.022	-0.0023	0.00064	0.00307	0.0064	0

dorsolateral prefrontal cortex was also noted in non-ASD patients; this manifests as higher FIQ and PIQ scores (Table 7).

DISCUSSION

The hypothesis was supported by the data, but only partially. Instead of general under-connectivity between default mode network hubs, there was only under-connectivity between two regions of the default mode network: the right posterior cingulate cortex and the right medial prefrontal cortex.

This project is just one step towards establishing a methodology for discovering more neurocognitive phenotypes of autism spectrum disorder. This is extremely useful considering that the primary method of diagnosing autism spectrum disorder in children is observing a child's behavior. Using resting-state fMRI to diagnose autism spectrum disorder allows doctors to diagnose autism spectrum disorder faster and potentially think of ways to reduce the most debilitating effects of autism spectrum disorder, such as delayed language and cognitive skills, epilepsy, and hyperactive or impulsive behavior.

CONCLUSION

In the future, larger collaborative datasets like ABIDE would be extremely useful for researchers. While ABIDE is comprehensive, much of the phenotypic data, such as intelligence scores or autism diagnostic scores, are not consistent between the 17 different research groups that supplied data. With a larger, more standardized dataset, phenotypic research and neuroimaging analysis would provide a much more detailed look at the neurophysiological causes of autism spectrum disorder. Once researchers discover a neural substrate for autism spectrum disorder, they can determine a therapeutic target for future gene therapies or drug therapies that can eliminate the most debilitating effects of autism spectrum disorder, like epilepsy or delayed development.

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ETHICAL CONSIDERATIONS

All data is anonymized; the only phenotypic data available for each patient is their age, their gender, any medications they have taken, and their scores on various autism spectrum disorder assessment tests.

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