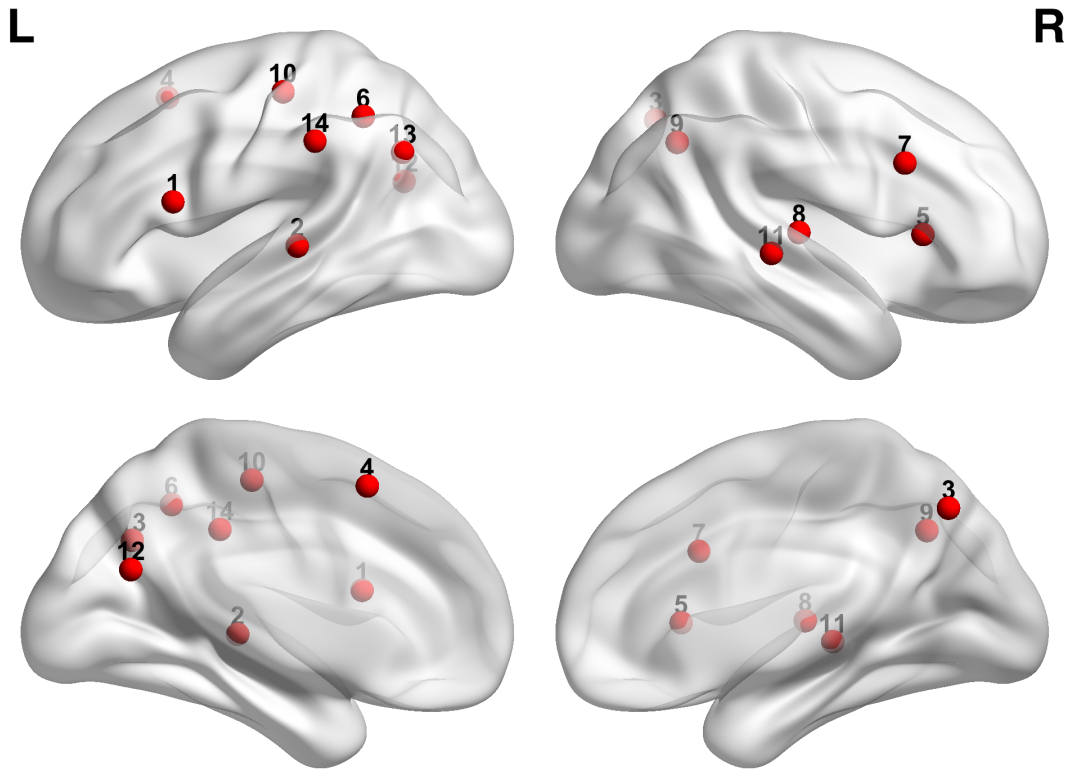# The language network in autism:

Atypical functional connectivity with default mode and visual regions

Gao Y, Linke A, Jao Keehn RJ, Punyamurthula S, Jahedi A, Gates K, Fishman I, & Müller R-A.

Supplemental Materials

Supplementary Figure 1. Regions of interest

Regions of interest extracted from statistical maps from ALE study of language comprehension (Rodd et al., 2015). 1. Left inferior frontal gyrus; 2. Left superior temporal sulcus; 3. Bilateral dorsal precuneus; 4. Bilateral supplementary motor area; 5. Right insula; 6. Left inferior parietal lobule; 7. Right inferior frontal sulcus; 8. Right Heschl's gyrus; 9. Right inferior parietal lobule; 10. Left pericentral region; 11. Right superior temporal sulcus; 12. Left precuneus/posterior cingulate cortex; 13. Left angular gyrus; 14. Left supramarginal gyrus

Supplementary Figure 2. GIMME models of PCC mediated iFC between Broca's area and visual cortex
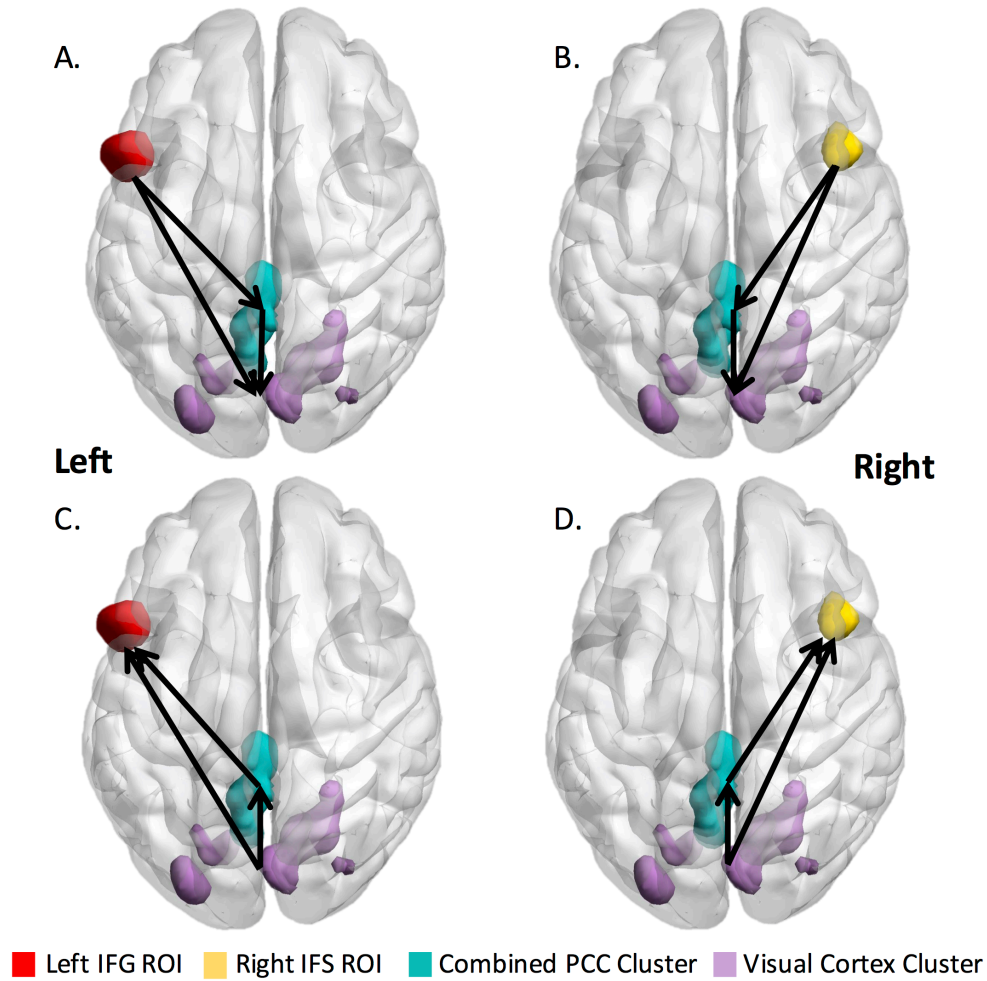
GIMME models that show posterior cingulate cortex (PCC) mediation of iFC between inferior frontal ROIs and the between-group results clusters in visual cortex from PCC ROI. Left inferior frontal gyrus (IFG) ROI is shown in red, right inferior frontal sulcus (IFS) ROI in yellow, combined PCC/Precuneus ROI and group-effects cluster from bilateral inferior frontal ROIs in blue, and visual cortex group-effects clusters in purple. Of 54 ASD subjects, 24 showed significant mediation effects from the PCC to connectivity between bilateral frontal language areas and visual cortex. **(A)** 4 participants showed significant mediation of iFC from left IFG to visual cortex by PCC. **(B)** 7 subjects showed significant PCC mediation of iFC from right

IFS to visual cortex. **(C)** 2 subjects showed significant PCC mediation of iFC from visual cortex to left IFG.

(D) 11 subjects had significant PCC mediation of connectivity from visual cortex to right IFS.

Supplementary Figure 3. Between group differences in language network iFC across preprocessing pipelines
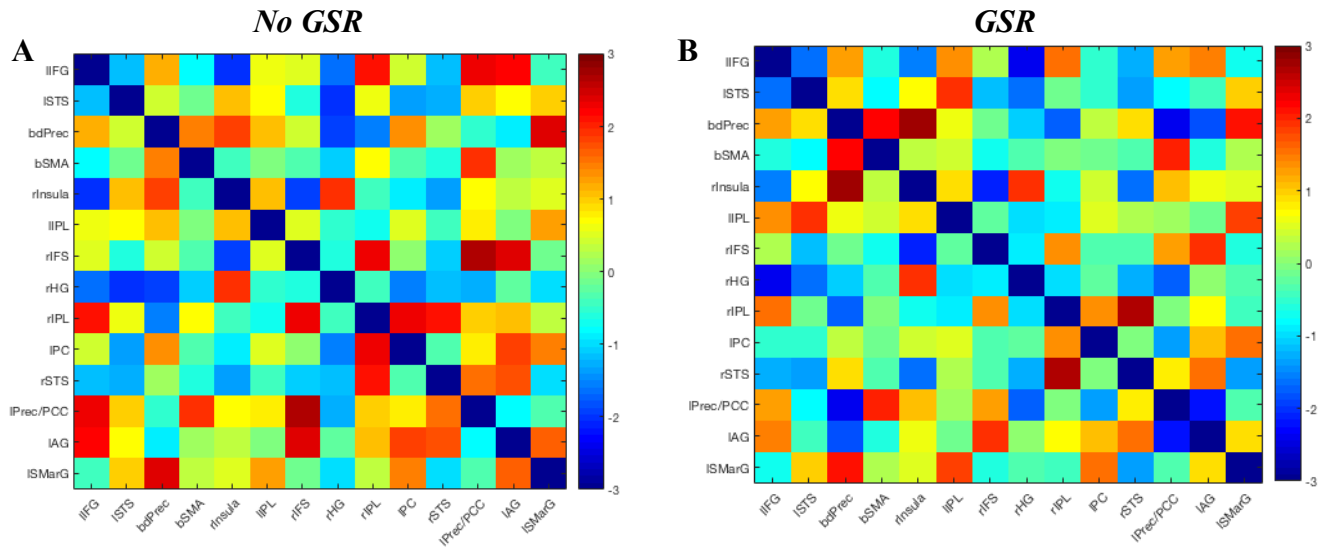
Between group differences for within language network iFC analysis illustrated with T-values. Separate preprocessing pipelines include **(A)** Original pipeline without global signal regression (GSR); **(B)** Pipeline with GSR. lIFG: left inferior frontal gyrus; lSTS: left superior temporal sulcus; bdPrec: bilateral dorsal precuneus; bSMA: bilateral supplementary motor area; rInsula: right insula; lIPL: left inferior parietal lobule; rIFS: right inferior frontal sulcus; rHG: right Heschl's gyrus; rIPL: right inferior parietal lobule; lPC: left pericentral region; rSTS: right superior temporal sulcus; lPrec/PCC: left precuneus/posterior cingulate cortex; lAG: left angular gyrus; lSMarG: left supramarginal gyrus.

Supplementary Table 1. **Significant between-group clusters from whole-brain iFC analysis**

Seed	Anatomical location	Cluster-Wise α	Cohen's d	Voxels	CM x	CM y	CM z
lIFG	Bilateral posterior cingulate cortex	< 0.03	0.84	35	-4	-51	35
rIFS	Bilateral posterior cingulate cortex	< 0.01	0.68	68	0	-38	32
	Bilateral posterior cingulate cortex	< 0.03	0.89	33	-3	-55	14
lPrec/PCC	Right lingual gyrus	< 0.01	0.82	280	15	-71	0
	Left middle occipital gyrus	< 0.01	0.83	73	-27	-84	24
	Left lingual gyrus	< 0.01	0.68	54	-18	-70	-10
	Right middle occipital gyrus	< 0.04	0.65	29	32	-78	27

Between group differences for whole-brain iFC analysis for the following ROIs: left inferior frontal gyrus (lIFG), right inferior frontal sulcus (rIFS), left precuneus/posterior cingulate cortex (lPrec/PCC). All resulting clusters exhibited increased connectivity with ROI in the ASD group relative to the TD group. Results were cluster-corrected for multiple comparisons using AFNI's 3dttest++ -ClustSim permutation tests with voxel-level p-threshold of 0.001; individual cluster-wise α are listed separately. All coordinates reflect center of mass (CM) of resulting cluster.

Supplementary Table 2. Subgroup information

	PCC Mediation Group (n = 24)		No Mediation Group (n =28)		
Gender	7 female		1 female		
Handedness	2 left		5 left		
	Mean (SD)	Range	Mean (SD)	Range	T, p-value
Age in years	13.4 (2.4)	9.2-18.0	14.0 (2.8)	9.2-17.8	-0.81, *p*=0.42
Head Motion					
Pre-censoring RMSD	0.070 (0.034)	0.021-0.148	0.065 (0.030)	0.019-0.140	0.58, *p*=0.56
Denoised RMSD	0.003 (0.002)	0.001-0.007	0.003 (0.002)	0.001-0.008	-0.68, *p*=0.50
TP Post-Censoring	177 (5.1)	158-189	178 (3.1)	169-180	-0.62, *p*=0.54
WASI					
Verbal IQ	103 (18.9)	70-147	101 (15.7)	73-131	0.35, *p*=0.73
Nonverbal IQ	106 (20.6)	53-140	106 (14.0)	70-136	0.12, *p*=0.90
Full-scale IQ	105 (20.2)	66-141	104 (12.8)	79-126	0.16, *p*=0.88
CELF-4*					
Core Language	96 (20.6)	56-120	102 (14.9)	60-120	-1.13, *p*=0.27
Receptive	96 (17.4)	64-131	101 (15.2)	60-119	-0.87, *p*=0.39
Expressive	93 (19.7)	55-120	99 (15.0)	63-118	-1.04, *p*=0.30
ADOS-2					
Social Affect	9.6 (4.2)	5-20	10.9 (3.4)	5-16	-1.16, *p*=0.25
Repetitive Behavior	2.8 (1.7)	0-5	3.6 (1.9)	1-8	-1.43, *p*=0.16
Total	12.3 (4.9)	7-24	14.5 (4.2)	6-21	-1.55, *p*=0.13
Severity	7.0 (2.0)	4-10	7.9 (1.9)	3-10	-1.42, *p*=0.16
ADI-R					
Social Interaction	18.3 (5.1)	7-28	18.5 (4.8)	11-28	-0.11, *p*=0.91
Communication	14.3 (5.9)	2-24	12.4 (4.2)	4-22	1.56, *p*=0.13
Repetitive Behavior	6.9 (2.4)	2-12	5.5 (2.0)	1-9	2.16, *p*=0.04

* CELF-4 scores were only available for 17 participants in the PCC Mediation Group and 24

participants in the No Mediation Group.

Supplementary Table 3. Correlations between language network iFC and ASD symptom severity

ROI Pairs	ADI Social			ADI Communication			ADOS Social Communication			ADOS Total		
	r	*p*-value	*q*-value	r	*p*-value	*q*-value	r	*p*-value	*q*-value	r	*p*-value	*q*-value
lIFG - lPrec/PCC	-0.150	0.305	0.611	-0.123	0.400	0.615	-0.104	0.477	0.668	-0.026	0.858	0.924
lIFG - lAG	-0.119	0.417	0.615	-0.018	0.902	0.936	*-0.317*	*0.026*	*0.247*	-0.264	0.064	0.415
bdPrec - lSMarG	-0.045	0.759	0.885	0.143	0.326	0.611	-0.257	0.074	0.415	-0.242	0.090	0.420
rIFS - rIPL	-0.217	0.134	0.537	-0.157	0.281	0.611	-0.063	0.668	0.813	-0.120	0.406	0.615
rIFS - lPrec/PCC	-0.196	0.177	0.611	-0.157	0.281	0.611	-0.091	0.535	0.681	-0.141	0.327	0.611
rIFS - lAG	-0.180	0.215	0.611	-0.119	0.414	0.615	-0.098	0.503	0.671	-0.173	0.229	0.611
rIPL - lPC	**-0.507**	**0.000**	**0.006**	*-0.370*	*0.009*	*0.124*	-0.003	0.986	0.986	0.032	0.824	0.923

The relationship between language ROI pairs and ASD symptom severity as measured by the ADOS and ADI-R subscale scores. The results were corrected for effects of age and in-scanner head motion. The significance of each Pearson correlations is shown in uncorrected *p*-values and FDR-adjusted *q*-values. Results that survived FDR correction (*q*<0.05) are bolded, and results that became non-significant after FDR correction (*q*>0.05) are italicized. lIFG: left inferior frontal gyrus; lPC: left pericentral region; lPrec/PCC: left precuneus/posterior cingulate cortex; lAG: left angular gyrus; lSMarG: left supramarginal gyrus; bdPrec: bilateral dorsal precuneus; rIFS: right inferior frontal sulcus; rIPL: right inferior parietal lobule.

Supplementary Table 4. Correlations between language network iFC and language scores

	ROI Pairs	CELF-4*					
		Core Language		Receptive Language		Expressive Language	
		r	*p*-value	r	*p*-value	r	*p*-value
ASD Group	lIFG - lPrec/PCC	-0.025	0.880	-0.245	0.133	-0.002	0.993
	lIFG - lAG	-0.068	0.682	-0.190	0.247	-0.031	0.852
	bdPrec - lSMarG	-0.068	0.682	0.058	0.727	-0.069	0.675
	rIFS - rIPL	-0.135	0.414	0.066	0.689	-0.146	0.374
	rIFS - lPrec/PCC	0.093	0.573	0.086	0.603	0.087	0.599
	rIFS - lAG	-0.184	0.261	-0.010	0.950	-0.171	0.299
	rIPL - lPC	0.163	0.321	0.169	0.303	0.112	0.498
TD Group	lIFG - lPrec/PCC	0.015	0.932	0.376	0.024	-0.015	0.932
	lIFG - lAG	-0.002	0.990	0.227	0.183	0.013	0.940
	bdPrec - lSMarG	-0.040	0.815	-0.131	0.448	-0.105	0.541
	rIFS - rIPL	0.097	0.575	0.068	0.692	0.086	0.616
	rIFS - lPrec/PCC	0.163	0.343	0.127	0.461	0.171	0.319
	rIFS - lAG	0.108	0.530	0.164	0.339	0.104	0.548
	rIPL - lPC	-0.081	0.638	-0.106	0.539	-0.107	0.536

The relationship between language ROI pairs and functional language abilities as measured by CELF-4 subscale scores. The results were corrected for effects of age and in-scanner head motion. Results were not corrected for multiple correction. * CELF-4 scores were only available for 41 ASD and 38 TD participants. lIFG: left inferior frontal gyrus; lPC: left pericentral region; lPrec/PCC: left precuneus/posterior cingulate cortex; lAG: left angular gyrus; lSMarG: left supramarginal gyrus; bdPrec: bilateral dorsal precuneus; rIFS: right inferior frontal sulcus; rIPL: right inferior parietal lobule.

Supplementary Table 5. Correlations between language network iFC results and language measures

	iFC Regions	CELF-4*								
		Core Language			Receptive Language			Expressive Language		
		r	*p*-value	*q*-value	r	*p*-value	*q*-value	r	*p*-value	*q*-value
PCC Mediation ASD Group	lIFG - PCC	-0.284	0.306	0.550	-0.247	0.374	0.594	-0.259	0.352	0.593
	rIFS - PCC	-0.355	0.194	0.389	-0.370	0.174	0.362	-0.337	0.219	0.422
	lPrec/PCC - rLG	*-0.641*	*0.010*	*0.067*	**-0.740**	**0.002**	**0.022**	*-0.647*	*0.009*	*0.067*
	lPrec/PCC - lMOG	-0.374	0.169	0.362	-0.547	0.035	0.129	-0.393	0.147	0.330
	lPrec/PCC - lLG	*-0.597*	*0.019*	*0.092*	*-0.661*	*0.007*	*0.067*	*-0.615*	*0.015*	*0.088*
	lPrec/PCC - rMOG	-0.525	0.044	0.149	-0.660	0.352	0.593	-0.546	0.035	0.129
No Mediation ASD Group	lIFG - PCC	0.071	0.754	0.955	-0.061	0.789	0.955	0.099	0.660	0.955
	rIFS - PCC	0.085	0.706	0.955	0.016	0.942	0.972	0.112	0.619	0.929
	lPrec/PCC - rLG	-0.048	0.831	0.955	0.093	0.680	0.955	-0.025	0.913	0.967
	lPrec/PCC - lMOG	0.027	0.904	0.967	0.013	0.954	0.972	0.048	0.832	0.955
	lPrec/PCC - lLG	0.031	0.890	0.967	0.201	0.369	0.594	0.041	0.858	0.965
	lPrec/PCC - rMOG	0.007	0.974	0.974	-0.060	0.789	0.955	0.076	0.738	0.955
TD Group	lIFG - PCC	-0.054	0.753	0.955	-0.129	0.452	0.697	-0.043	0.804	0.955
	rIFS - PCC	-0.351	0.036	0.129	**-0.550**	**0.001**	**0.009**	-0.309	0.067	0.212
	lPrec/PCC - rLG	-0.303	0.072	0.212	-0.260	0.126	0.296	-0.267	0.115	0.282
	lPrec/PCC - lMOG	**-0.557**	**0.000**	**0.009**	-0.300	0.075	0.212	**-0.593**	**0.000**	**0.008**
	lPrec/PCC - lLG	*-0.392*	*0.018*	*0.092*	*-0.383*	*0.021*	*0.095*	*-0.437*	*0.008*	*0.067*
	lPrec/PCC - rMOG	-0.272	0.109	0.279	-0.179	0.295	0.549	-0.297	0.079	0.212

Behavioral correlations between language scores and iFC results are shown for each of the three groups: ASD participants that show PCC-mediated iFC between frontal language region and visual cortex, ASD participants that do show a mediation effect, and TD participants. The results were corrected for effects of age and in-scanner head motion. The significance of each Pearson correlations is shown in uncorrected *p*-values and FDR-adjusted *q*-values. Results that survived FDR correction with *q*<0.05 are bolded. Results that are marginally significant after FDR correction (*q*<0.10) are italicized.

Supplementary Table 6. Between group differences in language network iFC across preprocessing pipelines

Pipeline	ROI Pairs	Between Group Comparisons		
		t-value	*p*-value	*q*-value
Without GSR	lIFG-lPrec/PCC	2.330	0.022	0.263
	lIFG-lAG	2.247	0.027	0.263
	bdPrec-lSMarG	2.407	0.018	0.263
	rIFS-rIPL	2.278	0.025	0.263
	rIFS-lPrec/PCC	2.660	0.009	0.263
	rIFS-lAG	2.429	0.017	0.263
	rIPL-lPC	2.320	0.022	0.263
With GSR	lIFG-rHG	-2.372	0.020	0.306
	bdPrec-bSMA	2.204	0.030	0.306
	bdPrec-rInsula	2.762	0.007	0.306
	bdPrec-lPrec/PCC	-2.374	0.020	0.306
	bdPrec-lSMarG	2.154	0.034	0.306
	rIPL-rSTS	2.663	0.009	0.306
	lPrec/PCC-lAG	-2.173	0.032	0.306

Between group differences for within language network iFC analysis. Separate preprocessing pipelines with and without global signal regression (GSR). lIFG: left inferior frontal gyrus; lPC: left pericentral region; lPrec/PCC: left precuneus/posterior cingulate cortex; lAG: left angular gyrus; lSMarG: left supramarginal gyrus; bdPrec: bilateral dorsal precuneus; rIFS: right inferior frontal sulcus; rIPL: right inferior parietal lobule.

Supplementary Table 7. Significant between-group clusters from whole-brain iFC analysis across preprocessing pipelines

Seed	Pipeline	Significant clusters Anatomical location	Directionality	Cluster-Wise α	Voxels	CM x	CM y	CM z
lIFG	**Without GSR**	**Bilateral posterior cingulate cortex**	**ASD > TD**	**< 0.03**	**35**	**-4**	**-51**	**35**
	With GSR	[Bilateral posterior cingulate cortex]	ASD > TD	> 0.10	58	-1	-51	37
rIFS	**Without GSR**	**Bilateral posterior cingulate cortex**	**ASD > TD**	**< 0.01**	**68**	**0**	**-38**	**32**
		Bilateral posterior cingulate cortex	**ASD > TD**	**< 0.03**	**33**	**-3**	**-55**	**14**
	With GSR	[Right posterior cingulate cortex]	ASD > TD	> 0.10	37	0	-40	32
lPrec/ PCC	**Without GSR**	**Right lingual gyrus**	**ASD > TD**	**< 0.01**	**280**	**15**	**-71**	**0**
		Left middle occipital gyrus	**ASD > TD**	**< 0.01**	**73**	**-27**	**-84**	**24**
		Left lingual gyrus	**ASD > TD**	**< 0.01**	**54**	**-18**	**-70**	**-10**
		Right middle occipital gyrus	**ASD > TD**	**< 0.04**	**29**	**32**	**-78**	**27**
	With GSR	**Bilateral posterior cingulate cortex**	**TD > ASD**	**< 0.01**	**67**	**3**	**-51**	**30**
		Bilateral anterior cingulate cortex	**TD > ASD**	**< 0.01**	**46**	**5**	**55**	**0**
		[Right middle occipital gyrus]	ASD > TD	> 0.01	52	32	-80	26

Between group differences for whole-brain iFC analyses across two preprocessing pipelines with and without global signal regression (GSR). lIFG: left inferior frontal gyrus; lPrec/PCC: left precuneus/posterior cingulate cortex; rIFS: right inferior frontal sulcus. Directionality of between groups differences in connectivity with seeds show mostly ASD > TD clusters. All results were cluster-corrected for multiple comparisons using AFNI's 3dttest++ -ClustSim permutation tests with bolded results surviving a voxel-level p-threshold of 0.001 and non-bolded results surviving a voxel-level p-threshold of 0.01; individual cluster-wise α are listed separately. Locations in square brackets indicate clusters with an uncorrected $p< 0.01$ that did not survive cluster correction. Coordinates reflect center of mass (CM) of resulting cluster in MNI space.