原 著 論 文

Task-related attention effects in the brain regions on autism spectrum disorder

Yul-Wan Sung[1], Uk-Su Choi[2], Seiji Ogawa[1]

[1]Kansei Fukushi Research Institute, Tohoku Fukushi University, Japan,

[2]Gwangju Alzheimer's Disease and Related Dementia Cohort Research Center, Chosun University, Korea

Abstracts

Brain function in autism spectrum disorder（ASD）has been studied by functional magnetic resonance imaging（fMRI）. In particular, task-based fMRI studies have examined brain regions in ASD using language or face stimuli while resting-state fMRI studies have investigated functional networks. Most of the studies have focused on the core features of ASD namely to social interaction deficits. In this study, we devised a novel experimental paradigm to combine task-based and resting-state fMRI to examine functional features of ASD. We provide data suggesting that our novel paradigm can provide an interesting path to explore in the search of biomarkers for ASD.

Keywords : resting state fMRI, repetitive-task fMRI, Autism Spectrum Disorder（ASD）, Functional connectivity.

Introduction

Autism spectrum disorder（ASD）is a neurodevelopmental condition [1,2] characterized by several deficits in behavior such as difficulties with communication [3-5] and social interactions [6,7], as well as restricted or repetitive patterns of behavior [8-10]. Although not considered as a major feature, attention problems such as intense focusing and concentration on a single item are also common in ASD [11]. Brain function in ASD patients have been studied by functional MRI（fMRI）. Specifically, task-based fMRI studies have examined brain regions involved in ASD by using language or face stimuli and resting-state fMRI studies have investigated functional networks [12-15]. Most of the studies have focused on the core ASD features related to deficits in social interactions.

Here, we propose a novel experimental paradigm combining task-based and resting-state fMRI to examine attention related features in ASD. We identified functional brain areas affected by ASD by meta-analysis（Neurosynth）. The functional connectivity between these brain regions was evaluated while the participants performed a repetitive task（finger tapping throughout the fMRI acquisition period）. This experimental paradigm does not provide fMRI response for events of the task because it has no rest period but provides the similar fMRI response time courses as seen in the resting-state fMRI.

As a proof-of-principle study, we performed fMRI on healthy participants and attempted to find functional connectivity differences between the typical resting-state fMRI and fMRI in the repetitive task condition（repetitive task-based fMRI）.

Materials and Methods

This study was approved by the Institutional Review Board of Tohoku Fukushi University (RS190607). Ten healthy volunteers participated to this study. MRI measurements were conducted by a 3-Tesla MRI scanner (Skyra-fit; Siemens) with a 20 channel matrix head coil. From the ten subjects' structural images (T 1) and functional images were measured. Parameters for structural images were repetition time 1900 ms, matrix size 256 × 256, in-plane resolution = 1 × 1 mm2, slice thickness = 1 mm, and number of slices = 192. The imaging orientation was sagittal. For functional fMRI measurements, the following parameters were used: repetition time = 1000 ms, echo time = 24 ms, matrix size = 64 × 64, in-plane resolution = 3.4 × 3.4 mm2, slice thickness = 3.4 mm, and number of volumes = 480. Repetitive-task fMRI and resting-state fMRI data were acquired from. In the resting-state fMRI session, subjects were asked to lie on the bed and not to wander their mind with their eyes open and to gently focus their eyes on the center of the visual field. The resting-state fMRI session was followed by repetitive-task fMRI session. In the task-fMRI session, subjects performed finger tapping by both hands continually throughout the 8 min scan with their eyes open. The lights in the room were turned off during all MRI scans.

The brain areas related to ASD were identified from Neurosynth. This is a platform for the large-scale, automated synthesis of fMRI data [17]. The keyword of ASD was used for the identification of brain areas.

Results and Discussion

Seventeen brain areas previously related to ASD were identified using Neurosynth[17]. Table 1 shows the coordinates and anatomical labels of these functional brain regions and SupplementFig. 1 shows the maps of the areas. To examine the connectivity between those brain regions we performed a correlation analysis (Pearson's correlation between two brain areas). The correlation maps were almost the same for the resting-state fMRI and the repetitive task-based fMRI (Fig. 2). The difference map and p-value map were obtained by subtracting the two brain maps from each other (Fig. 3). Only the left medial frontal cortex and the left occipital cortex had significant correlation value (Table 1 ; SupplementFig. 1).

These two functional areas affected by ASD are not implicated in the motor function involved in the repetitive task performed by the subject during the fMRI scan. The identified area in the left occipital cortex is known to process visual information related to faces, objects, and attention and the one in the left medial frontal cortex processes information related to behavioral control, attention, rewards, emotion, decision making etc. Therefore, the correlation changes observed in these brain regions might be due to a secondary function involved in the repetitive task, such as staying focused to perform the same task for several minutes [18-20]. One of the conceivable functions is the attention because the behavior of staying focused during the task can be interpreted as the task-related attention and both brain regions are involved in the attention processing[21-24]. This task-related attentional modulation of the functional connectivity may reflect plausible difference between ASD and typically developing controls (TDC)[21]. A previous study supports it by showing changes in cortical thickness of the left occipital cortex in relation with attention in which the change was a result of compensation of attentional network[24].

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

	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

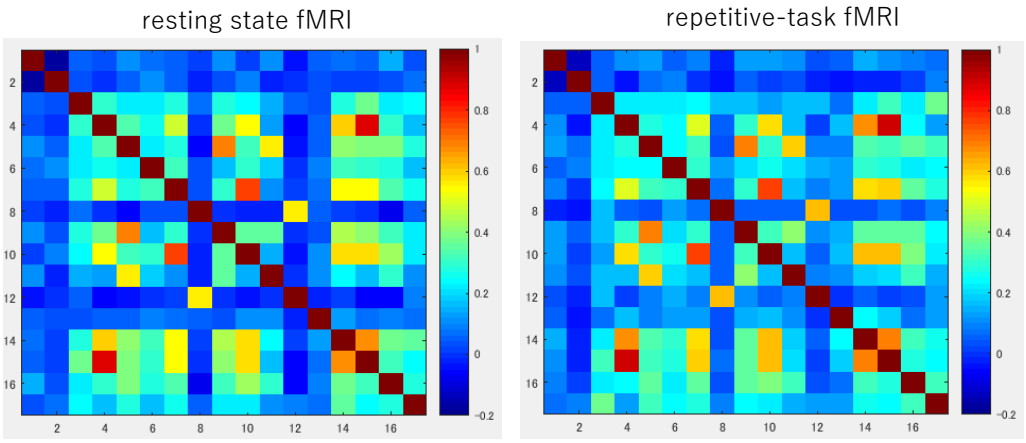


Figure 1. Correlation (Pearson's) maps for resting state fMRI (left) and repetitive-task fMRI (right)

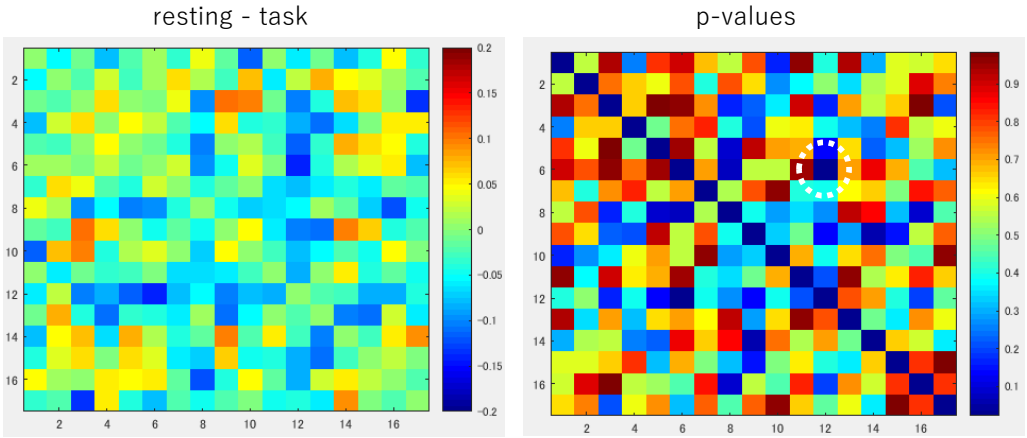


Figure 2. Difference map between resting state fMRI and repetitive-task fMRI (left) and the p-value (paired-t test) map corresponding to the difference map (right). The white dotted circle indicates the only connectivity difference satisfying the significant level of $p < 0.05$.

The connectivity change induced by the repetitive task in ASD related brain areas might be a candidate biomarker for ASD. However, further studies are needed. In particular, a comparison of the autism spectrum quotient score and the connectivity changes in ASD patients is necessary. Nevertheless, our paradigm has the advantage to use fMRI response induced by task performing and might be more sensitive than other methods based on resting-state fMRI because of focal activation resulting in a less partial volume effect. Moreover, the task is simple and easy to perform and does not require difficult or high cognitive skills.

In conclusion, this study shows that our novel experimental paradigm provides an interesting avenue to explore in the search for biomarkers for ASD.

Acknowledgement

This study was carried out as a part of the cooperative research project at the Kansei Research Institute of Tohoku Fukushi University, receiving a subsidy of the research facility operation support MEXT, and JSPS KAKENHI Grant Number 19H01111 & 19H00532.

References

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.

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.

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.

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.

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.

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.

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

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.

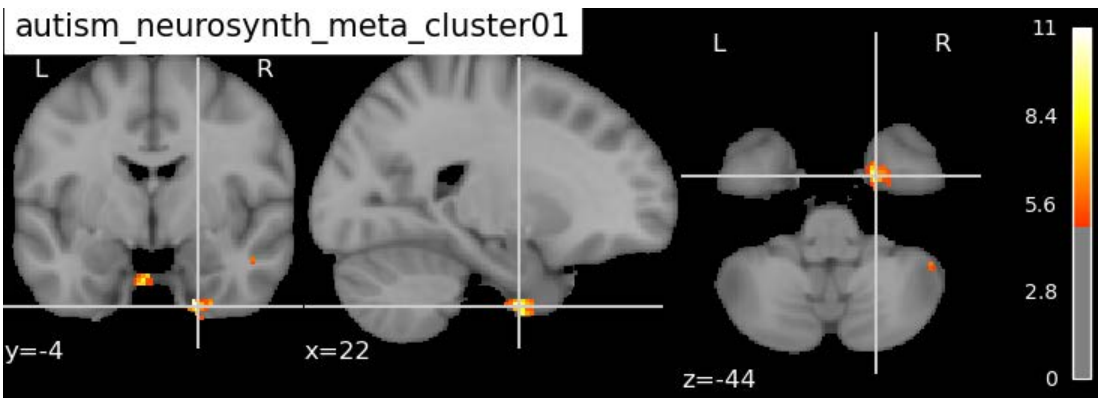
9）Watt N, Wetherby AM, Barber A, Morgan L. Repetitive and stereotyped behaviors in children with autism spectrum disorders in the second year of life. J Autism Dev Disord. 2008; 38: 1518-33.

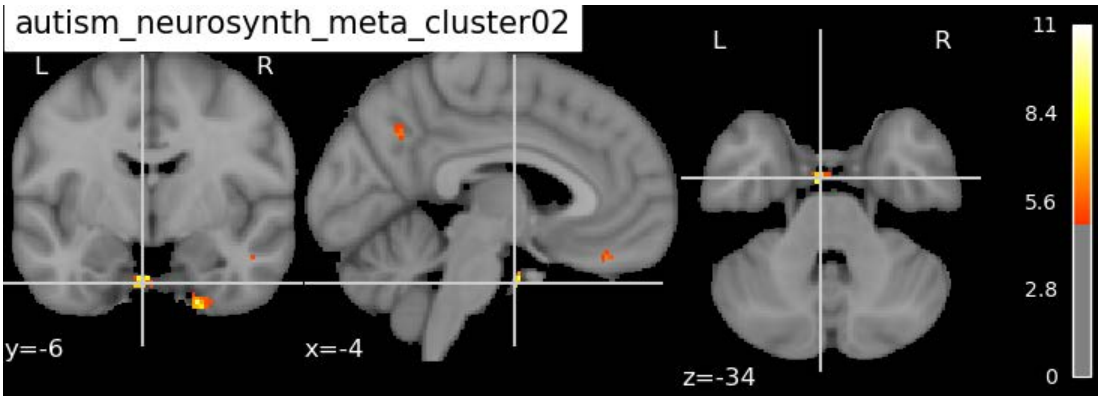
10）Richler J, Huerta M, Bishop SL, Lord C. Developmental trajectories of restricted and repetitive behaviors and interests in children with autism spectrum disorders. Dev Psychopathol. 2010; 22: 55-69.

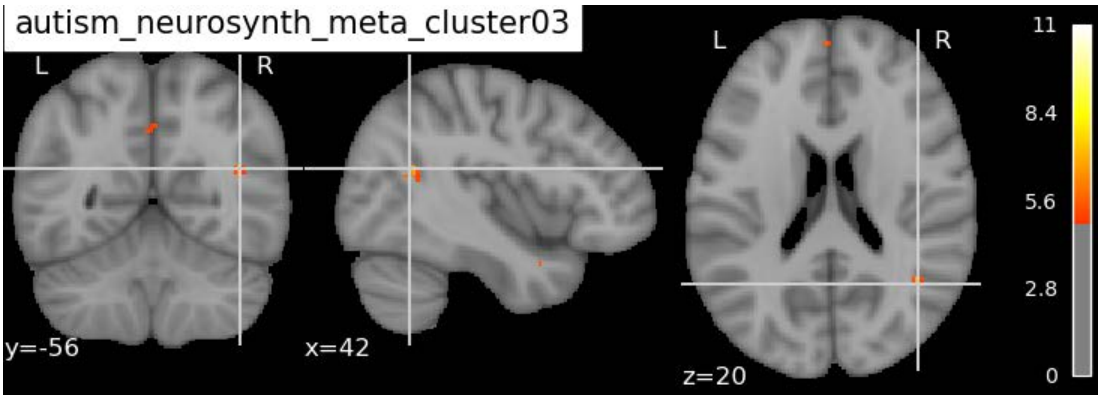
11）Bennett E, Heaton P. Is talent in autism spectrum disorders associated with a specific cognitive and behavioural phenotype? J Autism Dev Disord. 2012; 42: 2739-53.

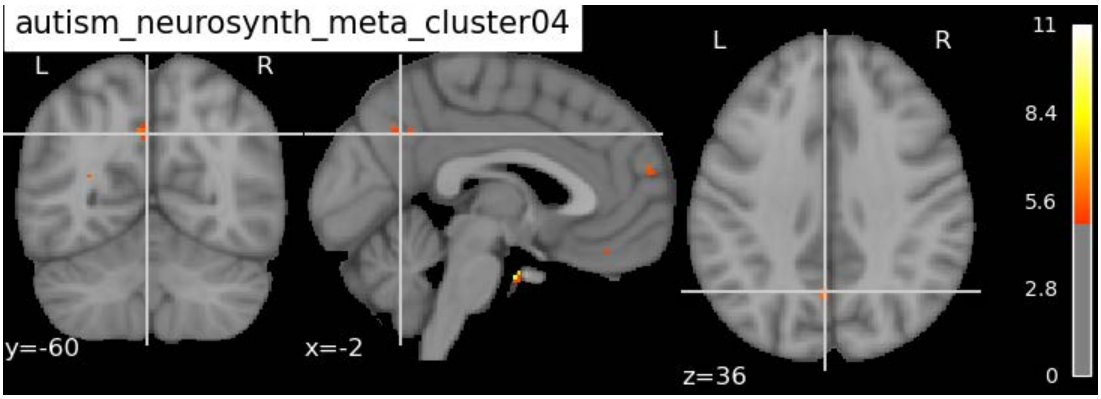
12）Knaus TA, Silver AM, Lindgren KA, Hadjikhani N, Tager-Flusberg H. fMRI activation during a language task in adolescents with ASD. J Int Neuropsychol Soc. 2008; 14: 967-79.
13）Bookheimer SY, Wang AT, Scott A, Sigman M, Dapretto M. Frontal contributions to face processing differences in autism: evidence from fMRI of inverted face processing. J Int Neuropsychol Soc. 2008; 14: 922-32.
14）Harris GJ, Chabris CF, Clark J, Urban T, Aharon I, Steele S, McGrath L, Condouris K, Tager-Flusberg H. Brain activation during semantic processing in autism spectrum disorders via functional magnetic resonance imaging. Brain Cogn. 2006; 61: 54-68.
15）Gao Y, Linke A, Jao Keehn RJ, Punyamurthula S, Jahedi A, Gates K, Fishman I, Müller RA.
16）The language network in autism: Atypical functional connectivity with default mode and visual regions. Autism Res. 2019; 12: 1344-1355.
17）Neurosynth.org; PRID:SCR_006798
18）Wolf RC, Philippi CL, Motzkin JC, Baskaya MK, Koenigs M. Ventromedial prefrontal cortex mediates visual attention during facial emotion recognition. Brain. 2014; 137: 1772-80.
19）van Honk J, Hermans EJ, d'Alfonso AA, Schutter DJ, van Doornen L, de Haan EH. A left-prefrontal lateralized, sympathetic mechanism directs attention towards social threat in humans: evidence from repetitive transcranial magnetic stimulation. Neurosci Lett. 2002; 319: 99-102.
20）Wang L, LaBar KS, McCarthy G. Mood alters amygdala activation to sad distractors during an attentional task. Biol Psychiatry. 2006; 60: 1139-46.
21）Choi US et al. Abnormal brain activity in social reward learning in children with autism spectrum disorder: An fMRI Study. Yonsei Med J. 2015; 56: 705-711.
22）Williams JM, Mohler EG, Bivens B. The role of the medial prefrontal cortex in attention: Altering predictability of task difficulty. Psychobiology. 1999; 27: 462-469.
23）Luritzen TZ, D'Esposito M, Heeger DJ, Silver MA. Top-down flow of visual spatial attention signals from parietal to occipital cortex. J. Vision. 2009; 9: 1-14.
24）Soros P et al. Inattention predicts increased thickness of left occipital cortex in men with attention-deficit/hyperactivity disorder. Front Psychiatry. 2017; 8: 170.

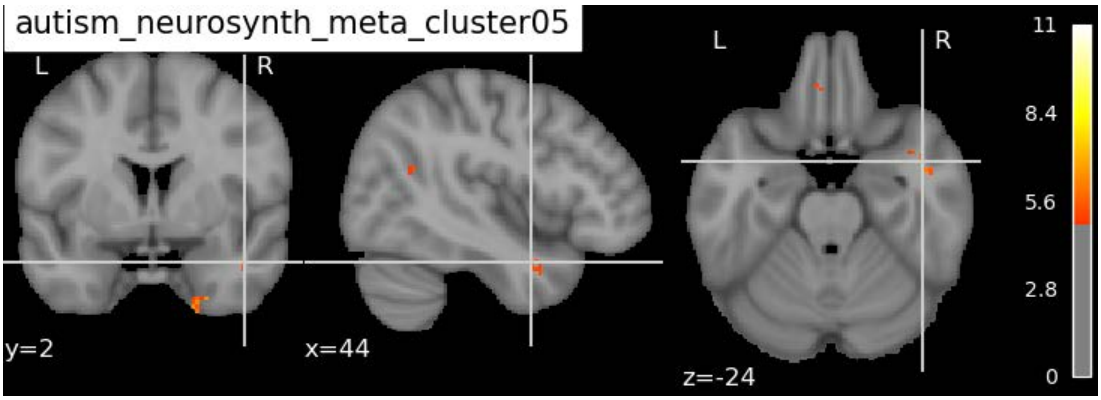
Supplementary Figure 1. Locations of the 17 functional brain areas identified.
The color bars stand for a statistical value（t-value）.

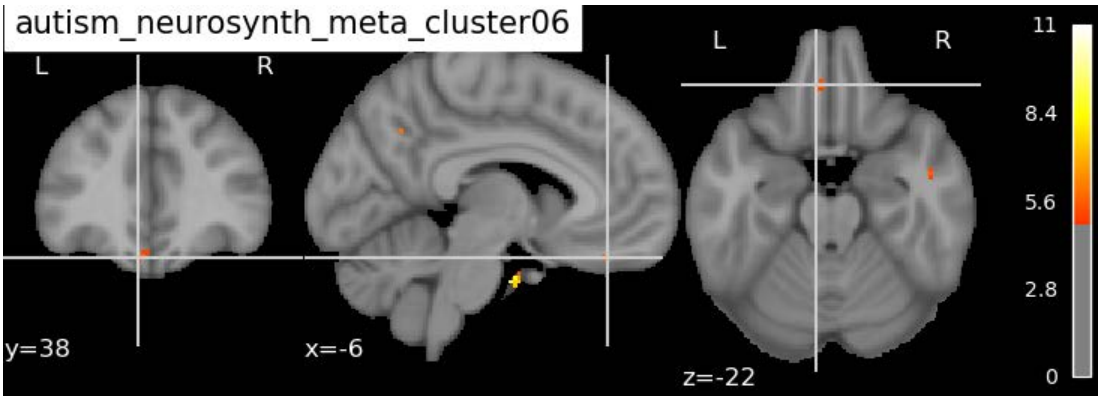


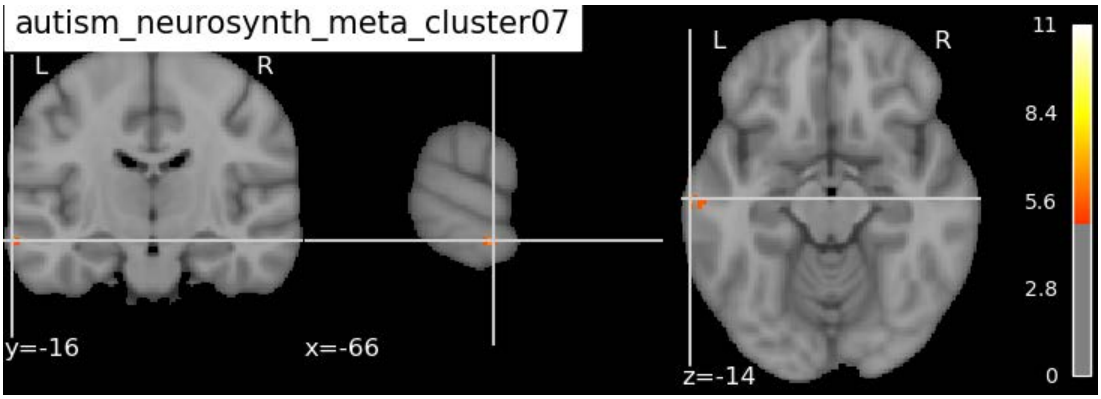

autism_neurosynth_meta_cluster02
L
R
y=-6
x=-4
L
R
z=-34
11
8.4
5.6
2.8
0

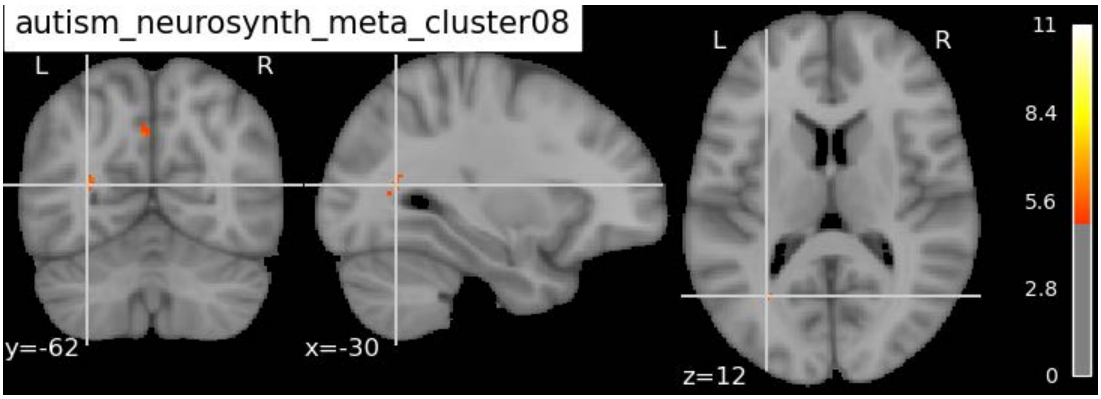

autism_neurosynth_meta_cluster03
L
R
y=-56
x=42
L
R
z=20
11
8.4
5.6
2.8
0

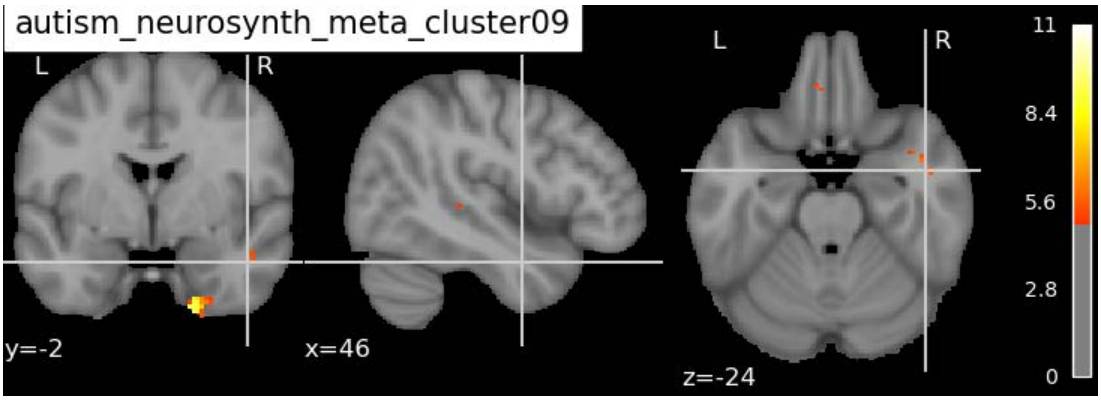

autism_neurosynth_meta_cluster04
L
R
y=-60
x=-2
L
R
z=36
11
8.4
5.6
2.8
0

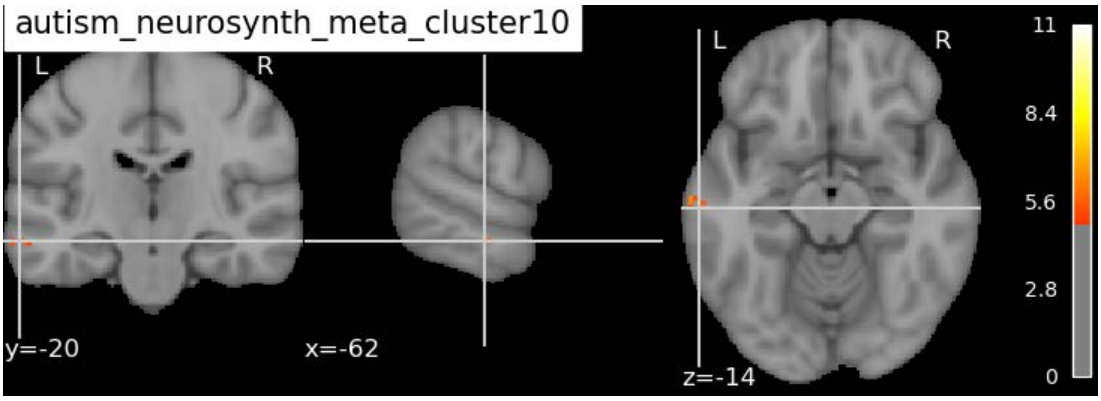

autism_neurosynth_meta_cluster05
L
R
y=2
x=44
L
R
z=-24
11
8.4
5.6
2.8
0

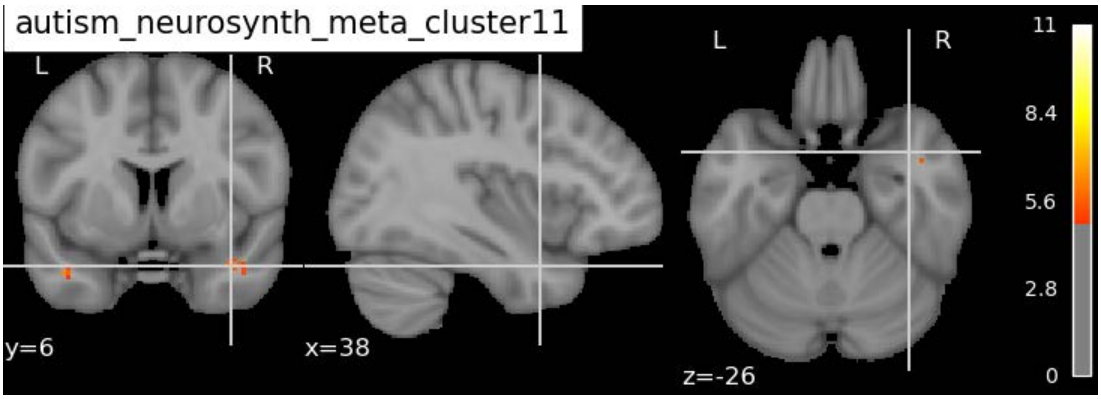

autism_neurosynth_meta_cluster06
L
R
y=38
x=-6
L
R
z=-22
11
8.4
5.6
2.8
0

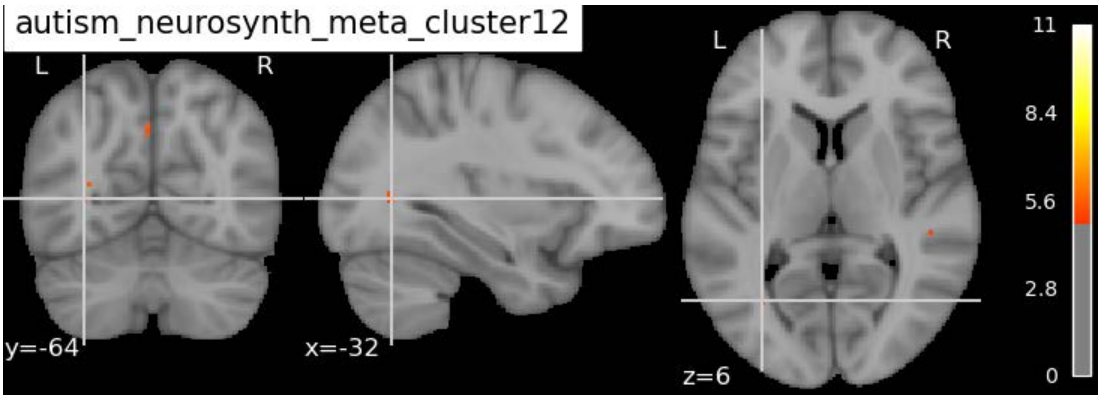

autism_neurosynth_meta_cluster07
L
R
y=-16
x=-66
L
R
z=-14
11
8.4
5.6
2.8
0

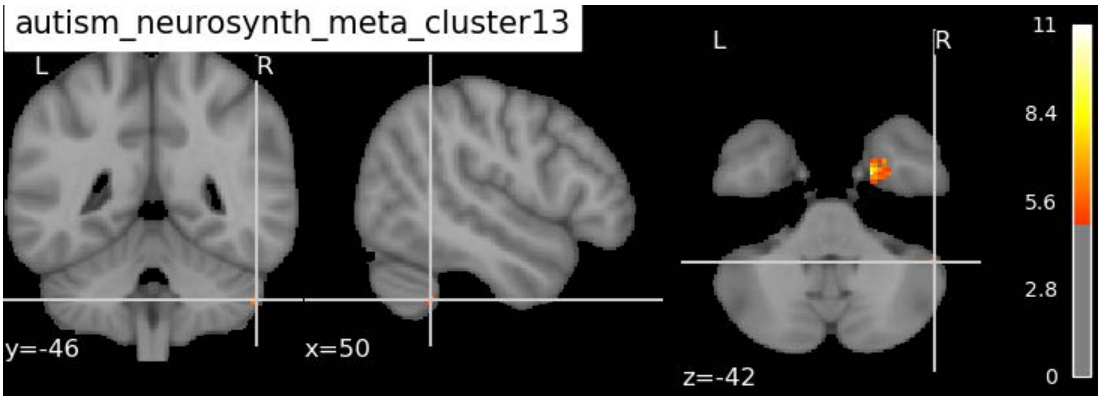

autism_neurosynth_meta_cluster08
L
R
y=-62
x=-30
L
R
z=12
11
8.4
5.6
2.8
0

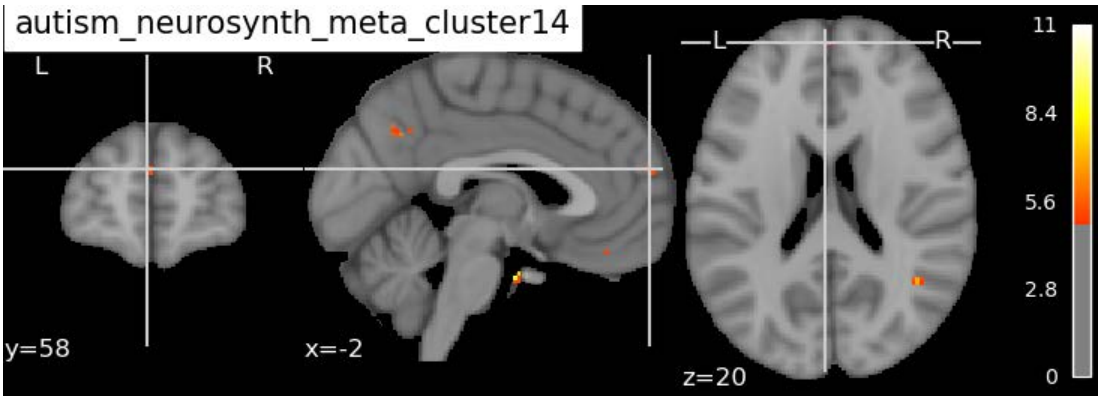

autism_neurosynth_meta_cluster09
L
R
y=-2
x=46
L
R
z=-24
11
8.4
5.6
2.8
0

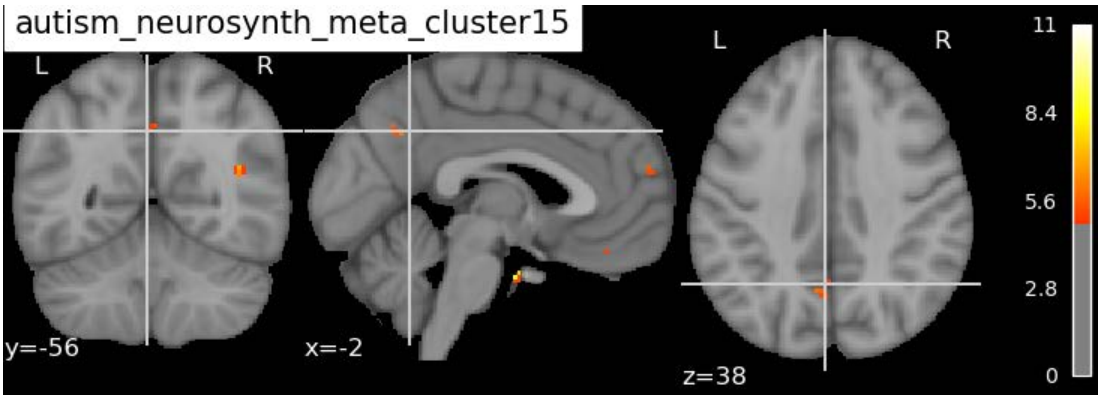

autism_neurosynth_meta_cluster10
L
R
y=-20
x=-62
L
R
z=-14
11
8.4
5.6
2.8
0

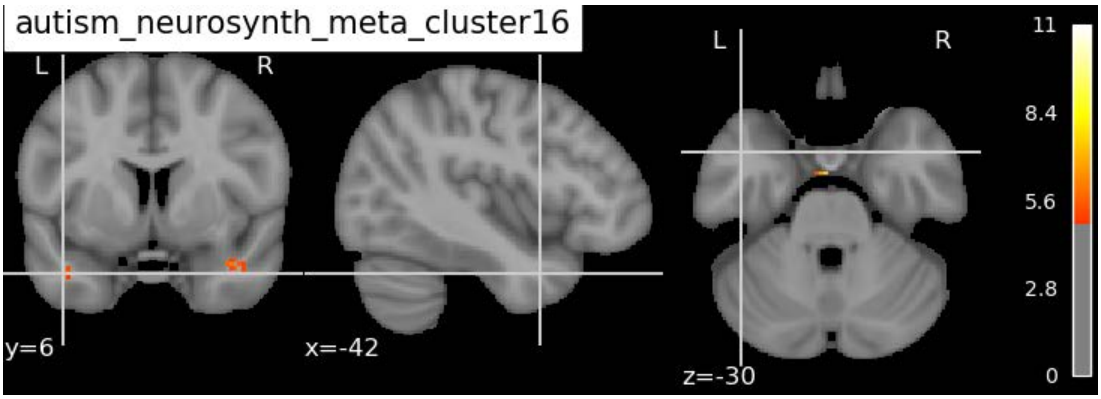

autism_neurosynth_meta_cluster11
L
R
y=6
x=38
L
R
z=-26
11
8.4
5.6
2.8
0

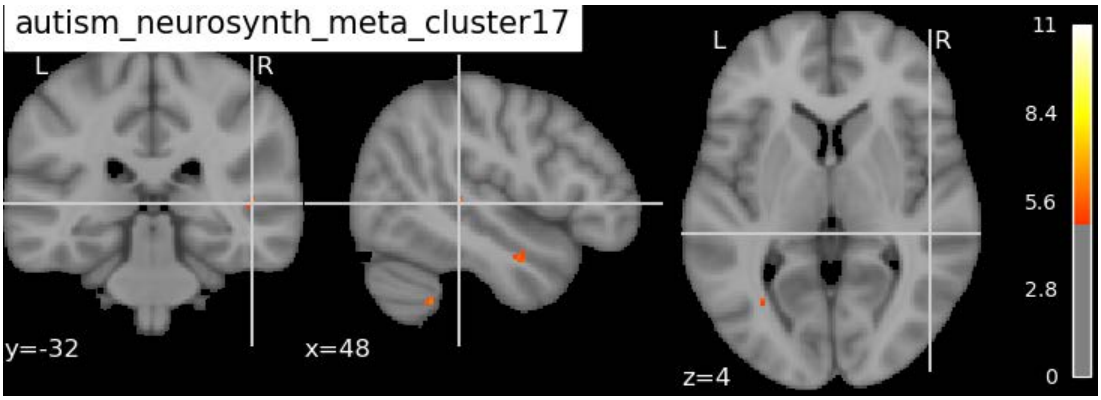

autism_neurosynth_meta_cluster12
L
R
y=-64
x=-32
L
R
z=6
11
8.4
5.6
2.8
0


autism_neurosynth_meta_cluster13
L
R
y=-46
x=50
L
R
z=-42
11
8.4
5.6
2.8
0


autism_neurosynth_meta_cluster14
L
R
y=58
x=-2
L
R
z=20
11
8.4
5.6
2.8
0


autism_neurosynth_meta_cluster15
L
R
y=-56
x=-2
L
R
z=38
11
8.4
5.6
2.8
0


autism_neurosynth_meta_cluster16
L
R
y=6
x=-42
L
R
z=-30
11
8.4
5.6
2.8
0


autism_neurosynth_meta_cluster17
L
R
y=-32
x=48
L
R
z=4
11
8.4
5.6
2.8
0