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The intrinsic functional organization of the brain is altered in autism

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In higher functioning individuals with autism, a striking disparity exists between impaired social and emotional abilities and relatively preserved sustained attention and goal-directed cognitive abilities. As these two functional domains appear to map onto two distinct large-scale brain networks, the Task-Negative Network and the Task-Positive Network, respectively, we examined their intrinsically defined functional organization in individuals with autism. Using resting functional connectivity MRI (fcMRI), we found that, in autism, there was altered functional organization of the network involved in social and emotional processing, but no group difference in the functional organization of the network involved in sustained attention and goal-directed cognition. We suggest that these findings might serve to relate the seemingly disparate strengths and weaknesses of the autistic behavioral, perceptual, and cognitive phenotype into a tractable neurofunctional framework. These results also highlight the usefulness of resting fcMRI for studying the brain in neuropsychiatric and neurodevelopmental disorders.

Keywords: Functional connectivity MRI (fcMRI); Rest; Default mode; Social; Emotion; Attention

A cardinal characteristic of autism that has puzzled parents, clinicians, and researchers alike for more than half a century is the imbalance between socioemotional incapacity and disinterest on the one hand and often spared or even heightened cognitive capacity and interest in non-social objects on the other. In the first clinical description of a child with autism, Kanner wrote, "when taken into a room, he completely disregarded the people and instantly went for objects, preferably those that could be spun" (Kanner, 1943). While this fascinating behavioral profile has been well documented anecdotally, clinically, and experimentally, we know little of the neural circuits responsible. Recent findings regarding the functional organization of the typical brain may help to inform the neural basis of this striking characteristic of autism.

In typically developing subjects, socioemotional and cognitive-attentional processes appear to map onto distinct large-scale brain networks. One of these networks, termed the Task-Positive Network (TPN) or dorsal attention network, includes pre-supplementary motor area, intraparietal sulcus, and superior precentral sulcus and activates during performance of externally directed cognitively demanding tasks (e.g., math calculations, sustained attention, working memory, Stroop task) (Cabeza and Nyberg, 2000; Corbetta and Shulman, 2002). The other network, termed the Task-Negative Network (TNN; also known as the default mode (Raichle et al., 2001)), includes medial prefrontal cortex, posterior cingulate/precuneus, and angular gyrus and activates during performance of social, emotional, and introspective (i.e., self-reflective) tasks, including theory of mind (Fletcher et al., 1995; Gallagher et al., 2000; Vogeley et al., 2001), social perception (Iacoboni et al., 2004), emotional processing (Maddock et al., 2003; Cato et al., 2004), experience of joint attention (Williams et al., 2005), episodic memory (Andreasen et al., 1995), viewing personally familiar faces (Gobbini et al., 2004; Pierce et al., 2004), and self and other-person reflection (Gusnard et al., 2001; Johnson et al., 2002; Kelley et al., 2002; Kjaer et al., 2002; Fossati et al., 2003; Lou et al., 2004; Macrae et al., 2004; D'Argembeau et al., 2005; Mitchell et al., 2005a,b; Ochsner et al., 2005; Moran et al., 2006) (for a meta-analysis of self studies, see Northoff et al., 2006). The TNN is so-named because it deactivates (i.e., displays negative activation) during performance of externally directed cognitively demanding tasks not of a social, emotional, or introspective nature. This deactivation of the TNN coincident with activation of the TPN further underscores the functional separation of these two networks.

Since autism is largely characterized by deficits in TNN-type processes (i.e., social, emotional, self-relevant) but relatively less impaired, entirely spared, or even heightened in TPN-type processes (Garretson et al., 1990; Allen and Courchesne, 2001) (i.e., cognitively demanding tasks not of a social, emotional, or self-related nature), we hypothesized that this might be due to dysfunction of the TNN but normal functioning of the TPN.

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To test this hypothesis, we used a methodological approach known as resting functional connectivity MRI (fcMRI). This approach relies on the fact that, even at rest, the brain exhibits coherent patterns of low frequency spontaneous fluctuations of the BOLD (blood oxygenation level-dependent) signal within functionally related regions (Buckner and Vincent, 2007). This phenomenon, termed "functional connectivity," was first documented for the somatomotor system (Biswal et al., 1995) but has since been observed in sensory networks (e.g., visual, auditory (Cordes et al., 2000)) as well as higher order cognitive networks (e.g., attention networks (Fox et al., 2006b), recollection memory networks (Vincent et al., 2006)), including the TPN (Fox et al., 2005, 2006b; Fransson, 2005) and TNN (Greicius et al., 2003; Greicius and Menon, 2004; Fox et al., 2005; Fransson, 2005, 2006; Damoiseaux et al., 2006; De Luca et al., 2006). Furthermore, these spontaneous oscillations persist during sleep (Fukunaga et al., 2006; Fransson et al., 2007; Redcay et al., 2007) and under light anesthesia (Kiviniemi et al., 2000) and have recently been documented to occur in anesthetized monkeys (Vincent et al., 2007). Importantly, because many, if not all, brain networks exhibit these low frequency spontaneous fluctuations, one can examine the functional organization of 2 or more intrinsically organized networks simultaneously—that is, within a single subject and single dataset.

Methods

We scanned a total of 15 male Autism Spectrum Disorder (ASD) and 13 male control subjects, whose only instructions were to stare at the plus on the screen, while remaining still, relaxed, and awake. One ASD subject was removed due to problems with data acquisition, and 2 ASD subjects and 1 control subject were removed from the analysis due to excessive movement during scanning, resulting in a final sample size of 12 ASD subjects (6 autism, 6 Asperger's syndrome) and 12 control subjects. Among those included in the final analyses, 5 of the ASD subjects, and none of the control subjects, participated in an earlier study on TNN functionality in autism (Kennedy et al., 2006). These subjects were selected independent of the earlier results. All participants or their legal guardian gave informed written consent and received monetary compensation for participation in the experiment. The protocol was approved by the Institutional Review Board of UCSD and Children's Hospital at San Diego. All ASD participants were diagnosed by a clinical psychologist using the Autism Diagnostic Interview-Revised (ADI-R) (Lord et al., 1994) and the Autism Diagnostic Observation Schedule (ADOS) (Lord et al., 2000), and all participants were administered the Wechsler Adult Intelligence Scale (WAIS) or WAIS-R (Revised). The mean ages of the autism participants (26.5 years) and the control participants (27.5 years) were not significantly different [$t(22)=.201$, $p>.80$]. Subject groups did not differ significantly in verbal, performance, or full-scale IQ [verbal: $t(21)=1.486$, $p=.152$; performance: $t(21)=1.793$, $p=.087$; full scale: $t(21)=1.973$, $p=.062$]. See Table 1 for detailed clinical information.

All images were acquired on a 3 Tesla GE Signa EXCITE scanner. Axial slices covering the entire brain were collected with a gradient-recalled echo-planar imaging (EPI) pulse sequence with the following parameters: TR (repetition time)= 2000 ms; TE (echo time)=30 ms; flip angle=90°; field of view (FOV)=220 mm; matrix=64×64 (3.44 mm^2 in-plane resolution); slice thickness= 4 mm; # of axial slices=32; # of volumes=215; total scan time=7 min, 10 s). T1-weighted anatomical images were collected during each scan session for co-registration with the functional images (FOV=256 mm; matrix=256×256 (1 mm^2 in-plane resolution); slice thickness=1 mm; # of axial slices= 124).

FcMRI analyses were carried out using the Analyses of Functional NeuroImages (AFNI) statistical software package (version 2.56; http://afni.nimh.nih.gov/afni) (Cox, 1996). In order to facilitate cross-study comparisons, we analyzed the data in a manner very similar to Fox et al. (2005). Briefly, the preprocessing steps were as follows: the first 5 TRs of each scan were removed to allow for T1 equilibration effects, field maps (which were acquired during the scan session) were used to correct for field inhomogeneities, functional volumes were corrected for motion using an automated alignment program (3dvolreg) that co-registers each volume in the timeseries to a middle volume of the scan using an iterative process, images were corrected for slice acquisition timing and spatially smoothed with a Gaussian filter (full-width half-maximum=6 mm), then temporally bandpass filtered ($0.01<f<0.1$), and converted to percent signal change. Due to the high sensitivity of fcMRI to subject motion, periods of excessive motion were entirely removed from the analysis. These periods were identified using an objective calculation based on the amount of rotational (roll, pitch, yaw) and translational (x, y, z) movement by the participant across time. This was calculated by first determining the square root of the sum of squares of the derivatives of the rotational and translational movements (calculated by 3dvolreg) for each TR. If the sum of these rotational and translational values exceeded a threshold of 0.30, that TR, along with the TR before and after, was removed from analysis. Subjects with more than 20% of the run removed were excluded entirely from the study (2 ASD, 1 control excluded). For the remaining participants, an average of 4.35% and 4.86% of the data from the control and autism groups, respectively, was removed from analysis. This difference was not significant ($p=.84$). Next, multiple linear regression analysis was used to model several types of noise in the functional data, which were then removed as regressors of no interest: the linear trend, the global signal (average intensity of every voxel across the entire brain calculated for each of the 215 time points), 6 motion parameters (3 rotational and 3 translational directions) and their 6 temporal derivatives. Finally, for group analysis, images were spatially normalized to Talairach space (Talairach and Tournoux, 1988) using AFNI's 12 sub-volume piecewise linear transformation based on manually defined landmarks.

The locations of the seed regions were identical to those used in Fox et al. (2005) to facilitate cross-study comparisons. The three task-positive seed regions (defined from a previous independent study of visual attention (Corbetta et al., 2002)) were the left intraparietal sulcus (−25, −57, 46), the right superior precentral sulcus (25, −13, 50), and the left middle temporal region (−45, −69, −2), while the three task-negative seed regions (defined from a previous meta-analysis of task-related deactivations (Shulman et al., 1997)) were the medial prefrontal cortex (MPFC; −1, 47, −4), posterior cingulate/precuneus (−5, −49, 40), and the left angular gyrus (−45, −67, 36). At each of these seed locations, the BOLD signal timecourse was extracted and used to calculate a correlation coefficient between that seed and all other voxels in the brain. Importantly, the resulting correlation maps (created from individual seed voxels at the coordinates listed above) were nearly identical to maps that were generated with a 12-mm diameter seed region

Table 1
Clinical information for autism and control participants

Subject	Diagnosis	Age	Sex	Handedness	IQ			ADI-R			ADOS		
					Verbal	Performance	Full scale	Social (cutoff=10)	Communication (cutoff=8)	Stereotypy (cutoff=3)	Social (cutoff=4)	Communication (cutoff=2)	Stereotypy
A1	Autism	15.7	M	Right	73	66	67	10	21	11	10	3	3
A2	Asperger's	16.2	M	Right	120	124	125	13	17	3	11	6	1
A3	Asperger's	17.4	M	Right	99	93	96	23	18	9	9	5	1
A4	Autism	17.7	M	Right	101	118	109	26	19	6	7	5	1
A5	Asperger's	18.3	M	Right	108	107	109	14	8	6	5	3	1
A6	Autism	18.8	M	Right	55	109	80	28	20	4	9	5	0
A7	Asperger's	22.9	M	Right	97	105	101	13	12	3	6	3	0
A8	Asperger's	24.0	M	Right	116	109	114	7	11	10	8	2	2
A9	Asperger's	27.7	M	Right	111	99	106	21	20	7	11	6	0
A10	Autism	41.3	M	Left	98	114	104	21	22	10	11	5	2
A11	Autism	46.4	M	Right	86	115	100	22	19	6	7	5	1
A12	Autism	52.0	M	Right	102	105	104	26	17	6	9	4	1
Mean (SD)		26.5 (12.8)			97.2 (18.4)	105.3 (14.9)	101.6 (15.2)						
C1	Control	15.9	M	Left	95	99	97						
C2	Control	16.2	M	Right	N/A	N/A	N/A						
C3	Control	17.8	M	Right	107	119	114						
C4	Control	19.0	M	Right	106	118	113						
C5	Control	20.6	M	Left	99	106	103						
C6	Control	22.9	M	Right	107	93	100						
C7	Control	25.3	M	Right	109	116	114						
C8	Control	29.4	M	Right	109	125	118						
C9	Control	32.3	M	Right	108	128	119						
C10	Control	40.7	M	Right	108	132	121						
C11	Control	44.6	M	Right	106	109	108						
C12	Control	45.4	M	Right	108	128	119						
Mean (SD)		27.5 (10.9)			105.6 (4.5)	115.7 (12.7)	111.5 (8.3)						

centered at those same coordinates (i.e., the procedure used by Fox et al., 2005).

Six one-sample *t*-tests for both autism and control groups were performed to find regions of significant correlation with the seed region. These correlation coefficient seed maps were then normalized using Fisher's *r*-to-*z*′ transformation and converted to *Z*-scores. For the control subjects and autism groups separately, the 3 TNN-seed maps were averaged to form a single TNN map, and the 3 TPN-seed maps were averaged to form a single TPN map. These TNN and TPN maps were set to an intensity threshold of $Z=3.88$, $p<.0001$, and a minimum cluster volume of 192 mm^3. The cluster size was calculated using an iterative Monte Carlo simulation using AFNI's AlphaSim program with a voxel-wise threshold of $p<.05$. Throughout the text, we refer to this volume threshold as "volume-corrected". The TNN and TPN maps derived for the control group were then used to extract timeseries data from individual autism and control subjects (see below). Additionally, this same procedure (e.g., 6 one-sample *t*-tests, Fisher's *r*-to-*z*′ transformation, conversion to *Z*-scores, and TNN-seed map and TPN-seed map averaging) was carried out on the data from both the autism and control subjects collapsed across group to yield a combined-group TNN and combined-group TPN map. All analyses (described below) were rerun using these combined-group TNN and TPN maps to ensure that results could not be accounted for by the potential bias of using a functional map derived from the control group alone to extract timeseries data from individual control and autism subjects. These combined-group maps were set at a threshold that yielded functional maps with approximately the same number of significant voxels as found in the control group maps (TNN, $p<.0000005$; TPN, $p<.0000001$; minimum cluster size=192 mm^3).

Next, to statistically compare the within-network functional connectivity between groups, all voxels within a particular node (i.e., cluster) were extracted and averaged together to yield a single timeseries for each TNN and TPN node for each individual. Then, using the SPSS statistical software package (Chicago, IL; version 12.0), a separate correlation coefficient was calculated between the timeseries of each node of a network (either TPN or TNN) and the timeseries averaged over the remaining nodes of that particular network. Repeated measures ANOVAs were run on the Fisher's *r*-to-*z*′ normalized correlation coefficients, with *z*′ values as the repeated measure and group (autism or control) as the between subjects factor. We report the multivariate test output of this analysis since, although a more conservative statistical test, it avoids the assumption of sphericity. Follow-up *t*-tests were run for all significant interactions and are reported without correction for multiple comparisons.

To statistically compare the between-network functional connectivity (i.e., degree of anticorrelation) between groups, the timeseries from all TPN voxels and all TNN voxels were extracted and averaged separately, which yielded the average TPN timeseries and the average TNN timeseries for each subject. Correlation coefficients between these average TPN and TNN timeseries were then calculated for each individual, normalized using Fisher's *r*-to-*z*′ transformation, and compared across groups with a two-sample *t*-test.

Results

For the control group, the TNN and TPN functional connectivity maps were very similar to that previously reported by Fox et al. (2005) and Fransson (2005). The TNN map included the dorsal and ventral MPFC, the posterior cingulate/precuneus, left and right angular gyrus, right temporal pole, and right superior temporal gyrus/sulcus ($p<.0001$, volume-corrected) (Fig. 1A, Table 2). At a more liberal threshold of $p<.001$ (volume-corrected), superior temporal gyrus/sulcus activation was seen bilaterally. The TPN map included bilateral inferior parietal lobule, bilateral superior precentral sulcus, right inferior frontal gyrus, bilateral middle occipital gyrus, bilateral middle temporal gyrus, and right fusiform gyrus ($p<.0001$, volume-corrected) (Fig. 2A, Table 2).

For the autism group, the TNN map only included the posterior cingulate/precuneus and the left angular gyrus (Fig. 1A, Table 2). At a more liberal threshold of $p<.001$ (volume-corrected), however, the TNN map also included the dorsal and ventral MPFC, right angular gyrus, and bilateral superior temporal gyrus/sulcus. The TPN map included all the regions seen in the control group (Fig. 2A, Table 2) and also included bilateral pre-supplementary motor area, left fusiform gyrus, and left putamen. Fig. 1B and Fig. 2B show regions of overlap between groups for the TNN and TPN respectively.

To directly test whether there were group differences in within-network functional connectivity of the TNN nodes ($n=6$) or the TPN nodes ($n=7$), we ran two repeated-measures ANOVAs. As hypothesized, there was a main effect of group on TNN connectivity [$F(1,22)=5.453$, $p=.029$], with reduced connectivity in the autism group, and a significant group by node interaction [$F(5,18)=6.690$, $p=.001$]. Furthermore, there was no main effect of group on TPN connectivity [$F(1,22)=3.659$, $p=.069$] nor a group by node interaction [$F(6,17)=.640$, $p=.698$]. Importantly, this pattern of results did not change when verbal IQ, performance IQ, and full-scale IQ were used as covariates in the analysis {TNN main effect: [$F(1,18)=4.890$, $p=.040$], TNN group by node interaction: [$F(5,14)=4.797$, $p=.009$]; TPN main effect: [$F(1,18)=$

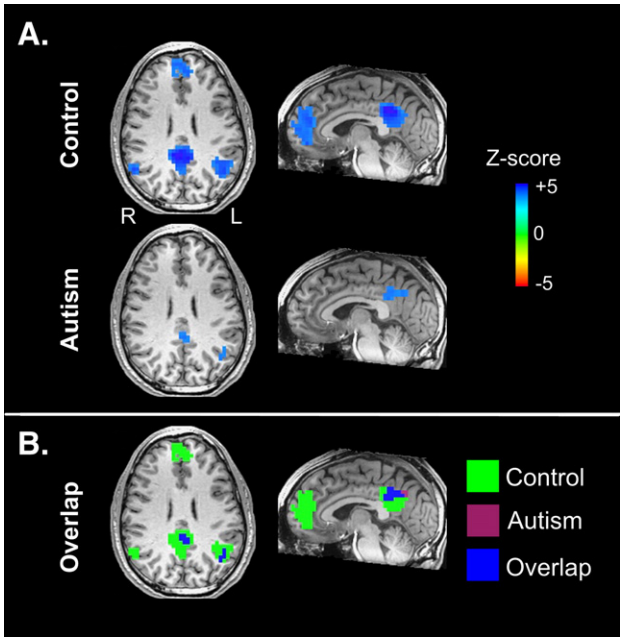

Fig. 1. Intrinsically defined functional connectivity maps of the TNN (shown at $p<.0001$, volume-corrected). (A) TNN maps for control and autism groups (Scale bar represent *Z*-score). (B) Overlap of control and autism TNN maps.

Table 2
Talairach locations of peak significance of the intrinsically defined TNN and TPN functional connectivity maps for control and autism groups

Network	Region	Control		Autism	
		(*x*, *y*, *z*)	*Z*-value	(*x*, *y*, *z*)	*Z*-value
TNN	Ventral MPFC	(2, −47, −4)	4.47		
	Dorsal MPFC	(−6, −43, 36)	4.47		
	Posterior cingulate	(−2, 45 32)	5.16	(6, 45, 36)	4.33
	Left angular gyrus	(45, 65, 32)	4.62	(38, 65, 24)	4.14
	Right angular gyrus	(−54, 61, 24)	4.68		
	Right temporal pole	(−54, 1, −16)	4.17		
	Right superior temporal gyrus/sulcus	(−58, 13, −4)	4.27		
	Left superior frontal gyrus			(10, −27,44)	4.03
TPN	Left inferior parietal lobule	(26, 45, 56)	4.97	(22, 57, 48)	4.61
	Right inferior parietal lobule	(−26, 53, 56)	4.74	(−30, 37, 44)	4.64
	Left superior precentral sulcus	(18, 5, 48)	4.28	(22, 9, 56)	4.41
	Right superior precentral sulcus	(−22, 5, 52)	4.32	(−34, 13, 44)	4.39
	Bilateral pre-supplementary motor area			(10, 1, 52)	4.43
	Right inferior frontal gyrus	(−50, −7, 17)	4.12	(−46, −3, 24)	4.18
	Left middle gyrus	(26, 69, 20)	4.42	(26, 69, 24)	3.97
	Right middle occipital gyrus	(−38, 69, 16)	4.10		
	Left middle temporal gyrus	(46, 69, 0)	4.57	(46, 69, 0)	4.58
	Right middle temporal gyrus	(−46, 57, 0)	4.95	(−38, 65, 8)	4.17
	Right fusiform gyrus	(−42, 45, −12)	4.49		

1.752, $p=.202$], TPN group by node interaction: [$F(6,13)=.512$. $p=.798$]}. Follow-up *t*-tests revealed that reduced TNN connectivity was regionally specific to the medial prefrontal cortex (MPFC) [$t(22)=3.593$, $p=.002$] and left angular gyrus [$t(22)=2.732$, $p=.012$; all other regions, $p>.10$] (see Fig. 3). Finally, there was a negative correlation (i.e., anticorrelation) between the TNN and TPN in the control group [$z'=-.281$; $t(11)=2.379$, $p=.037$], consistent with previous findings by Fox et al. (2005) and Fransson (2005). However, network anticorrelation was not significantly different from zero in the autism group [$z'=-.140$; $t(11)=1.132$, $p=.282$]. The difference between groups was not significant [$t(22)=.822$, $p=.420$].

To further ensure that IQ did not affect our primary results, we reran the analyses excluding the two ASD subjects that had the lowest full-scale IQ scores (subjects A1 and A6; see Table 1). After removing these subjects, there was no significant group difference in full-scale, verbal, or performance IQ (all $p>.15$). We again obtained a similar pattern of results to those described above for both the TNN {main effect of group: [$F(1,20)=5.625$, $p=.028$], group by node interaction: $F(5,16)=6.295$, $p=.002$]} and the TPN {main effect of group: [$F(1,20)=2.167$, $p=.157$], group by node interaction: [$F(5,16)=.763$, $p=.610$]}, demonstrating reduced and altered connectivity of the TNN but normal connectivity of the TPN. Follow-up analyses of the TNN again revealed significant

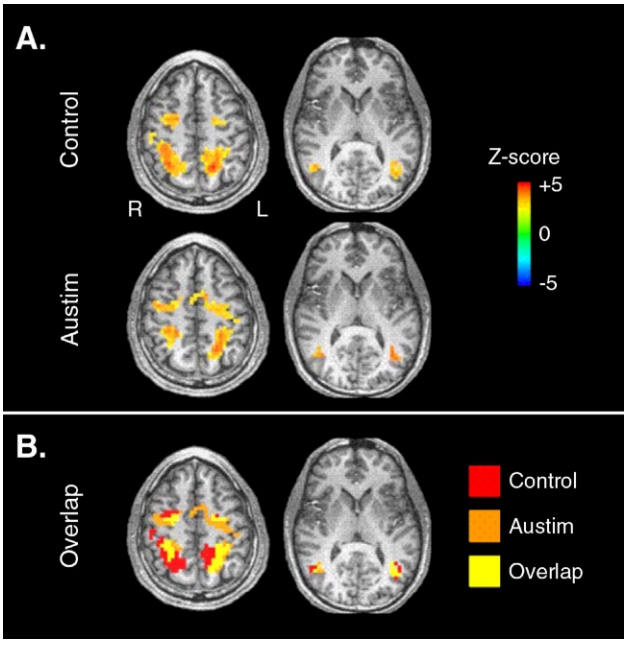

Fig. 2. Intrinsically defined functional connectivity maps of the TPN (shown at $p<.0001$, volume-corrected). (A) TPN maps for control and autism groups (Scale bar represents *Z*-score). (B) Overlap of control and autism TPN maps.

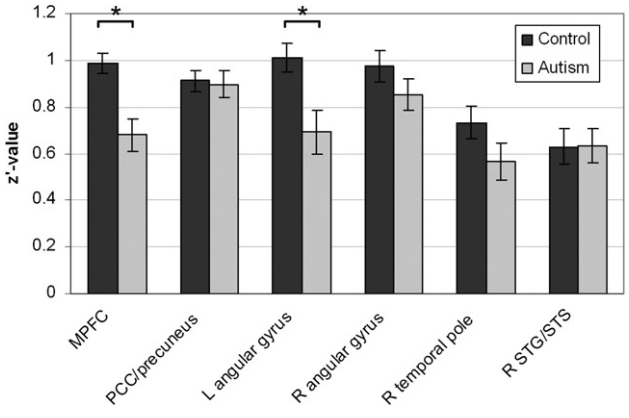

Fig. 3. Localized abnormalities of the TNN in autism. The reduced functional connectivity within the TNN in the autism group was specific to 2 regions: the MPFC and left angular gyrus (*, $p<.05$). There was no significant difference in any of the other regions ($p>.05$). Brackets show standard error of the mean (PCC, posterior cingulate; STG, superior temporal gyrus; STS, superior temporal sulcus).

regional abnormality of the MPFC [$t(20)=3.245$, $p=.004$] and the left angular gyrus [$t(20)=2.780$, $p=.012$], but also included the right temporal pole [$t(20)=2.272$, $p=.034$]. The TPN–TNN anticorrelation was again non-significantly different from zero in the autism group [$z'=-.126$; $t(9)=.875$, $p=.404$], but the group difference in network anticorrelation remained non-significant [$t(20)=.841$, $p=.410$]. These results suggest that the inclusion of the two lowest full-scale IQ ASD subjects did not account for the above described group functional connectivity differences of the TNN and provide further evidence that the present results are not accounted for by IQ.

Four of the twelve ASD subjects were taking psychoactive medication at the time of scanning. Reanalysis of the data excluding these 4 subjects slightly altered the results described above. We still found group differences in TNN connectivity {main effect of group: [$F(1,18)=6.924$, $p=.017$], group by region interaction: [$F(5,14)=5.928$, $p=.004$]}. Additionally, follow-up analyses still revealed reduced TNN functional connectivity of the MPFC [$t(18)=4.499$, $p=.0003$)] and left angular gyrus [$t(18)=2.387$, $p=.028$], but also including the right angular gyrus [$t(18)=2.211$, $p=.04$]. There was also a main effect of group on TPN activity [$F(1,18)=6.479$, $p=.020$], but again no group by region interaction [$F(6,13)=.354$, $p=.895$]. Thus, while medication status did not affect TNN connectivity, it is possible that it might modulate TPN connectivity. However, this influence is not robust as a follow-up non-parametric Wilcoxon rank-sum test revealed that the average TPN connectivity was not significantly different between medicated and non-medicated subjects ($p>.35$). Furthermore, this same analysis using the combined-group TPN map failed to replicate this finding (described below), though all other results were identical.

Finally, all of the above analyses were repeated using data extracted from the combined-group TNN and TPN maps (derived from all subjects collapsed across group) to ensure that using a control map to extract the timeseries data did not account for the above described findings. The combined-group TNN and combined-group TPN maps were largely similar to the control TNN and TPN maps used in the above analyses, with the only exception being that the right temporal pole and right superior temporal gyrus/sulcus nodes were not part of the combined-group TNN map. We again found a main effect of group on TNN connectivity [$F(1,22)=9.765$, $p=.005$] and a group by node interaction [$F(3,20)=15.94$, $p=.00002$], which was not effected by including verbal, performance, and full-scale IQ as covariates {main effect: [$F(1,18)=5.753$, $p=.028$], group by node interaction: [$F(3,16)=12.526$, $p=.00018$]}. Furthermore, these results remained significant after excluding the 2 lowest IQ subjects {main effect: [$F(1,20)=8.088$, $p=.010$], group by node interaction: [$F(3,18)=14.61$, $p=.000045$]} and removing the 4 medicated autism subjects {main effect: [$F(1,18)=10.301$, $p=.005$], group by node interaction: [$F(3,16)=14.74$, $p=.000072$]}. As before, follow-up t-tests revealed that the reduced functional connectivity of the TNN in the autism group was regionally specific to the MPFC [$t(22)=3.043$, $p=.006$] and left angular gyrus [$t(22)=5.055$, $p=.00005$]. These results were also obtained after removing the two lowest IQ subjects {MPFC: [$t(20)=2.535$, $p=.020$], left angular gyrus: [$t(20)=4.728$, $p=.0001$]} and after removing the 4 medicated autism subjects {MPFC: [$t(18)=3.921$, $p=.001$], left angular gyrus: [$t(18)=4.620$, $p=.0002$]}. This latter analysis excluding the 4 medicated subjects additionally identified reduced connectivity in the autism group for the right angular gyrus [$t(18)=2.195$, $p=.042$], identical to the above findings.

Using the combined-group TPN map, there was again no main effect of group on TPN connectivity nor a group by node interaction {main effect: [$F(1,22)=.210$, $p=.651$], group by node interaction: [$F(6,17)=2.346$, $p=.078$]}, even after using verbal, performance, and full-scale IQ as covariates {main effect: [$F(1,18)=.004$, $p=.950$], group by node interaction: [$F(6,13)=1.676$, $p=.204$}, removing the 2 lowest IQ subjects {main effect: [$F(1,20)=.007$, $p=.934$], group by node interaction: [$F(6,15)=1.910$, $p=.145$]}, and removing the 4 medicated subjects {main effect: [$F(1,18)=1.378$, $p=.256$], group by node interaction: [$F(6,13)=1.901$, $p=.156$]}.

Finally, using the combined-group maps, we again found a negative correlation between the TPN and TNN in the control group [$t(11)=2.276$, $p=.044$] but not the autism group [$t(11)=1.359$, $p=.201$], although this group difference was not significant [$t(22)=.566$, $p=.577$]. This pattern was also found after removing the 2 lowest IQ subjects {control: [$t(11)=2.276$, $p=.044$], autism: [$t(9)=1.020$, $p=.334$)], group difference: [$t(20)=.650$, $p=.523$]} and after removing the 4 medicated subjects {control: [$t(11)=2.276$, $p=.044$], autism: [$t(7)=1.263$, $p=.247$], group difference: [$t(18)=.524$, $p=.607$]}.

Altogether, these additional analyses using the combined-group maps demonstrate that the results cannot be explained by a bias in the selection of regions from which the data were extracted.

Discussion

We found evidence for disrupted intrinsic functional organization of the TNN in autistic patients but, at the same time and within the same patients, intact organization of the TPN. These findings make sense in light of the disrupted and intact abilities of higher functioning individuals with autism and the putative functional roles of these two networks. The altered organization of the TNN, which normally supports social, emotional, and introspective processes, may underlie these deficits in autism. The entirely normal organization of the TPN, which supports goal-directed cognitive and attentional processes, may underlie the relative sparing and even enhanced abilities in these general domains in individuals with autism. We also failed to observe the normal anticorrelated functional relationship between the TPN and TNN in the autism group, although this relationship was present in the control group. Together, these findings suggest that there is an *unevenness* and *imbalance* in the functioning of these two large-scale brain networks. We suggest that this imbalance may either bias or reflect a bias of the autistic individual away from social and emotional processing, but toward a particular non-social and non-emotional cognitive processing style.

It is interesting to speculate on the relationship between the current findings and Baron-Cohen's theory that suggests that the autism cognitive phenotype reflects one extreme end of a continuum of brain types—one that is heavily biased toward "systemizing" rather than "empathizing" (Baron-Cohen, 2002). While systemizers are driven "to analyze the variables in a system, to derive the underlying rules that govern the behaviour of a system," empathizers are driven "to identify another person's emotions and thoughts," thus enabling one to predict another person's behavior (Baron-Cohen, 2002; Baron-Cohen et al., 2003). Interestingly, the TNN seems to be involved in "empathizing"-type functions (e.g., social and emotional interactions, mentalizing), while the TPN seems to underlie functions necessary for "systemizing" (e.g., goal-directed cognitive operations, sustained atten-

tion). Although speculative, one could imagine how early dysfunction in the neural circuitry underlying "empathizing" might bias the autistic cognitive style away from such functions, but toward developing functions which rely on the intact neural circuitry supporting "systemizing" functions. Furthermore, the relationship between cognitive style and network functionality is likely to be reciprocally reinforcing, such that a cognitive bias might, in turn, reinforce the disparity between the functioning of these two networks. The resting fcMRI approach might be particularly well-suited to study both the early emergence and subsequent refinement of network functionality as this approach is minimally demanding for participants (and can even be performed during natural sleep (Fukunaga et al., 2006; Fransson et al., 2007; Redcay et al., 2007) and under anesthesia (Kiviniemi et al., 2000)), thus allowing for the inclusion of participants of a wide range in age and cognitive ability (for examples, see Redcay et al., 2007 and Fransson et al., 2007).

Interestingly, even the seemingly intact social and emotional abilities of high-functioning autistic individuals (such as the majority of participants in this study) are thought to rely heavily on cognitive decisions and memorized scripts rather than the intuitive and fluid responses that characterize normal social and emotional interactions. This has been exemplified in research on theory of mind, or mentalizing, abilities in high-functioning individuals with autism. Research suggests that they can solve certain mentalizing problems by using an "explicit" or cognitive theory of mind, based on logical reasoning (reviewed in Frith, 2004). However, they fail at tests that rely on "intuitive" mentalizing, such as automatically attributing mental states to moving geometric objects (Klin, 2000; Castelli et al., 2002). We suggest that this pattern of mentalizing ability and inability in autism may be accounted for by the spared TPN and defective TNN functional organization. Social and emotional cues, normally disambiguated by the TNN, must be evaluated by the unsuited but functionally intact TPN. A cognitive TPN-supported approach to mentalizing (and other social and emotional tasks) may be sufficient in certain circumstances, but such an approach would be more likely to fail during naturalistic tests or real-life situations.

Our results demonstrate that the connectivity abnormalities in autism are specific, both within and across functional networks, rather than reflecting global non-specific reductions in connectivity. We found that the overall reduction of functional connectivity within the TNN was due to specific abnormalities of the MPFC and left angular gyrus alone, while other regions of this same network demonstrated the typical pattern of coherent spontaneous BOLD signal fluctuations (Fig. 3). Furthermore, we found that the functional connectivity of the TPN was entirely normal, thus demonstrating selective, rather than pervasive, network abnormality of the TNN. As previously suggested (Kennedy et al., 2006), this specificity may be related to the uniquely high metabolic activity of the TNN, which has been hypothesized to confer particular susceptibility to damage and dysfunction (Raichle et al., 2001; Buckner et al., 2005). Importantly, although the functional connectivity abnormalities were regionally specific, there are likely widespread and far-reaching functional consequences of these localized disruptions. Regions of the TNN have rich cortical and subcortical anatomical connectivity (Ongur and Price, 2000; Parvizi et al., 2006), such that an early insult affecting the anatomical or functional development of even one region of the TNN would very likely affect the subsequent functionality of the network as a whole.

Abnormalities of the TNN have also recently been found in a separate autism functional connectivity study (Cherkassky et al., 2006), although their method of reporting the results makes direct comparison with the present findings difficult. They reported that within the TNN, 94% of the pairwise connectivities computed were reduced in the autism group relative to the control group. While this finding might suggest pervasive and widespread reductions of functional connectivity, this is not necessarily the case. In fact, if we analyze the present data in the identical pairwise fashion, we find that 86.7% (13/15) of the pairwise TNN connectivities are lower in the autism group. Importantly, abnormalities of only 2 of the 6 regions account for reductions in 9 of the 15 pairwise comparisons (60%). Assuming the results of the remaining 6 of 15 comparisons are due to chance, we would expect a total of 80% (12/15) of the pairwise connectivities to be reduced in the autism group — a result very close to the observed 86.7% (13/15). Furthermore, this method of data representation is highly susceptible to outlier subjects as reduced or increased values in just several subjects within a group could affect the group mean and bias all pairwise comparisons in a particular direction. Thus, as apparently high percentages can result either from localized connectivity abnormalities, outlier subjects, and non-specific widespread reductions in connectivity, care should be taken in resolving these alternative possibilities.

Importantly, there are at least two independent factors that could have contributed to the findings of reduced functional connectivity of the TNN in autism. First, as previously described, there are spontaneous low frequency BOLD signal fluctuations, which seem to be a pervasive feature of many, if not all, brain networks (Vincent et al., 2007). Because these fluctuations persist across different levels of consciousness (e.g., sleep, sedation), they are not simply a reflection of spontaneously occurring thoughts and cognitive processes (Biswal et al., 1995; Kiviniemi et al., 2000; Fox et al., 2006a; Fukunaga et al., 2006; Vincent et al., 2007). Furthermore, Fox et al. (2006a) cleverly demonstrated that spontaneous fluctuations are a unique component of the fMRI BOLD signal and are separable from task-evoked or cognition-evoked BOLD responses. Thus, these spontaneously occurring intrinsic oscillations could be disrupted in autism, suggestive of an underlying functional disorganization of this network and accounting for the present findings. Additionally, however, it should also be recognized that, during the time these spontaneous fluctuations are occurring, ongoing spontaneous mental activity is also occurring. Such mental activity can drive correlated activity increases or decreases across several brain regions, thus affecting the degree of measured functional connectivity between those regions. More specifically, as social, emotional, and introspective tasks are known to modulate activity of the TNN, group differences in the propensity to naturally default to these types of thoughts would presumably affect the measured functional connectivity between regions of the TNN. Consistent with this idea, we previously found that the uniquely high resting metabolic activity of the TNN (or default network) was reduced in autism, providing evidence that this network is doing something different at rest in individuals with autism (Kennedy et al., 2006). One particularly interesting behavioral study lends additional support for this idea (Hurlburt et al., 1994). When individuals with autism or Asperger's syndrome were asked to report on the contents of their minds at random times throughout their day, qualitative differences in the types of ongoing thoughts were found (Hurlburt et al., 1994; Frith and Happe, 1999). The design of the current experiment cannot

resolve which of these two factors – either differences in spontaneous fluctuations or differences in resting cognition – contributed to the reduced functional connectivity of the TNN in autism. However, future experiments may be able to address this issue. For instance, one could examine functional connectivity of the TNN during continuous performance of a cognitively demanding task that is known to reduce stimulus independent thought (e.g., the two-back working memory task (Fransson, 2006)) and TNN activity (McKiernan et al., 2006), thus reducing or removing the influence of differences in spontaneous mental and subsequent functional activity on TNN connectivity.

In summary, we speculate that our findings may provide a neurofunctional framework for understanding one of the most profound differences between the typically developing child and the autistic child. While the former possesses a strong interest in and capacity for social and emotional relationships, the child with autism lacks these interests, but instead often possesses an equally powerful interest in objects, rules, and regularities. The autistic individual lives in a TNN-decipherable world but might lack the proper neural machinery to disambiguate the rather complex and subtle cues of social and emotional communication. Therefore, perhaps they develop an alternative cognitive style and alternative approach to interacting with the world—focused on their cognitive and attentional strengths rather than their social and emotional weaknesses. We are hopeful that further study of the cognitive strengths and weaknesses of individuals with autism, as well as the neural underpinnings of these abilities, will have important implications for developing and measuring the effectiveness of early intervention programs.

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