Supplementary Material

Autism: Reduced Functional Connectivity between Cortical Areas Involved in Face Expression, Theory of Mind, and the Sense of Self

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Table S1. The demographic and clinical characteristics of participants satisfying inclusion criteria.

Variables	Number of sites	Number of subjects	Control			Autism			Group comparisons	
			Sub n	Mean	SD	Sub n	Mean	SD	Statistic	p value
AGE_AT_SCAN	16	927	509	16.4	7.08	418	17.17	7.97	-1.55	0.12
FIQ	16	856	471	110.62	11.93	385	105.7	14.16	5.44	<0.001
VIQ	12	789	428	111.10	12.84	361	104.5	15.87	6.43	<0.001
PIQ	13	787	425	107.24	12.56	362	105.3	15.17	1.89	0.058
ADOS_TOTAL	13	323	30	1.30	1.393	293	11.64	3.761	/	/
ADOS_COMM	12	301	30	0.533	0.681	271	3.771	1.507	/	/
ADOS_SOCIAL	12	301	30	0.766	0.971	271	7.952	2.751	/	/
ADOS_STEREO_BEHAV	8	264	30	0.066	0.253	234	1.995	1.532	/	/
ADI_R_SOCIAL_TOTAL_A	13	285	/	/	/	285	19.84	5.620	/	/
ADI_R_VERBAL_TOTAL_BV	13	286	/	/	/	286	15.82	4.618	/	/
ADI_RRB_TOTAL_C	13	285	/	/	/	285	6.119	2.586	/	/
ADI_R_ONSET_TOTAL_D	11	220	/	/	/	220	3.195	1.272	/	/
Sex (male/female)	16	927	424/85	/	/	367/51	/	/	3.71	0.0541
Handedness (right/others)	16	927	458/51	/	/	359/59	/	/	3.68	0.055
EYE_STATUS_AT_SCAN (open/ closed)	16	927	369/140	/	/	306/112	/	/	0.058	0.808
DSM_IV_TR (autism/others)	14	384	/	/	/	279/105	/	/	/	/
MEDICATION (yes/no)	12	293	/	/	/	99/194	/	/	/	/

Number of sites: The number of sites including the Variables
Number of subjects: The number of subjects including the Variables
Sub n: The number of subjects including the Variables in controls or in the autistic group
AGE_AT_SCAN: Age at time of scan in years
FIQ: Full IQ
VIQ: Verbal IQ
PIQ: Performance IQ
ADOS_TOTAL: Classic Total Autism Diagnostic Observation Schedule (ADOS) Score
ADOS_COMM: Communication Total Subscore of the Classic ADOS
ADOS_SOCIAL: Social Total Subscore of the Classic ADOS
ADOS_STEREO_BEHAV: Stereotyped Behaviors and Restricted Interests Total Subscore of the Classic ADOS
ADI_R_SOCIAL_TOTAL_A: Reciprocal Social Interaction Subscore (A) Total for Autism Diagnostic Interview-Revised (ADI-R)
ADI_R_VERBAL_TOTAL_BV: Abnormalities in Communication Subscore (B) Total for ADI-R
ADI_RRB_TOTAL_C: Restricted, Repetitive, and Stereotyped Patterns of Behavior Subscore (C) Total for ADI-R
ADI_R_ONSET_TOTAL_D: Abnormality of Development Evident at or Before 36 Months Subscore (D) Total for ADI-R
EYE_STATUS_AT_SCAN: Eye Status During Rest Scan
DSM_IV_TR: DSM_IV_TR Diagnostic Category
MEDICATION: Information on use of medications within the month prior to the scan

Table S2. The names and abbreviations of the regions of interest (ROIs)

NO.	Regions	Abbr.	NO.	Regions	Abbr.
1, 2	Precentral gyrus	PreCG	47, 48	Lingual gyrus	LING
3, 4	Superior frontal gyrus, dorsolateral	SFGdor	49, 50	Superior occipital gyrus	SOG
5, 6	Orbitofrontal cortex, superior part	ORBsup	51, 52	Middle occipital gyrus	MOG
7, 8	Middle frontal gyrus	MFG	53, 54	Inferior occipital gyrus	IOG
9, 10	Orbitofrontal cortex, middle part	ORBmid	55, 56	Fusiform gyrus	FFG
11, 12	Inferior frontal gyrus, opercular part	IFGoperc	57, 58	Postcentral gyrus	PoCG
13, 14	Inferior frontal gyrus, triangular part	IFGtriang	59, 60	Superior parietal gyrus	SPG
15, 16	Orbitofrontal cortex, inferior part	ORBinf	61, 62	Inferior parietal	IPL
17, 18	Rolandic operculum	ROL	63, 64	Supramarginal gyrus	SMG
19, 20	Supplementary motor area	SMA	65, 66	Angular gyrus	ANG
21, 22	Olfactory cortex	OLF	67, 68	Precuneus	PCUN
23, 24	Superior frontal gyrus, medial	SFGmed	69, 70	Paracentral lobule	PCL
25, 26	Orbitofrontal cortex, superior medial	ORBsupmed	71, 72	Caudate nucleus	CAU
27, 28	Gyrus rectus	REC	73, 74	Lenticular nucleus, putamen	PUT
29, 30	Insula	INS	75, 76	Lenticular nucleus, pallidum	PAL
31, 32	Anterior cingulate & paracingulate gyri	ACG	77, 78	Thalamus	THA
33, 34	Cingulate & paracingulate gyri	DCG	79, 80	Heschl gyrus	HES
35, 36	Posterior cingulate gyrus	PCG	81, 82	Superior temporal gyrus	STG
37, 38	Hippocampus	HIP	83, 84	Temporal pole: superior	TPOsup
39, 40	Parahippocampal gyrus	PHG	85, 86	Middle temporal gyrus	MTG
41, 42	Amygdala	AMYG	87, 88	Temporal pole: middle	TPOmid
43, 44	Calcarine fissure & surrounding cortex	CAL	89, 90	Inferior temporal gyrus	ITG
45, 46	Cuneus	CUN			

Table S3. The result of classification based on the voxel-based ROI-wise analysis.

Sites	Sensitivity	Specificity	Accuracy
Caltech	84.21	89.47	86.84
KKI	56.25	87.09	76.59
Leuven	41.37	100.00	73.01
MaxMun	100.00	75.00	92.30
NYU	69.56	87.50	80.00
OHSU	90.90	100.00	96.15
Olin	82.35	87.50	84.84
Pitt	64.28	88.88	76.36
SBL	93.33	66.66	80.00
SDSU	81.81	95.45	90.90
Stanford	100.00	94.44	95.00
Trinity	77.27	79.16	78.26
UCLA	68.29	82.22	75.58
UM	71.42	80.51	76.69
USM	90.38	67.50	80.43
Yale	85.71	80.76	82.97

Table S4. Significant regions of interest (ROIs) identified by the first and second dataset in the voxel-based whole brain analysis. We highlighted regions that exhibit abnormalities in three different cases: whole dataset, the first half and the second half.

ROIs identified by the first split half data							ROIs identified by the second split half data						
No.	**Areas**	**Cluster size #Voxels**	**Peak MA value**	**Peak MNI coordinates**			**No.**	**Areas**	**Cluster size #Voxels**	**Peak MA value**	**Peak MNI coordinates**		
ROI 1	PreCG.L	39	-195	-45	-15	57	**ROI 1**	**PreCG.R**	**29**	**108**	**33**	**-18**	**54**
ROI 2	**PreCG.R**	**164**	**-245**	**36**	**-24**	**54**	**ROI 2**	**SFGdor.L**	**108**	**637**	**-18**	**27**	**45**
ROI 3	**SFGdor.L**	**28**	**231**	**-21**	**27**	**42**	ROI 3	SFGdor.R	73	-986	24	33	57
ROI 4	**MFG.L**	**88**	**-307**	**-39**	**45**	**24**	**ROI 4**	**MFG.L**	**154**	**382**	**-39**	**45**	**24**
ROI 5	**MFG.R**	**30**	**-482**	**51**	**48**	**3**	**ROI 5**	**MFG.R**	**157**	**-376**	**51**	**48**	**3**
ROI 6	IFGoperc.R	70	-112	54	18	21	ROI 6	IFGtriang.L	74	311	-45	42	9
ROI 7	IFGtriang.R	142	-470	51	45	3	ROI 7	IFGtriang.R	53	-288	51	45	6
ROI 8	ROL.R	22	93	66	-6	12	**ROI 8**	**SMA.R**	**26**	**160**	**6**	**-24**	**54**
ROI 9	SMA.L	44	-169	0	18	45	ROI 9	SFGmed.L	51	-225	0	66	3
ROI 10	**SMA.R**	**125**	**201**	**9**	**-21**	**72**	ROI 10	SFGmed.R	90	-296	3	63	3
ROI 11	**ORBsupmed.L**	**26**	**-268**	**0**	**63**	**-3**	**ROI 11**	**ORBsupmed.L**	**80**	**-460**	**0**	**66**	**-3**
ROI 12	**ORBsupmed.R**	**97**	**-433**	**3**	**60**	**-3**	**ROI 12**	**ORBsupmed.R**	**128**	**-530**	**3**	**66**	**-3**
ROI 13	REC.L	31	-143	0	51	-18	ROI 13	REC.L	37	-203	-3	51	-15
ROI 14	REC.R	23	260	6	57	-15	ROI 14	INS.R	31	159	45	18	-9
ROI 15	INS.L	102	-140	-39	3	0	ROI 15	ACG.L	177	-361	-6	42	6
ROI 16	INS.R	65	-102	45	15	-9	ROI 16	ACG.R	124	-186	3	42	3
ROI 17	DCG.L	74	470	0	-39	48	ROI 17	PHG.L	27	-246	-27	-30	-15
ROI 18	DCG.R	129	-330	3	15	42	**ROI 18**	**PoCG.L**	**45**	**-205**	**-54**	**-18**	**51**
ROI 19	CAL.L	58	-421	-9	-63	21	**ROI 19**	**PoCG.R**	**43**	**105**	**39**	**-21**	**48**
ROI 20	**CUN.L**	**64**	**-532**	**-9**	**-66**	**24**	ROI 20	IPL.L	28	-171	-57	-36	54
ROI 21	CUN.R	40	167	18	-78	27	ROI 21	SMG.R	105	-168	57	-36	45
ROI 22	LING.L	21	123	-9	-48	3	**ROI 22**	**PCUN.L**	**57**	**-139**	**-9**	**-57**	**27**
ROI 23	SOG.R	87	163	18	-81	30	**ROI 23**	**PCUN.R**	**64**	**-149**	**6**	**-54**	**24**
ROI 24	MOG.L	55	72	-27	-87	18	ROI 24	CAU.L	37	434	-12	-6	18
ROI 25	MOG.R	28	99	30	-81	27	**ROI 25**	**CAU.R**	**24**	**243**	**15**	**-15**	**21**
ROI 26	IOG.L	21	-89	-21	-90	-9	ROI 26	PUT.L	55	-260	-21	3	-6
ROI 27	**PoCG.L**	**415**	**-1065**	**-54**	**-15**	**48**	ROI 27	PUT.R	39	-152	24	9	3
ROI 28	**PoCG.R**	**380**	**-498**	**39**	**-27**	**54**	ROI 28	PAL.L	23	-241	-21	6	-3
ROI 29	IPL.L	46	-336	-51	-18	39	ROI 29	PAL.R	27	-93	21	6	3
ROI 30	SMG.R	49	262	60	-36	42	**ROI 30**	**THA.L**	**154**	**368**	**-9**	**-9**	**15**
ROI 31	**PCUN.L**	**225**	**-302**	**-9**	**-48**	**9**	**ROI 31**	**THA.R**	**188**	**322**	**15**	**-12**	**18**
ROI 32	**PCUN.R**	**173**	**-362**	**6**	**-51**	**27**	**ROI 32**	**STG.L**	**101**	**147**	**-54**	**-24**	**3**
ROI 33	**PCL.L**	**124**	**-198**	**0**	**-24**	**54**	**ROI 33**	**MTG.L**	**129**	**136**	**-54**	**-27**	**3**
ROI 34	PCL.R	77	175	12	-24	72	**ROI 34**	**MTG.R**	**37**	**-263**	**60**	**0**	**-30**
ROI 35	**CAU.R**	**52**	**761**	**15**	**-6**	**18**	ROI 35	ITG.L	41	-400	-57	-6	-30
ROI 36	**THA.L**	**182**	**514**	**-6**	**-18**	**12**	**ROI 36**	**ITG.R**	**91**	**-305**	**48**	**-6**	**-36**
ROI 37	**THA.R**	**173**	**874**	**12**	**-6**	**12**							
ROI 38	**STG.L**	**84**	**291**	**-54**	**6**	**-12**							
ROI 39	STG.R	137	-238	51	-39	12							
ROI 40	TPOsup.L	35	-296	-54	9	-15							
ROI 41	TPOsup.R	65	505	51	9	-6							

ROI 42	**MTG.L**	**252**	**261**	**-63**	**-21**	**0**	
ROI 43	**MTG.R**	**102**	**-609**	**54**	**-3**	**-27**	
ROI 44	TPOmid.L	21	146	-48	15	-30	
ROI 45	**ITG.R**	**76**	**257**	**60**	**-6**	**-30**	

Figure S1. Location of the altered functional network of the voxel-level whole brain association study. The left side of the brain is on the right of each coronal slice. Voxels with overall increased connectivity are in red, and with reduced connectivity in blue.

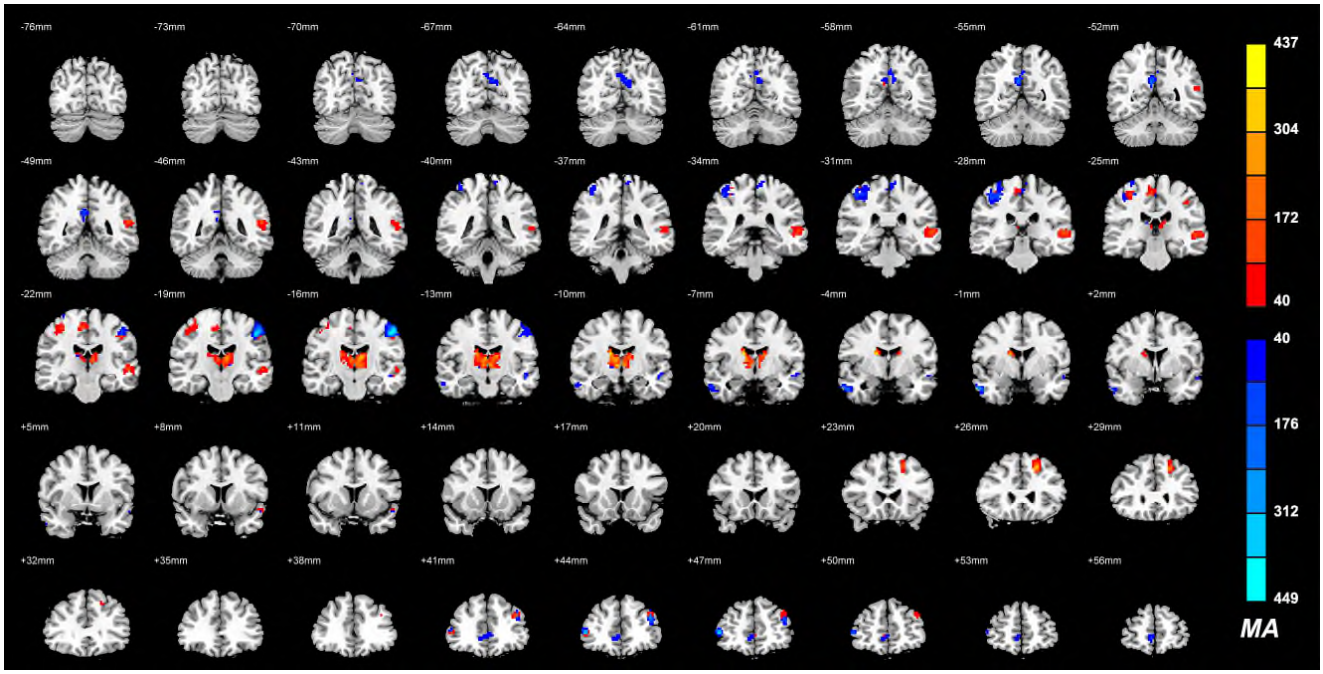

Figure S2. Voxels with different functional connectivity in autism (Bonferroni correction, in this case the effect of IQ was not regressed). **A.** Manhattan plot showing the probability values for each link being different in the autistic group compared to the control group. Each dot is a functional connectivity link between two voxels. Note there are a total of $47636 \times 47635 / 2$ links, and we only plot a dot if $p<10^{-5}$. The red dotted line is the Bonferroni correction threshold 4.4×10^{-11}. The regions indicate the AAL areas in which the voxels were located, with the numbers for each region specified in Table S2. **B.** Location of the voxels that had significantly different altered functional connectivity with other voxels (using whole brain Bonferroni correction). The color bar represents the measure of association (MA, see text) given by the number of significantly affected links relating to each voxel. Voxels that had functional connectivities in the autism population that were weaker than in controls are shown in blue, and that had stronger functional connectivity in the autism population are shown in red. Five main groups of voxels are evident, in the middle temporal gyrus (MTG), ventromedial prefrontal cortex (ORBsupmed), precuneus (PCUN) and paracentral lobule (PCL), the post- and pre-central cortex (PoCG and PreCG), and a medial region of the thalamus (THA). SFGmed - superior frontal gyrus, medial part.

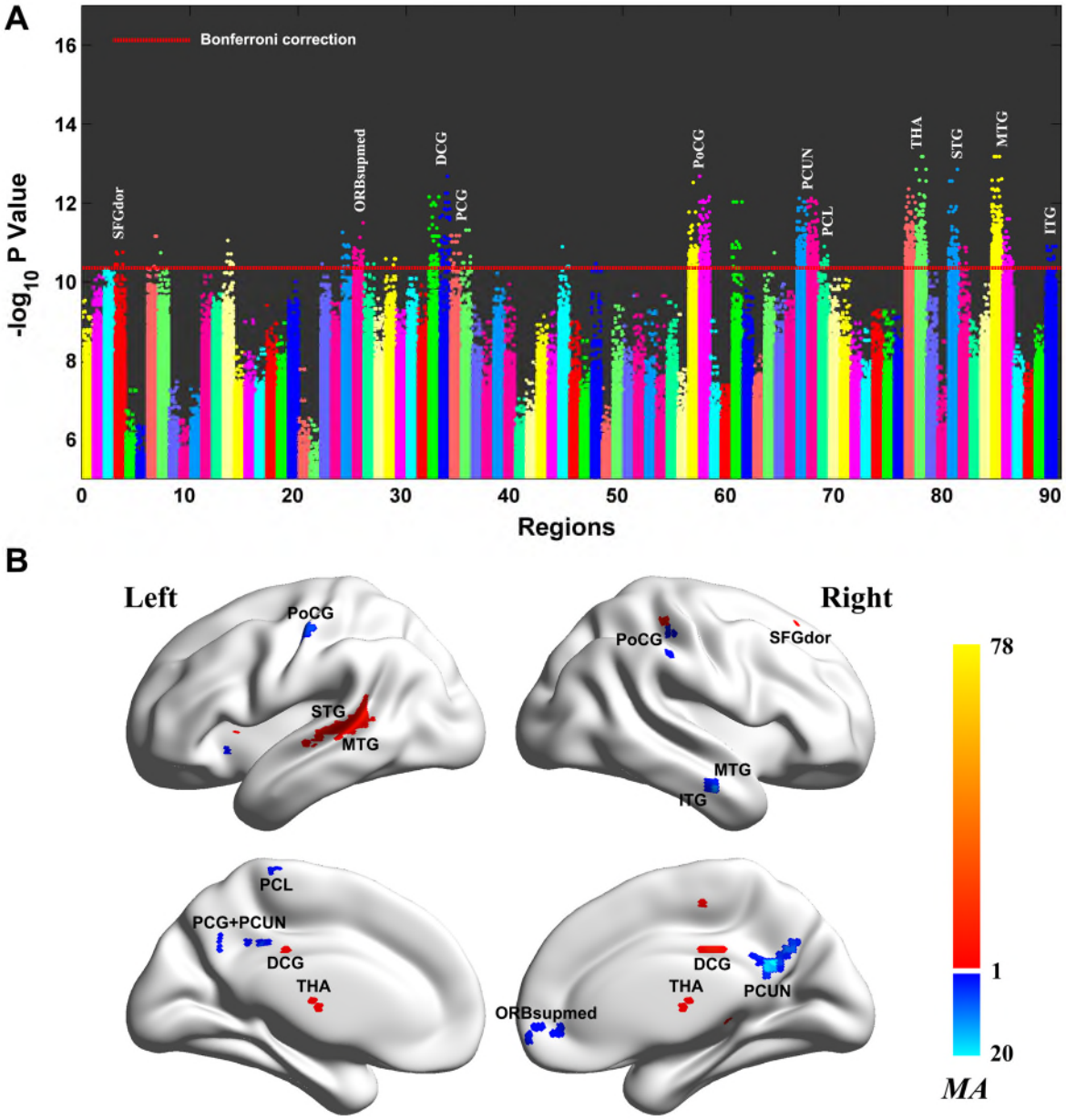

Figure S3. The locations of all voxels in the brain that have significantly different functional connectivities between the autistic and the control population for both datasets (FDR correction, 0.05, *MA* >40, cluster size >30 voxels for the first half and the second half dataset). We highlighted regions that exhibit abnormalities in three different cases: whole dataset, the first half and the second half.

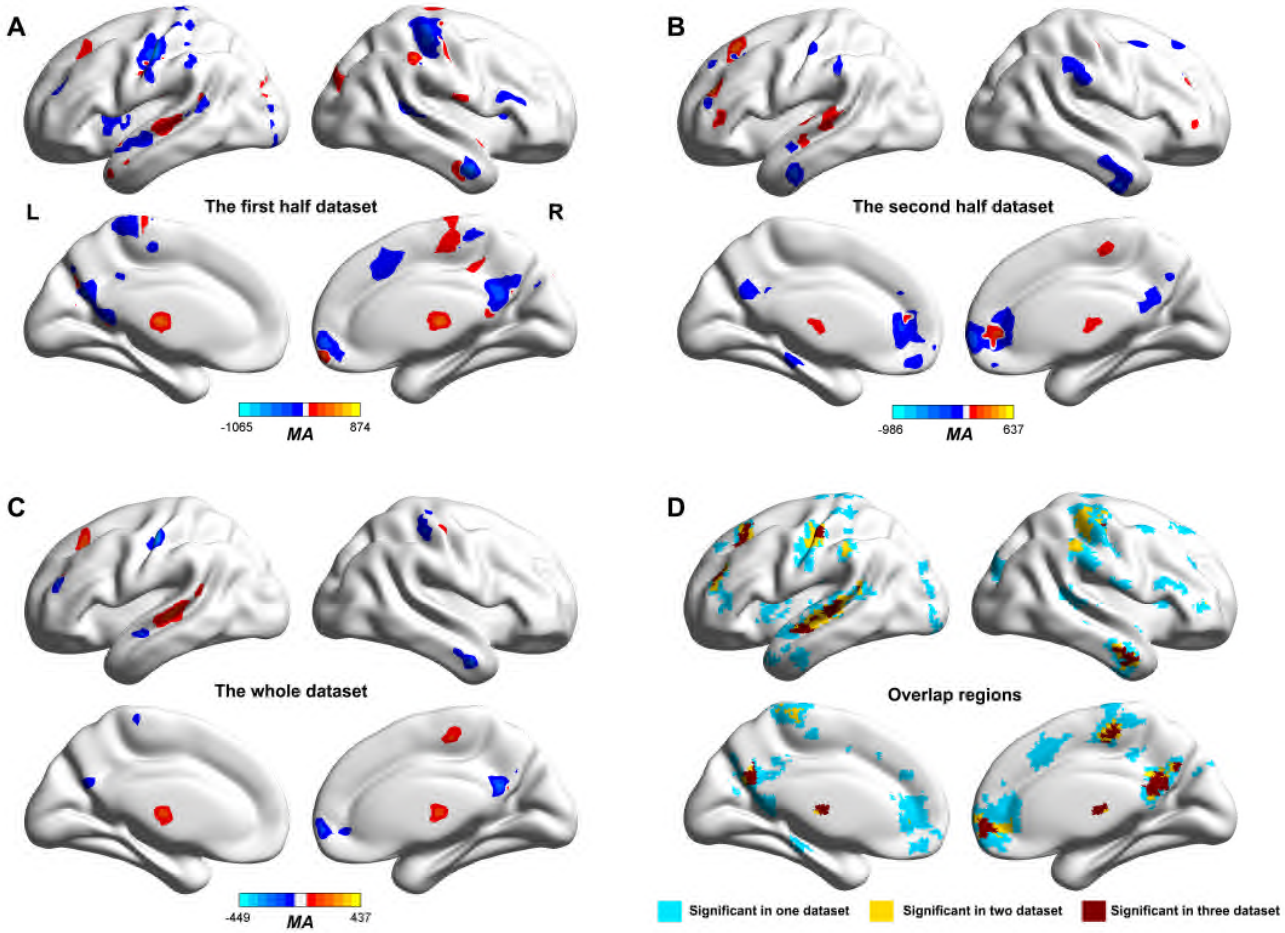

Figure S4. The robustness of ROI-wise analysis. A) The pattern of altered functional connectivity of the first half dataset. The functional connectivity matrix calculated from the BOLD signals in ROIs identified by the first half dataset. B) The pattern of altered functional connectivity of the second half dataset based on the ROIs identified by the first half dataset. C) The correlation of statistics (ROI-wise two-sample t test) between the two datasets. Although the ROIs were defined by the first half dataset, the functional connectivity among those ROIs was also significantly different between the autistic and control populations in the second half dataset in a very similar manner. D, E, F) A similar result to that above. When we used the second half dataset to find the significant ROIs, the first dataset also show similar changed patterns.

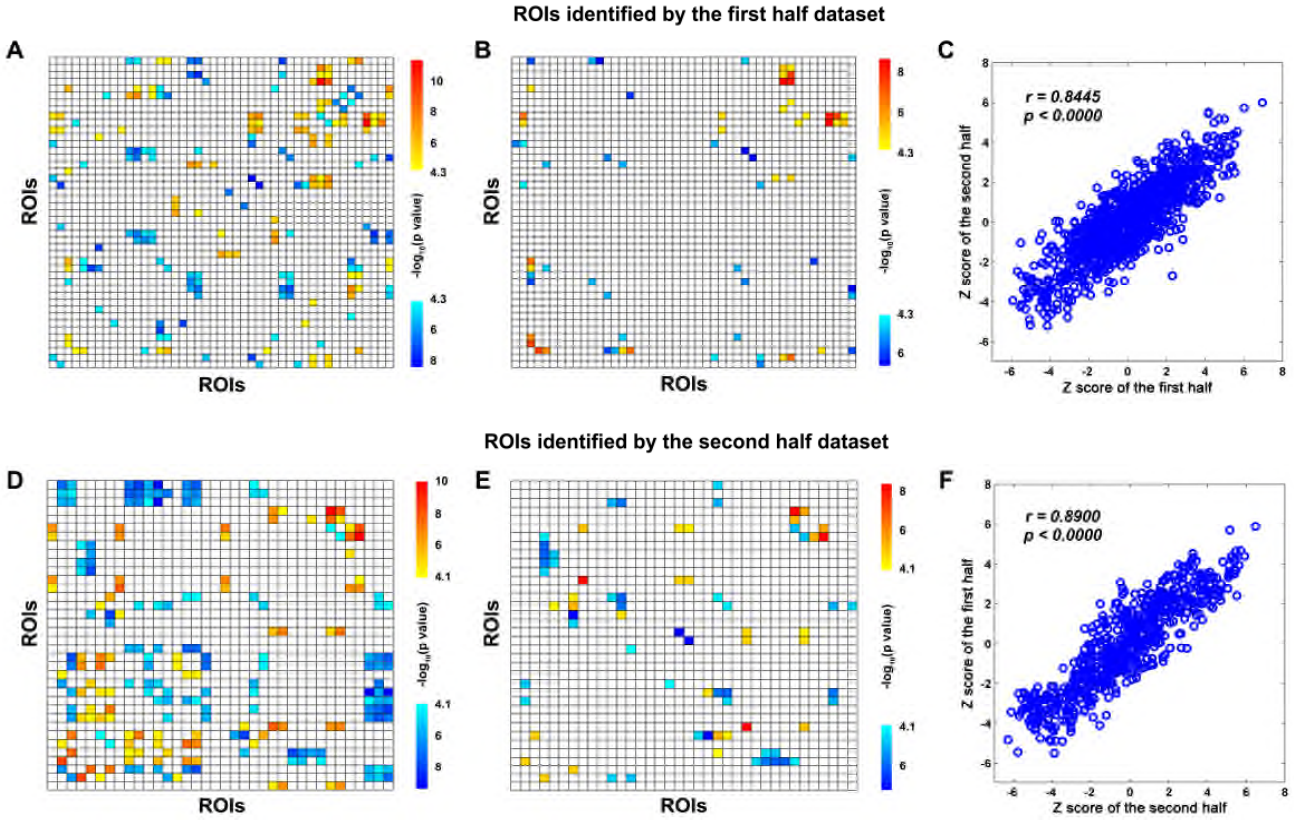

Figure S5. The robustness of classification. A) The first dataset was used to identify the significant ROIs and train the SVM classifier, then the second dataset was used to test classification accuracy of the trained model. B) The second dataset was used to identify the significant ROIs and train the SVM classifier, then the first dataset was used to test classification accuracy of the trained model.

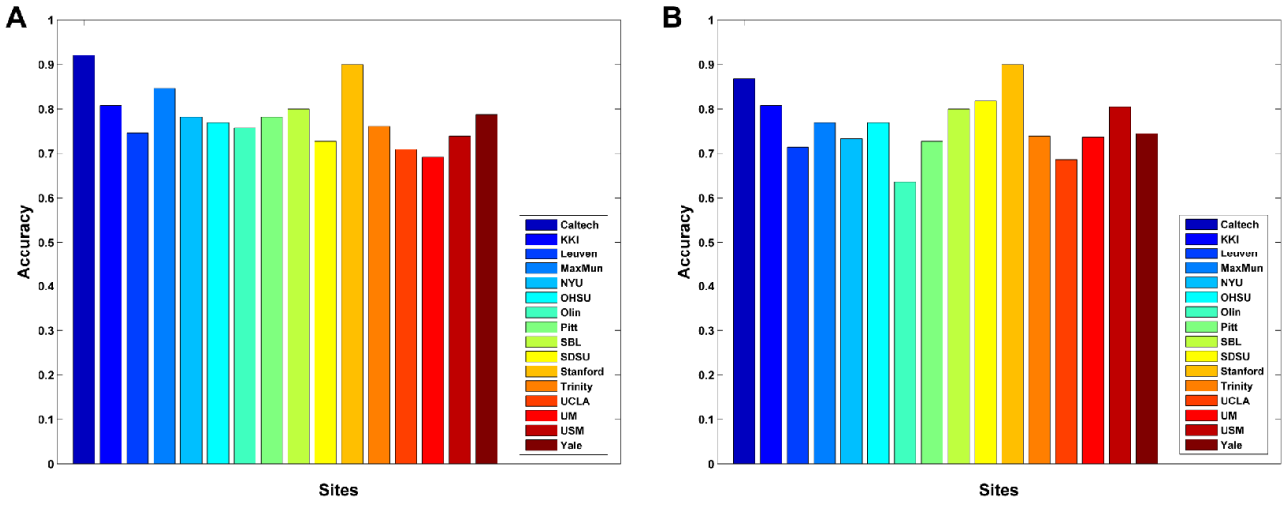

Figure S6. Comparison between the results with (A) and without (B) the global signal.

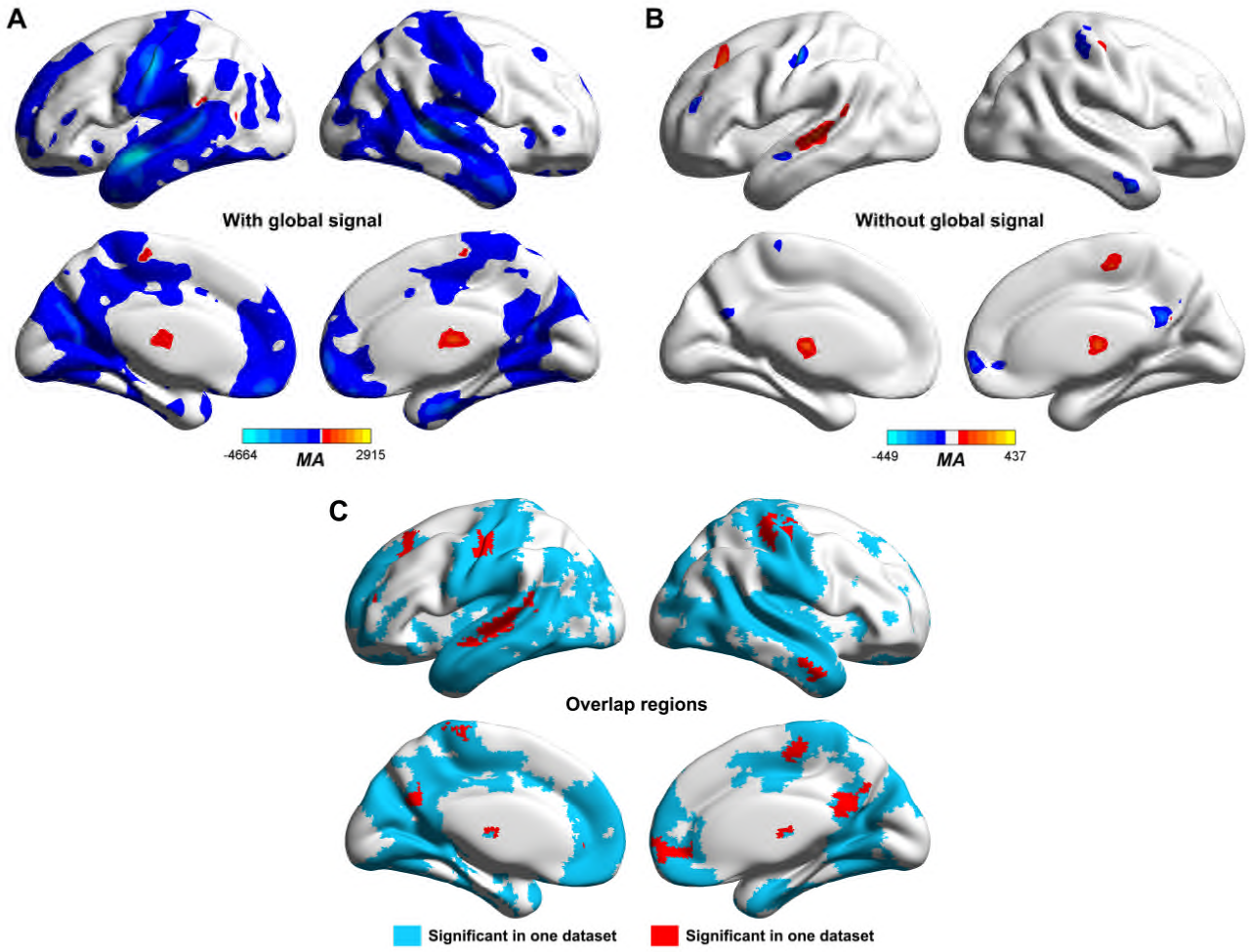

Figure S7. Forest plots showing a meta-analysis of the association of the significant functional connectivities (top 15 links) with autism. We can see that the altered patterns of functional connections were consistent across the datasets from the 16 different imaging centers.

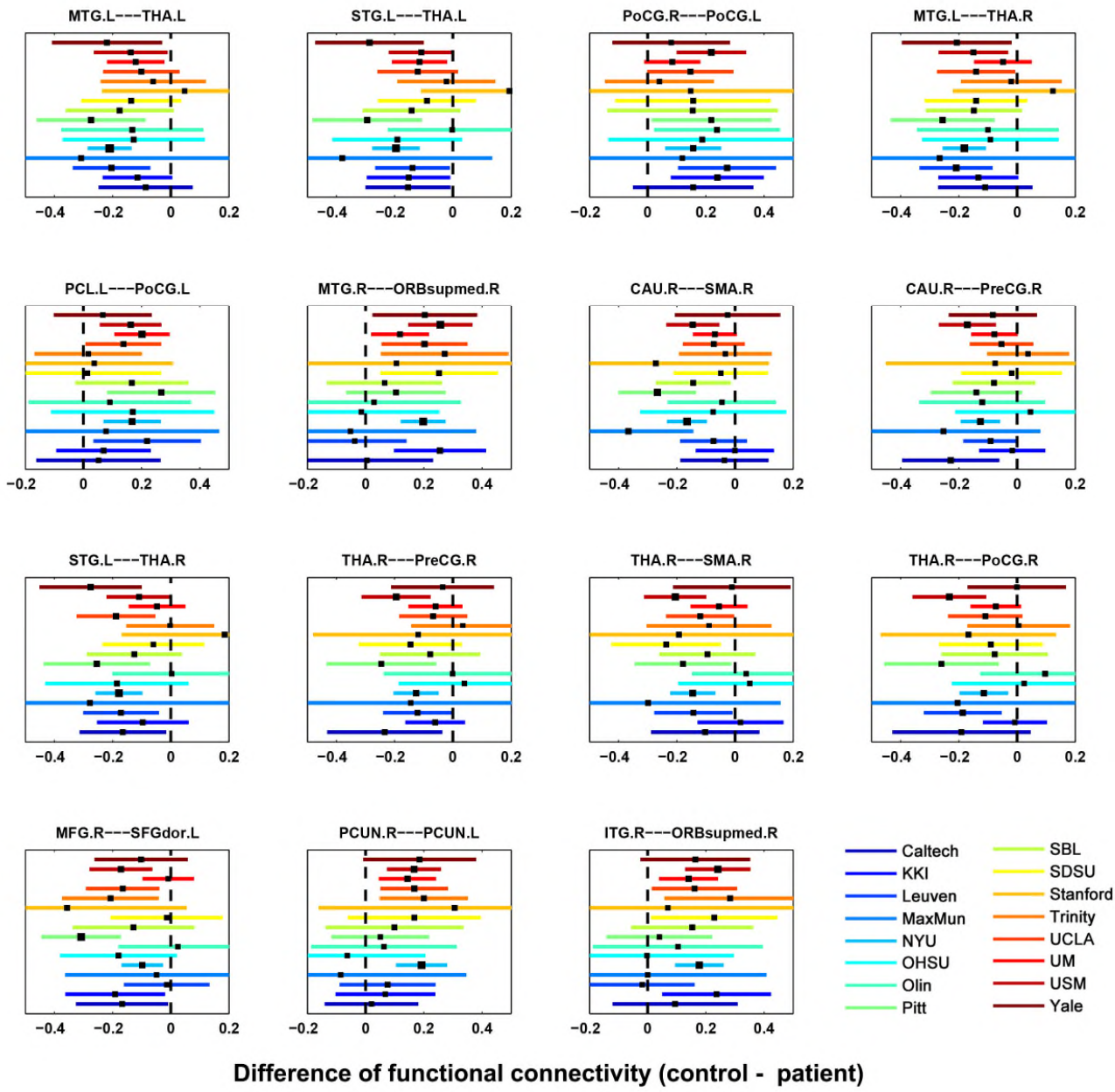

Figure S8. The pair-wise voxel-level functional connectivity that was different between the autistic group and the control group. Each connecting line is a link between two voxels that was different in the autistic and control group. The colors are chosen to be different for links between the different AAL regions. The abbreviations for each brain region are in Table S2.