原 著 論 文

Assessing brain function in self-identified individuals suspected of being on the autism spectrum using fMRI: a case study.

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Abstract

Autism Spectrum Disorder (ASD) is a widely recognized neurodevelopmental disorder that has gained recognition among both the general public and professional groups such as physicians and researchers. However, with this increasing awareness, some individuals have begun to suspect that they may be autistic based on their own knowledge and understanding. This suspicion can lead to unnecessary anxiety and other difficulties in one's life. A simple objective method of assessment prior to formal diagnosis would be beneficial for those who suspect they may have autism. Thus, we posited that measuring brain function would be a viable candidate for this. As a preliminary study, we evaluated the brain function of an individual who suspected he may be autistic using our developed estimator of human characteristics. Additionally, we also compared this individual to a cohort of typical subjects based on functional networks consisting of previously identified ASD-related brain regions. The individual was determined to be typical by our estimator, however, the comparison with the normal group indicated deviation in brain regions such as the precuneus and ventral prefrontal cortex from the normal group. These results suggest that the individual is considered normal, but some brain functions may deviate from the normal group. Brain function measuring may be a good assessment method for those who suspect they may have autism.

Keywords : Resting state fMRI (rsfMRI), Functional connectivity, Autism spectrum disorder, Self-identified, Estimator

(Introduction)

Autism Spectrum Disorder (ASD) is a neurodevelopmental condition[1, 18)] characterized by a plethora of behavioral deficits, including difficulties with communication[7,16,22)] and social interactions[9,11)], as well as restrictive or repetitive patterns of behavior[19,20,25)].

ASD is now recognized as a significant societal problem. Knowledge about ASD has become widely disseminated among the general public as well as among professionals such as physicians and researchers. Alongside this societal trend, some individuals have begun to suspect that they may be autistic based on their own knowledge and understanding.

Similarly, in the case of dementia, another major societal problem, the general public has become quite knowledgeable, and some individuals are now self-assessing their dementia based on their memory in everyday life, a phenomenon known as subjective cognitive impairment. This self-reported experience of memory deterioration or loss is relatively objective and assessable.

However, in the case of ASD, it is less clear what clues an individual may use when he or she reports that he or she is likely autistic. There is no corresponding term to subjective cognitive impairment in the case of ASD. Suspicion that one may be autistic can engender unnecessary anxiety and other obstacles in one's life. An objective method of assessment, prior to professional diagnosis, would benefit those who suspect they may have autism.

In this study, in order to examine the possibility of developing an objective and simple evaluation method, we sought to determine whether there are any differences in the brain of an individual who suspects they may have autism from the brains of other individuals.

In a prior study, we identified functional brain networks by measuring activity at the resting brain using functional magnetic resonance imaging (resting-state fMRI) that reflect human characteristics such as social, cognitive, and emotional quotients, and also developed a machine learning algorithm which can estimate these human characteristics.

We attempted to evaluate the brain function of an individual who suspects he may have autism using this estimator. Additionally, we compared the functional brain connectivity of this individual to that of typical subjects based on brain regions previously identified as being associated with ASD.

(Materials and Methods)

MRI experiments

This study was approved by the Institutional Review Board of Tohoku Fukushi University (RS190607). Twenty-four healthy volunteers, with an average age of 22.8 ± 2.0, participated in the study. Of these, 12 were male and 12 were female. Twenty-three participants were typical subjects, while one was a self-identified individual suspected of having autism spectrum disorder (ASD). MRI measurements were conducted using a 3-Tesla MRI scanner (Skyra-fit; Siemens) with a 20-channel matrix head coil. Both structural and functional images were acquired. The parameters for structural images were as follows: repetition time of 1900 ms, matrix size of 256 × 256, in-plane resolution of 1 × 1 mm^2, slice thickness of 1 mm, and a total of 192 slices. The imaging orientation was sagittal. For functional images, the following parameters were used: repetition time of 1000 ms, echo time of 24 ms, matrix size of 64 × 64, in-plane resolution of 3.4 × 3.4 mm^2, slice thickness of 3.4 mm, and a total of 480 volumes. During the resting-state fMRI session, subjects were instructed to lie on the bed, keep their eyes open, and avoid thinking about anything in particular while gently focusing their eyes on the center of the visual field. The room lights were turned off during all MRI scans.

The assessment of ASD and functional connectivity was calculated from the resting-state fMRI data.

Data analysis

The resting-state fMRI image data were preprocessed using the DPABI software. The preprocessing steps included slice-scan time correction, 3D motion correction (with a maximum threshold of 1.5 mm and 1.5 degrees), removal of head motion effects using the Friston 24-parameter model, bandpass temporal filtering (between 0.01 and 0.1 Hz), and artifact rejection based on the CSF signals. The two-dimensional functional images were then incorporated into 3D anatomical images and spatially smoothed using a full width at half maximum (FWHM) of 5.0 mm. Correlation was calculated in Matlab (Mathworks Co, Natick, USA) between 17 ASD regions of interest (ROIs) identified in our previous study.[23]). The correlation was compared between the 23 typical subjects and the self-identified individual suspected of having autism spectrum disorder (ASD). The regions identified are listed in Table 1. The assessment of whether the self-identified individual suspected of having autism was conducted using a home-made toolbox, called human characteristics estimator, which was developed using the algorithm for estimating human characteristics reported in a previous study. [24].

(Results and Discussions)

The values for ASD-related characteristics estimated by the resting state fMRI data of self-identified individuals suspected of having ASD were in the median range of 3 to 5 out of a possible range of 1 to 8, with a minimum estimated value of 1 and a maximum of 8. The ASD-related networks identified were social skills, attention switching, attention to detail, and communication[24]. This suggests that the individual who self-identifies as having autism may not have the condition. The analysis of connectivity was performed by comparing edges (correlation values between 17 brain regions associated with autism) between the self-identified individuals and 23 normal subjects. It revealed significant differences at 21 out of a total of 136 edges. Three edges had values above the maximum of the normal group (Fig. 1a) and 18 edges had values below the minimum of the normal group (Fig. 1b) (two sample t-test, $p<0.05$). These results suggest that brain function related to those edges (or brain regions) may be different in the self-identified individual as compared to other normal subjects. The connectivity networks consisting of those edges are shown in Figure 2. The figures show that, among the brain regions that make up the edges showing significant differences, the left medial frontal cortex and the left precuneous cortex are major hubs of the networks in which they are involved.

The precuneous cortex is known to be involved in various functions such as self-consciousness[10], episodic memories related to the self[14], visuospatial processing relate to attention[4] and executive processing related to response inhibition[15]. Previous studies have found the precuneous cortex in relation with ASD. The medial frontal cortex (ventro-medial prefrontal cortex) is also known to be involved various functions such as emotion regulation[8, 12] and decision making[2]. This medial frontal cortex has been found to be associated with ASD in developmental studies and meta-analysis studies[17, 26].

The estimated values reflect sub-parameters of social skills, attention switching, attention to detail, and communication that are associated with autism. Based on this evaluation, the self-identified individuals may be considered normal. Therefore, the ASD-related values estimated by the human characteristic estimator suggest that the self-identified individuals suspected of having autism may not have the condition. However, the comparison of functional connectivity based on brain regions associated with autism suggests that there may be differences in some brain functions when compared to other normal individuals. The connectivity comparison also suggests the possibility of abnormality in some brain functions related to brain regions belonging to the networks such as the precuneous and prefrontal cortices.

Taken together, although this study is a case study of one self-identified individual suspected of having autism and the results are preliminary, it suggests that even a person who is considered normal may have some abnormal brain function locally. The results also suggest that the assessment of autism by the estimator may be improved by including brain regions and their functional networks in future updates.

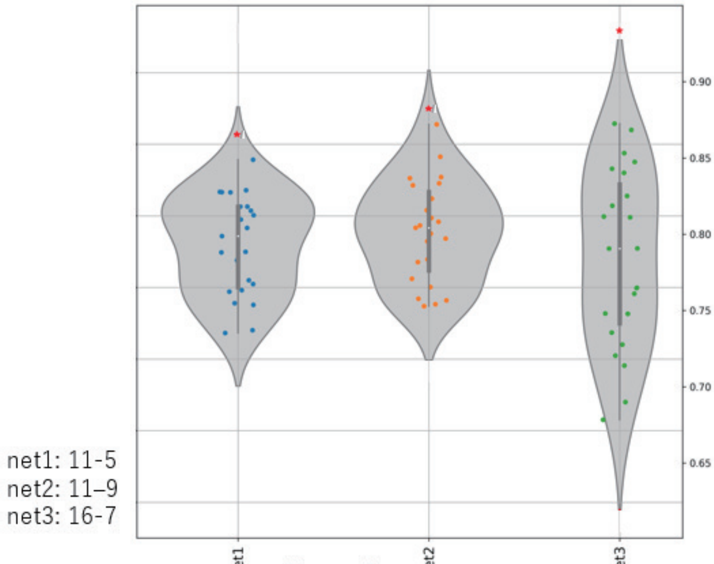

Figure 1a

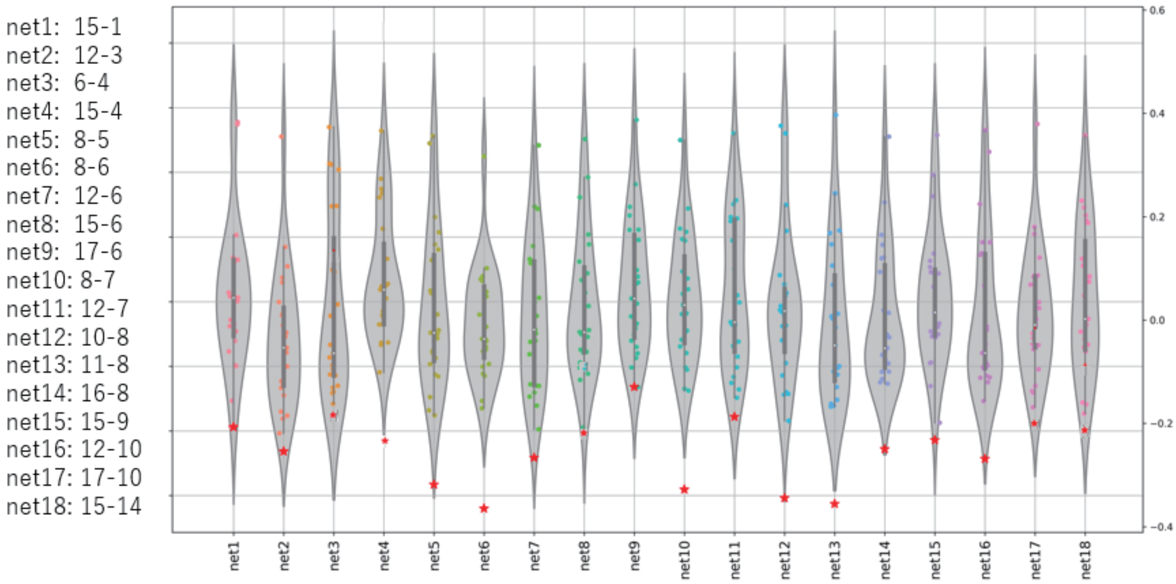

Figure 1b

Figure 1. Distribution of edge values（correlation values）of normal group and the self-identified individual suspected of having autism.（a）self-identified individual > maximum of normal group（b）self-identified individual < minimum of normal group. The red stars represent the self-identified individual.

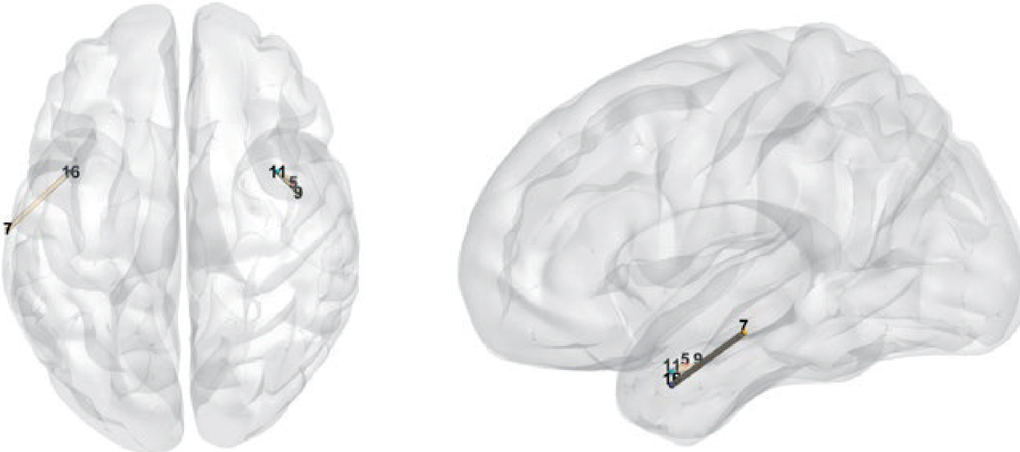

Figure 2a

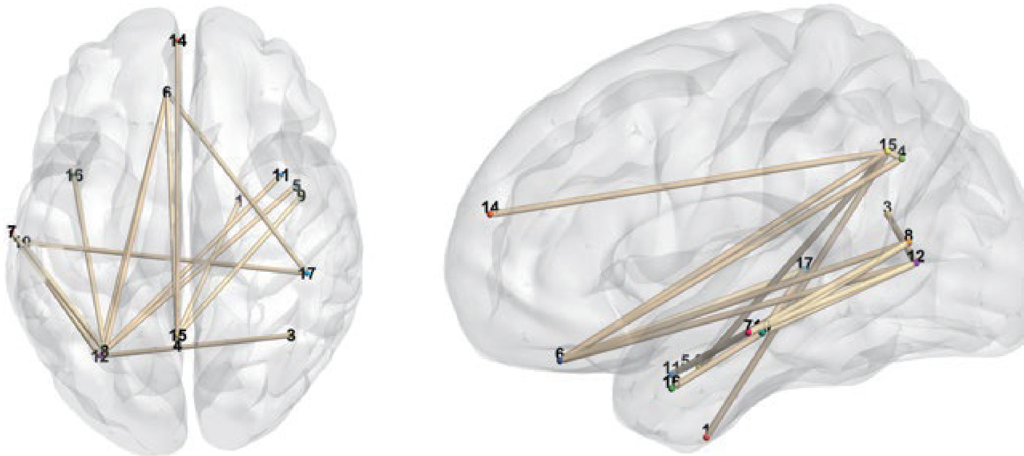

Figure 2b

Figure 2. Networks consisting of the edges of Figure 1.（a）network of Figure 1a（b）network of Figure 1b. Brain regions corresponding to the numbers can be found in Table 1.

Table 1. The brain areas related to ASD identified from Neursynth[23].

	peak_x	peak_y	peak_z	(MNI coordinates)
1	22	-4	-44	R.Fusiform Gyrus
2	-4	-6	-34	L. Pituitary
3	42	-56	20	R. Angualar Gyrus
4	-2	-60	36	L.Precuneous Cortex
5	44	2	-24	R. Temporal Pole
6	-6	38	-22	L. Medial Frontal Cortex
7	-66	-16	-14	L. Middle Temporal Gyrus
8	-30	-62	12	L. Precuneous Cortex
9	46	-2	-24	R. Superior Temporal Gyrus
10	-62	-20	-14	L. Middle Temporal Gyrus
11	38	6	-26	R. Temporal Pole
12	-32	-64	6	L. Occipital Cortex
13	50	-46	-42	R. Cerebellum
14	-2	58	20	L. Frontal Pole
15	-2	-56	38	L. Precuneous Cortex
16	-42	6	-30	L. Temporal Pole
17	48	-32	4	R. Superior Temporal Gyrus

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References

1) [2] Armstrong NC, Anderson RC, McDermott KW. Reelin: Diverse roles in central nervous system development, health and disease. Int J Biochem Cell Biol. 2019; 112:72-75.

2) [21] Bechara A, Tranel D, Damasio H. Characterization of the decision-making deficit of patients with ventromedial prefrontal cortex lesions. Brain 2000; 123: 2189–2202.

3) [16] Blanken L, Mous S, Ghassabian A, Muetzel R, Schoemaker N, Marroun H, et al. Cortical morphology in 6- to 10-year old children with autistic traits: a population-based neuroimaging study. Am J Psychiatry 2015; 172:479-486.

4) [13] Cavanna A, Trimble M. The precuneus: a review of its functional anatomy and behavioural correlates. Brain 2006; 129: 564–583.

5) [15] Cheng W, Rolls ET, Gu H, Zhang J, Feng J. Autism: reduced connectivity between cortical areas involved in face expression, theory of mind, and the sense of self. Brain 2015; 138:1382-1393.

6) [22] Fellows LK, Farah MJ. The role of ventromedial prefrontal cortex in decision making: judgment under uncertainty or judgment per se?. Cerebral Cortex 2007; 17: 2669–2674.

7) [4] Gerow S, Hagan-Burke S, Rispoli M, Gregori E, Mason R, Ninci J. A systematic review of

parent-implemented functional communication training for children with ASD. Behav Modif. 2018; 42: 335-363.

8) [19] Hänsel A, von Känel R. The ventro-medial prefrontal cortex: a major link between the autonomic nervous system, regulation of emotion, and stress reactivity?. BioPsychoSocial Medicine 2008; 2: 21.

9) [7] Jordan R. Social play and autistic spectrum disorders: a perspective on theory, implications and educational approaches. Autism. 2003; 7: 347-60.

10) [11] Kjaer TW, Nowak M, Lou HC. Reflective self-awareness and conscious states: PET evidence for a common midline parietofrontal core. NeuroImage 2002; 17: 1080–1086.

11) [6] Knott F, Dunlop AW, Mackay T. Living with ASD: how do children and their parents assess their difficulties with social interaction and understanding? Autism. 2006;10: 609-17.

12) [20] Koenigs M, Young L, Adolphs R, Tranel D, Cushman F, Hauser M, Damasio A. Damage to the prefrontal cortex increases utilitarian moral judgements. Nature 2007; 446: 908–911.

13) [24] Lau WKW, Leung M-K, Zhang R. Hypofunctional connectivity between the posterior cingulate cortex and ventromedial prefrontal cortex in autism: Evidence from coordinate-based imaging meta-analysis. Prog Neuropsychopharmacol Biol Psychiatry 2020; 103:109986.

14) [12] Lou HC, Luber B, Crupain M, Keenan JP, Nowak M, Kjaer TW, Sackeim HA, Lisanby SH. Parietal cortex and representation of the mental Self. Proceedings of the National Academy of Sciences of the United States of America 2004; 101: 6827–6832.

15) [14] Marakshina J, Vartanov A, Buldakova N. Effect of eye dominance on cognitive control". European Proceedings of Social and Behavioral Sciences. The European Proceedings of Social and Behavioural Sciences 2018; 49: 402–408.

16) [3] Mitchell S, et al. Early language and communication development of infants later diagnosed with autism spectrum disorder. J Dev Behav Pediatr. 2006; 27: S69-78.

17) [23] Murphy CM, Christakou A, Giampietro V, Brammer M, Daly EM, Ecker C, Johnston P et al. Abnormal functional activation and maturation of ventromedial prefrontal cortex and cerebellum during temporal discounting in autism spectrum disorder. Hum Brain Mapp. 2017; 38:5343-5355.

18) [1] Park HR, Lee JM, Moon HE, Lee DS, Kim BN, Kim J, Kim DG, Paek SH. A short review on the current understanding of autism spectrum sisorders. Exp Neurobiol. 2016; 25:1-13.

19) [8] Richler J, Bishop SL, Kleinke JR, Lord C. Restricted and repetitive behaviors in young children with autism spectrum disorders. J Autism Dev Disord. 2007; 37: 73-85.

20) [10] Richler J, Huerta M, Bishop SL, Lord C. Developmental trajectories of restricted and repetitive behaviors and interests in children with autism spectrum disorders. Dev Psychopathol. 2010; 22: 55-69.

21) [18] Rolls ET, Zhou Y, Cheng W, Gilson M, Deco G, Feng J. Effective connectivity in autism. Autism Res 2020; 13:32-44.

22) [5] Salomone E, Settanni M, Ferrara F, Salandin A; CST Italy Team. The Interplay of communication skills, emotional and behavioural problems and parental psychological distress. J Autism Dev Disord. 2019 ; 49: 4365-4374.

23) Sung YW, Choi U-S, Ogawa S. Task-related attention effects in the brain regions on autism spectrum disorder. Annual Reports Kansei Fukushi Res. Inst. 2020; 9-17.

24) Sung YW, Kawachi Y, Choi US, Kang D, Abe C, Otomo Y, Ogawa S. A Set of Functional Brain Networks for the Comprehensive Evaluation of Human Characteristics. Front Neurosci. 2018; Mar 14:12:149.
25) [9] Watt N, Wetherby AM, Barber A, Morgan L. Repetitive and stereotyped behaviors in children with autism spectrum disorders in the second year of life. J Autism Dev Disord. 2008; 38: 1518-33.
26.) [17] Yang J, Lee J. Different aberrant mentalizing networks in males and females with autism spectrum disorders: Evidence from resting-state functional magnetic resonance imaging. Autism 2018; 22:134-148.