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Functional and Anatomical Cortical Underconnectivity in Autism: Evidence from an fMRI Study of an Executive Function Task and Corpus Callosum Morphometry

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The brain activation of a group of high-functioning autistic participants was measured using functional magnetic resonance imaging during the performance of a Tower of London task, in comparison with a control group matched with respect to intelligent quotient, age, and gender. The 2 groups generally activated the same cortical areas to similar degrees. However, there were 3 indications of underconnectivity in the group with autism. First, the degree of synchronization (i.e., the functional connectivity or the correlation of the time series of the activation) between the frontal and parietal areas of activation was lower for the autistic than the control participants. Second, relevant parts of the corpus callosum, through which many of the bilaterally activated cortical areas communicate, were smaller in cross-sectional area in the autistic participants. Third, within the autism group but not within the control group, the size of the genu of the corpus callosum was correlated with frontal–parietal functional connectivity. These findings suggest that the neural basis of altered cognition in autism entails a lower degree of integration of information across certain cortical areas resulting from reduced intracortical connectivity. The results add support to a new theory of cortical underconnectivity in autism, which posits a deficit in integration of information at the neural and cognitive levels.

Keywords: autism, corpus callosum, executive function, fMRI, functional connectivity

Introduction

Newly emerging theories of neurological functioning in autism are highlighting interregional functional and anatomical connectivity as a likely key feature of the pathophysiology. Several recent functional neuroimaging studies provide evidence of a lower degree of coordination among activated brain areas in autism. A recent study of sentence comprehension (Just and others 2004) found that the brain activity was less synchronized across activated brain areas (i.e., there was reduced functional connectivity) in autism. Studies of social cognition (Castelli and others 2002) and working memory (Luna and others 2002) also suggest aberrant functional connectivity in the brains of individuals with autism. The cortical underconnectivity theory of autism (Just and others 2004) provides an integrating framework for the new findings and also provides useful extensions to previous theories of autism. Very briefly, underconnectivity theory proposes that autism is a cognitive and neurobiological disorder associated with underfunctioning of integrative circuitry, resulting in a deficit in integration of information at the neural and cognitive levels.

In addition to functional imaging studies, anatomical studies also present evidence for abnormal connectivity in autism. Courchesne and others (2001) found an abnormal developmental trajectory of white matter in autism, such that 2- to 3-year-old boys with autism had increased cerebral and cerebellar white matter volume. Herbert and others (2004) found localized white matter enlargement in the outer radiate compartment of the white matter in children with autism. Herbert and others suggested an ongoing postnatal process involving white matter in autism that primarily affects intrahemispheric and corticocortical connections. A diffusion tensor imaging study found reduced fractional anisotropy (indicating a lower degree of coherence of directionality) in white matter adjacent to the ventromedial prefrontal cortices, anterior cingulate gyri, temporoparietal junctions, and in the corpus callosum (Barnea-Goraly and others 2004). At a much more fine-grained level, Casanova and others (2002) found more numerous and abnormally narrow minicolumns in the frontal and temporal cortex in autism, creating an abundance of short connective fibers relative to long ones, which may indicate a deficiency in long distance (interregional) connectivity. The converging findings of functional connectivity abnormalities and white matter abnormalities in autism in several studies suggest that alterations in cortical connectivity and the communication among cortical regions may be part of the pervasive core processing deficits in autism (Herbert and others 2004).

One of the anatomical regions that has emerged as a target of autism research is the corpus callosum, which mediates the interhemispheric communication among cortical areas underpinning higher level cognitive function. Several morphometric studies report abnormalities, especially reduction in size, in various subregions of the corpus callosum in autism (e.g., Piven and others 1997; Manes and others 1999; Hardan and others 2000; Vidal and others 2003). Chung and others (2004) found lower white matter density (an index for neural connectivity) in the genu, rostrum, and splenium of the corpus callosum in individuals with autism and suggested that this reduction might result in impaired interhemispheric connectivity in frontal, temporal, and occipital regions. The interhemispheric fibers from the inferotemporal and occipital lobes (posterior areas) traverse the splenium (the posterior part of the corpus callosum), whereas fibers from the frontal lobes traverse the genu and rostrum (Pandya and Seltzer 1986). Therefore, it is possible that abnormalities in the subregions of the corpus callosum could disrupt the functional connectivity among cortical regions in the 2 hemispheres.

The particular task used for examining brain activation in the current functional magnetic resonance imaging (fMRI) study, the Tower of London (TOL) puzzle, is considered a test of executive function. Some of the strongest experimental evidence for executive dysfunction in autism so far involves the TOL, a task requiring planning and goal-management ability.

Several investigations using Tower tasks have found significant impairments in autism relative to matched controls (Ozonoff and others 1991; Hughes and others 1994; Ozonoff and McEvoy 1994; Bennetto and others 1996; Ozonoff and Jensen 1999; Minshew and others 2002). The executive processing in the TOL task has been shown in normal individuals to evoke prominent activation bilaterally in prefrontal and parietal areas (Newman and others 2003).

Brain activation during tests of executive function has not been widely investigated in autism (Hill and Frith 2003). It is not known whether executive function deficits in autism are due to impairment within prefrontal cortex itself or to some other underlying system-wide deficit such as its connectivity to other regions. If there is general reduction in the functional connectivity among the brain regions in autism, as shown in a sentence comprehension task (Just and others 2004), then one would expect reduced communication and integration among the brain regions to also undermine executive function in TOL.

Our study focused on the interdependence of functionally related brain regions during the performance of a TOL task. The theoretical rationale for this focus is that it is becoming clear that thinking is an emerging property of a large-scale network of collaborating cortical areas. Therefore, to characterize neural functioning in autism, it may be necessary to examine the cortical activation at a systems level rather than at the level of local brain regions (Just and others 2004). One way to measure the synchronization among brain regions is to compute the correlation or covariance between the activation levels in 2 activated areas over some time period. This measure generally shows systematic synchronization between areas modulated by a number of variables. The synchronization is taken as evidence of "functional connectivity" (Friston 1994; Horwitz and others 1998). The term functional connectivity has been used to describe the interdependence of functionally related brain regions. The synchrony of the blood flow fluctuations in the functionally related brain regions implies the existence of neuronal connections that facilitate coordinated activity. Functional connectivity between 2 brain regions is assessed as the correlation between pairs of measurements of cerebral blood flow positron emission tomography (PET) or blood oxygenation level (fMRI). Castelli and others (2002) used PET-based correlation of activation levels between 2 regions of interest (ROIs) across the participants in a theory of mind study and predicted that the visual areas may not be properly connected with the cognitive areas in autism. Two older functional imaging studies using coarser grain measures (e.g., Horwitz and others 1988; Zilbovicius and others 1995) implicated lower interregional brain connectivity in autism.

In fMRI studies, functional connectivity measurements are based on the correlation of the activation time series in pairs of brain areas. The time series in this study included an observation every 3 s (i.e., a time repetition [TR] of 3 s) while participants were performing the TOL task. The general assumption is that the functioning of voxels whose activation levels rise and fall together is coordinated. The functional connectivity was measured between some of the key areas involved in executive processing and then was compared between the autism and control participants. The main hypothesis was that there would be a lower level of functional connectivity among the autism participants in the frontal–parietal network.

The functional connectivity in the TOL task, which is known to engage prefrontal and parietal areas bilaterally (Newman and others 2003), might well depend on the corpus callosum as part of the biological infrastructure that permits communication among brain areas. This study measured the size of the various segments of the corpus callosum of each participant in the functional imaging study, hypothesizing that the sizes of key areas would be smaller in the autistic participants, following similar previous findings in purely morphometric studies (Egaas and others 1995; Piven and others 1997; Hardan and others 2000). Moreover, for the first time, this study tests for a correlation between the size of various corpus callosum segments and frontal–parietal functional connectivity. The secondary hypothesis was that in the participants with autism, there would be a positive correlation because the size of the corpus callosum is constraining the functional connectivity. In the control group, there should be no correlation because there is no constraint on information processing imposed by the size of their corpus callosum and their neural connectivity. That is, their neural resources and neural connectivity are assumed to always be adequate to meet these task demands.

Methods

Participants

Eighteen high-functioning individuals with autism (mean age 27.1 years, standard deviation (SD) = 11.9) and 18 healthy participants (mean age 24.5 years, SD = 9.9) were included in the study (Full-Scale and Verbal intelligent quotient [IQ] scores of 80 or above, as shown in Table 1). The diagnosis of autism was established using the Autism Diagnostic Interview-Revised (Lord and others 1994), the Autism Diagnostic Observation Schedule-General (ADOS-G, Lord and others 2000) and confirmed by expert clinical diagnosis. Nine of the participants with autism were taking psychotropic medications. Of these, 6 were taking only one medication, a serotonin reuptake inhibitor, but not on the day of the scan. All participants were required to be in good medical health. Potential autistic participants were excluded if they had evidence of an associated infectious, genetic, or metabolic disorder, such as fragile-X syndrome or tuberous sclerosis. Potential control and autistic participants were also excluded if found to have evidence of birth asphyxia, head injury, or a seizure disorder. Exclusions were based on neurologic history and examination, physical examination, and chromosomal analysis or metabolic testing if indicated. Written informed consent was obtained from participants and/or their guardians, using procedures approved by the University of Pittsburgh Medical Center Institutional Review Board.

The control participants were community volunteers recruited to match the autistic participants on age, Full-Scale IQ, gender, race, and family of origin socioeconomic status, as measured by the Hollingshead method (Hollingshead 1957). Potential control participants were screened by questionnaire, telephone, face-to-face interview, and observation during screening psychometric tests such as the Wechsler Abbreviated Scales of Intelligence (Wechsler 1999) and The Wide Range Achievement Test 3. Family history of developmental and neuropsychiatric disorders was obtained using a questionnaire specifically developed for the Collaborative Program of Excellence in Autism research program. Exclusionary criteria, evaluated through these procedures, included current or past history of psychiatric and neurologic

Table 1
Age, IQ, handedness, and gender of participants

		Autism	Control
Age (years)	Mean ± SD	27.1 ± 11.9	24.5 ± 9.9
Verbal IQ	Mean ± SD	112.2 ± 17.0	107.6 ± 10.9
Full-Scale IQ	Mean ± SD	109.3 ± 17.7	108.1 ± 13.8
Handedness	Right:left	15:3	16:2
Gender	Male:female	17:1	15:3

Note: VIQ, Verbal IQ; FSIQ, Full-Scale IQ.

disorders, birth injury, developmental delay, school problems, acquired brain injury, learning disabilities, and medical disorders with implications for the central nervous system or those requiring regular medication usage. Potential control participants were also screened to exclude those with a family history of autism, developmental cognitive disorder, learning disability, affective disorder, anxiety disorder, schizophrenia, obsessive compulsive disorder, or other neurologic or psychiatric disorder thought to have a genetic component. There were no statistically reliable differences between the autistic and control participants in age or IQ. All participants were Caucasian. Twelve of the participants with autism and 9 control participants were previously included in a study of functional connectivity in a sentence comprehension task (Just and others 2004), and one participant with autism was previously included in a study of functional connectivity in a verbal working memory task (Koshino and others 2005).

Task

In the TOL task, the subject must rearrange the positions of 3 distinctive balls in 3 suspended pool pockets, until they match a specified goal configuration. Although some of the easier problems can be solved with a straightforward perceptual strategy, the harder problems require planning several moves ahead in order to satisfy various goals and subgoals. That is, more difficult problems require more executive processing (Newman and others 2003). The standard TOL task was modified for use in the scanner, such that the participants did not move any physical ball, but indicated in a forced-choice response how many moves the optimal solution would require.

The left side of the display shows the initial state and the right side shows the goal state, as illustrated in Figure 1. On each trial, the subject is asked to work out how the balls could be rearranged in a sequence of moves such that the configuration on the right comes to be the same as the configuration on the left, in the minimum number of moves. The rules governing the movements of the balls are: only one ball can be moved at a time, a ball cannot be moved out of a pocket if another ball is on top of it, and a ball must be moved to the lowest unoccupied location in the destination pocket. In this example, the first move is to place the white ball in the rightmost pocket, then to move the spotted ball to the left pocket, and finally to move the white ball to the left pocket. Thus, the answer to this problem is "3." The participant indicates the minimum number of moves required, by pressing the appropriate button in the response panel, and the next problem is presented. The study was implemented as a "block design" with 2 experimental conditions. The "easy" condition contained 70% 1-move problems and 30% 2-move problems, whereas the "hard" condition contained 70% 3-move problems and 30% 2-move problems.

Data Acquisition and Analysis

Each fMRI scanning session consisted of a structural spoiled gradient recall (SPGR) scan and functional echo-planar scan. The fMRI data were collected using General Electric Medical Systems 3.0 or 1.5 T scanners (University of Pittsburgh Medical Center). An echo-planar pulse sequence with TR = 3000 ms, echo time (TE) = 25 ms (50 ms at 1.5 T), flip angle = 90°, and a matrix of 128 × 64 (field of view [FOV] = 40 × 20 cm) was used. Fourteen oblique axial slices (5-mm thick, 1-mm gap, 3.125 × 3.125–mm in-plane resolution) were imaged. Structural images (124-slice SPGR volume scan with TR = 25 ms, TE = 4 ms, matrix 256 by 256; FOV = 24 × 24 cm, 1.5-mm slice thickness) were taken in the axial plane. Equal numbers of participants from both groups were tested at each field strength, but after preliminary analyses indicated similar results at 1.5 and 3.0 T, the data from the 2 scanners were pooled.

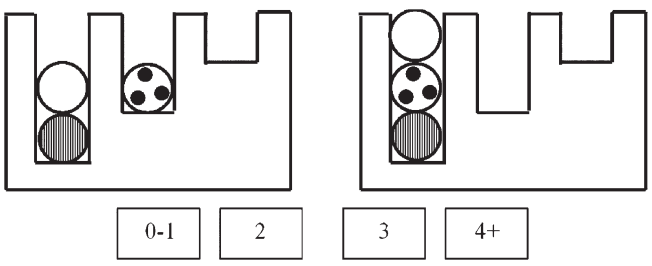

Figure 1. A sample TOL problem, with the start state on the left and the goal state on the right. The participant's task is to indicate the number of moves required to solve the problem using the response buttons.

Distribution of Activation

To compare the participating groups in terms of the distribution of activation, the data were analyzed using statistical parametric mapping (SPM99). Images were corrected for slice acquisition timing, motion corrected, normalized to the Montreal Neurological Institute (MNI) template, resampled to 2 × 2 × 2–mm voxels, and smoothed with an 8-mm Gaussian kernel to decrease spatial noise. Statistical analysis was performed on individual and group data by using the general linear model and Gaussian random field theory as implemented in SPM99 (Friston and others 1995). Group analyses were performed using a random effects model. Preliminary analyses indicated no reliable interaction between the effect of easy versus hard problems (although both groups showed increased activation with increased difficulty), so the data from the 2 conditions were combined into a single experimental condition that was contrasted with the fixation condition. Additionally, contrasts reflecting the complexity effects for each group, group by complexity interactions, and the group differences in the distribution of activation relative to fixation were computed. For the group differences contrasts, possible differences in deactivation (relative to fixation condition) were excluded. An uncorrected height threshold of $P = 0.005$ and an extent threshold of 6 8-mm^3 voxels were used.

Functional Connectivity

The functional connectivity was computed (separately for each participant) as a correlation between the average time course of all the activated voxels in each member of a pair of ROIs. Fifteen ROIs were defined to encompass the main clusters of activation in the group activation map for each group in the TOL-Fixation contrast. Labels for these 15 ROIs (the medial frontal gyrus plus 7 bilateral ROIs, namely, dorsolateral prefrontal cortex [DLPFC], inferior frontal gyrus [IFG], lingual gyrus [LG], intraparietal sulcus, precuneus [PC], fusiform gyrus, and middle occipital gyrus [MOG]) were assigned with reference to the parcellation of the MNI single-subject T_1-weighted data set carried out by Tzourio-Mazoyer and others 2002). A sphere was defined for each cluster (with a radius from 10 to 12 mm) that best captured the cluster of activation in the map for each group. The ROIs used in the analysis were each the union of the 2 spheres—one encompassing the activation of the group with autism and the other encompassing the activation of the control group. This common set of 15 ROIs was used for the 2 groups.

The activation time course for each ROI was extracted separately for each participant and was based on the normalized and smoothed images, which had been low-pass filtered and had the linear trend removed. Furthermore, the participant's activation time course was based on only the activated voxels within the ROI. The correlation between the time courses of 2 ROIs was computed on only the images belonging to the experimental condition and excluded the fixation condition, so it reflects the interaction between the activation in 2 areas while the subject is performing the task. The analysis of an ROI pair eliminated any participant who had fewer than 23 activated (2 × 2 × 2 mm) voxels in one of the ROIs. Fisher's r to z' transformation was applied to the correlation coefficients, and these transformed correlations were used in all reported analyses (Fisher 1921 showed that a simple transformation of the Pearson product moment correlation coefficient of the form $z' = (0.5) \ln (1 + r/1-r)$ produces a statistic with a nearly normal sampling distribution and a standard error that depends only on n. Following Cohen J and Cohen P (1983), we refer to these transformed correlation coefficients as z' to avoid confusion with the standard normal deviate). To carry out analyses of variance on various pairwise functional connectivities, the connectivity measures were aggregated within each lobe (frontal, parietal, temporal, and occipital) and hemisphere (left and right) by averaging each participant's z'-transformed correlations, resulting in 8 large-scale regions and 28 connectivity measures for each participant. These connectivity measures were further categorized in 2 ways in the analyses of variance. In

one analysis, functional connectivities were classified as either involving frontal–parietal connections (left frontal and left parietal, left frontal and right parietal, right frontal and left parietal, and right frontal and right parietal) or involving other possible connections. In a second analysis, frontal–parietal connectivities were further classified as involving either intrahemispheric or interhemispheric connections.

Factor Analysis

A factor analysis of the functional connectivities was performed to indicate the groupings of the 15 ROIs into networks based on the similarities of their time courses (Koshino and others 2005). For each ROI pair, mean z'-transformed values of the functional connectivity measures were computed across participants for each group. The mean z'-transformed values were then converted back to correlation coefficients, and a correlation matrix was constructed for each group. The functional ROIs in left IFG and right IFG were excluded from factor analysis because only 50% of control subjects and 44% of subjects with autism showed enough activation (defined as having at least 23 2 × 2 × 2–mm activated voxels) in these areas for estimating the functional connectivity. The resulting connectivity matrices included 13 functional ROIs. An exploratory factor analysis (e.g., McLaughlin and others 1992; Peterson and others 1999) was then performed for each group separately. The logic behind the factor analyses was that each factor would correspond to a large-scale network of brain regions executing some high-level function (see Mesulam 1990, 1998). Factor loadings represent the degree to which each of the ROIs correlates with each of the factors, and ROIs that had factor loadings of 0.4 or greater were taken into consideration in interpretation.

Corpus Callosum Morphometry

The cross-sectional area of the midsagittal slice of the corpus callosum was segmented (into rostrum, genu, rostral body, anterior midbody, posterior midbody, isthmus, and splenium) using the parcellation scheme described by Witelson (1989), as shown in Figure 2. For each participant, the corpus callosum's outer contour was first manually traced in the midsagittal plane (with an interrater reliability of 0.87), and then the interior segmentation into the 7 areas and the area computations were performed by image processing software. In addition, the gray matter, white matter, and cerebrospinal fluid (CSF) volumes of each participant were measured by segmenting the T_1-weighted structural brain image into 3 masks using SPM2 routines. Because a preliminary analysis revealed a trend toward a larger total brain volumes in the participants with autism (autism mean = 1009 mm^3, standard error [SE] = 24 mm^3, control mean = 946 mm^3, SE = 23 mm^3, $t_{17} = 1.92$, $P = 0.072$), the corpus callosum area measurements were normalized (divided by) by the total brain volume (exclusive of CSF) for each participant.

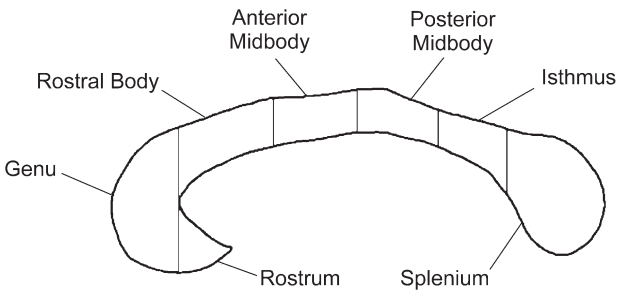

Figure 2. Subdivisions of the midsagittal slice of the human corpus callosum (adapted from Witelson, 1989).

Results

Overview

High-functioning individuals with autism showed a distribution of brain activation that was spatially similar to the control participants in most of the brain ROIs. However, the functional connectivity among brain regions was consistently lower for participants with autism in the frontal–parietal network, a pathway central to the performance of the TOL task. In addition, 2 segments of the corpus callosum were smaller in the autism group (the genu and the splenium). Finally, for the autism group only, the functional connectivity between frontal–parietal activated cortical regions was reliably correlated with the size of the genu of the corpus callosum, which is likely to provide at least some of the anatomical connectivity. In controls, by contrast, there was no such systematic correlation.

Behavioral Results

Low error rates in both groups indicated that the participants were able to perform the task proficiently. The percentage of errors was slightly greater in the autism group in both easy (5%) and hard (12%) conditions compared with the control group (2% and 8%, respectively). A 2 (group) × 2 (difficulty) mixed analysis of variance (ANOVA) showed that neither the main effect of group nor the interaction was significant, although there was a reliable main effect of problem difficulty ($F_{1,34}$ = 26.79, $P < 0.01$). For the response times, there was also no significant main effect of group, and there was a reliable main effect of difficulty ($F_{1,34} = 68.73$, $P < 0.01$) and a reliable group by difficulty interaction ($F_{1,34} = 5.56$, $P < 0.05$), resulting from the control participants responding faster than those with autism only in the hard condition.

Brain Activation

The activation in the group with autism and the control group occurred in similar areas to those reported for normal subjects in previous TOL studies (e.g., Newman and others 2003). Figure 3 displays the activation for the group with autism (for the

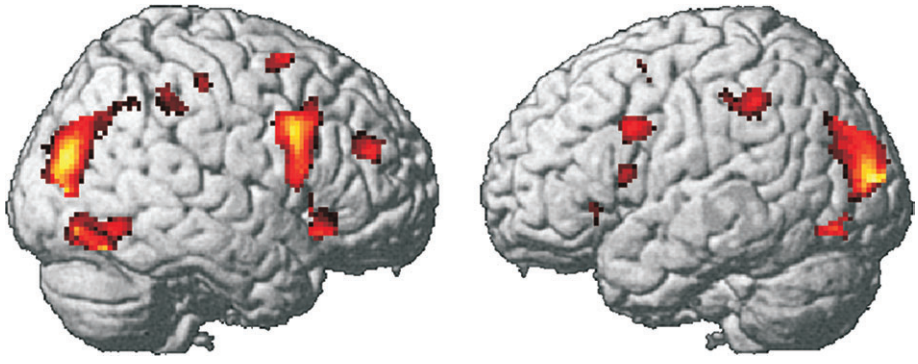

Figure 3. Activation in the autism group in the TOL task (contrast with fixation condition).

contrast between the TOL task and the fixation condition). Table 2 contains the results for both groups. The autism group and the control group generally showed similar areas of activation, especially in frontal brain areas such as DLPFC, which was found to play a key role in the TOL task in previous studies. Alongside these overall activation similarities, there were also a few group differences. The autism group activated approximately the same parts of the cortex as the control group, but the autism group did so with a greater number of smaller noncontiguous clusters of activation. The statistical subtraction between the 2 groups revealed only a small number of areas where the controls had reliably greater activation: bilaterally in inferior and superior parietal areas, angular gyri, superior, and mid occipital areas, middle frontal gyri, and the right precentral gyrus, superior frontal and the left inferior frontal gyri, as shown in Figure 4. The autism group showed more activation than the control group in left and right hippocampus, thalamus, and the left LG.

Table 2
Areas of activation for the contrast of the TOL task with fixation for the 2 groups

Location of peak activation	Cluster size	t_{34}	MNI coordinates		
			x	*y*	*z*
Participants with autism					
Bilateral lingual, inferior occipital, fusiform, calcarine, and cerebellum; left middle occipital and superior occipital; right inferior temporal	4285	9.34	−24	−96	10
R superior occipital, middle occipital, and inferior parietal	990	7.88	30	−74	24
R postcentral and inferior parietal	24	4.79	56	−24	52
R inferior parietal	85	3.81	42	−38	40
L inferior parietal	340	6.32	−38	−40	38
L inferior parietal	17	3.37	−58	−30	46
Bilateral superior medial frontal, middle cingulate, and supplementary motor area	277	5.82	6	28	40
R middle frontal, inferior frontal, and precentral	753	4.82	56	22	38
R middle frontal and inferior frontal	104	4.17	48	44	26
R middle frontal and superior frontal	74	3.85	28	6	60
R insula and inferior orbital frontal	289	6.77	34	22	2
L middle frontal, inferior frontal, and precentral	135	4.02	−48	10	32
L middle frontal and superior frontal	28	3.87	−24	0	52
L inferior frontal	41	3.45	−58	14	10
L insula and inferior frontal	40	3.83	−34	24	2
R thalamus, hippocampus, and lingual	139	5.02	24	−24	−8
R thalamus	29	3.92	10	−14	10
L thalamus, hippocampus, and lingual	111	5.75	−20	−28	−2
L thalamus	7	3.31	−12	−20	10
Normal control participants					
Bilateral lingual, inferior occipital, middle occipital, superior occipital, fusiform, calcarine, cerebellum, and inferior parietal	11206	12.65	−28	−74	30
Bilateral precuneus	10	3.61	2	−64	44
Bilateral cuneus	16	3.28	4	−86	32
Bilateral superior medial frontal, middle cingulate and supplementary motor area	561	6.31	0	14	52
R middle frontal, inferior frontal, and precentral	2146	6.98	26	2	52
R insula and inferior frontal	87	4.01	32	26	−2
L middle frontal, inferior frontal, and precentral	925	8.86	−42	42	32
L middle frontal, superior frontal, and precentral	206	5.52	−24	−2	54
L middle frontal and superior frontal	21	4.28	−32	64	8
L insula and inferior frontal	84	4.24	−32	28	0
Bilateral cerebellum and right lingual	13	3.21	6	−42	0
R thalamus	44	4.51	20	−28	10
L thalamus	47	4.37	−20	−30	8

Note: L, left; R, right. The threshold for significant activation was $P < 0.005$ for a spatial extent of at least 6 voxels, uncorrected for multiple comparisons. Region labels apply to the entire extent of the cluster. *t*-values and MNI coordinates are for the peak activated voxel in each cluster only.

Both the autism and the control group showed the difficulty effect between easy and hard conditions of the TOL task (i.e., more activation in the condition where more moves were required). Cortical areas of common activation across groups for the contrast between hard and easy conditions included left and right parietal regions, left and right superior, middle, and inferior frontal regions, and left hemisphere pre-and postcentral gyri. In order to assess whether these difficulty effects interacted with group membership, hard versus easy contrasts between the groups were directly compared in a random effects model. This analysis indicated that only a small cluster of 8 voxels in the right MOG showed a larger difficulty effect in the group with autism (peak $F_{1,34} = 7.72$; $P < 0.01$). There were no areas that showed a larger difficulty effect for the control group in this analysis. The 2 difficulty levels were subsequently collapsed in the remaining analyses.

Functional Connectivity

Because the functional connectivity hypothesized to be most affected by autism in the TOL task was between frontal and parietal areas, a 2 (group) by 2 (connection type) mixed ANOVA was conducted with ROI pairs separated into frontal–parietal versus other. This analysis thus contrasted the mean functional connectivities between frontal and parietal areas (left frontal and left parietal, left frontal and right parietal, right frontal and right parietal, and right frontal and left parietal), with the mean connectivities among all other pairs of regions. This analysis indicated reliably lower functional connectivities in the autism group ($F_{1,34} = 4.45$, $P < 0.05$), a reliable main effect of connection type ($F_{1,34} = 22.29$, $P < 0.0001$), and a reliable interaction ($F_{1,34} = 6.30$, $P < 0.02$). Tests of the simple main effect of group within each type of connection showed that the mean frontal–parietal connectivity was lower for the group with

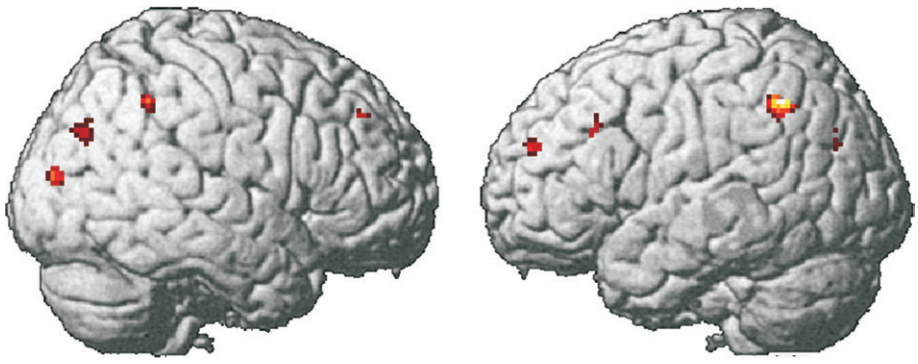

Figure 4. Group contrast showing areas where control participants have more activation than the autism group in the TOL task.

autism (mean = 0.37) than for controls (mean = 0.51, $F_{1, 34}$ = 6.98, $P < 0.02$), but there was no reliable group difference for the means of the other connections (autism mean = 0.51, control mean = 0.55, $F_{1, 34}$ = 1.18, $P = 0.28$). These results reveal a functional underconnectivity in the autism group during the performance of the TOL task focused in the frontal–parietal network, the network believed to underpin the planning and problem solving.

To determine whether autism differentially affected interhemispheric versus intrahemispheric frontal–parietal functional connectivity (particularly in light of the corpus callosum group differences reported below), another 2 (group) by 2 (connection type) mixed ANOVA was conducted, but this time with connections categorized as interhemispheric or intrahemispheric. There was a reliable main effect of group ($F_{1,34}$ = 6.00, $P < 0.02$), with the autism group having lower overall frontal–parietal connectivity (mean = 0.39) than the control group (mean = 0.52), repeating the main result in a slightly different statistical design. However, there was no suggestion of a group by connection type interaction ($F_{1,34} = 0.00$), indicating that autism similarly affects inter- and intrahemispheric functional connectivity in this task. Intrahemispheric functional connectivities were marginally higher than interhemispheric functional connectivities across groups ($F_{1,34} = 3.48$, $P = 0.071$).

The factor analysis yielded another perspective on the functional underconnectivity in autism, by grouping the areas that had similar time courses into separate factors. The factor analysis revealed 3 factors for the autism group (explaining 66% of the variance) but only 2 factors for the control group (62% of the variance), indicating a lower degree of synchronization among the activation clusters in autism. The striking difference between the 2 groups was in the connectivity patterns among frontal–parietal areas. In the autism group, the frontal and parietal ROIs were distributed over 2 factors (F2 and F3), whereas in the control group, the frontal and parietal ROIs were included in a single factor (F1), as shown in Table 3. (Each group had yet another factor, F1 for autism and F2 for controls that had approximately the same composition of inferior temporal and occipital ROIs for the 2 groups.) In other words, the frontal and parietal ROIs functioned within a single coordinated system in the control group, but within 2 separate networks for the autism group. Hence, the factor analysis also reflects a lack of integrative connectivity or underconnectivity in the frontal–parietal network in autism.

Table 3
Results of the factor analysis

Region	Autism group[a]			Control group[b]	
	F1	F2	F3	F1	F2
L DLPFC	—	—	0.73	0.69	—
L fusiform gyrus	0.72	—	—	—	0.69
L intra parietal sulcus	—	0.66	0.42	0.79	—
L LG	0.85	—	—	—	0.82
L MOG	0.55	0.61	—	0.51	0.65
L PC	—	0.77	—	0.72	—
Medial frontal gyrus	—	—	0.80	0.6	—
R DLPFC	—	—	0.61	0.64	—
R fusiform gyrus	0.61	—	—	—	0.65
R intraparietal sulcus	—	0.73	—	0.77	—
R LG	0.78	—	—	—	0.82
R MOG	0.58	0.6	—	0.45	0.69
R PC	—	0.79	—	0.72	—

Note: L, left; R, right. [a]F1: inferior temporal and occipital bilaterally, F2: parietal and occipital bilaterally, F3: frontal bilaterally and left intraparietal sulcus. [b]F1: frontal, parietal, and occipital bilaterally, F2: inferior temporal and occipital bilaterally.

Further Data Explorations of the Functional Connectivity Group Differences

The lower functional connectivity in autism in the frontal–parietal connections could be due to several characteristics of the data, and several hypotheses concerning such differences were investigated in the data, but rejected. For example, the time courses were not more variable in autism. More generally, detailed quantitative comparisons of the activation time courses for left DLPFC and the right and left PC revealed very similar patterns across the regions for the 2 groups. There was also no indication of there being a phase shift (delayed correlation) of one of the time courses in autism. (Additional functional connectivity measures computed for these regions with positive or negative lags between the regions showed that the correlations between regions were highest for both groups with no lag and that the correlations decreased similarly and monotonically for both groups as the lag was increased.) Furthermore, there was no evidence that low- versus high-frequency components of the time course contributed differentially to the group difference in functional connectivity. (To test the hypothesis, the time course data were temporally filtered with a Gaussian low-pass filter [full width half maximum {FWHM} = 3 s] or high-pass filter [FWHM = 10 s], and the resulting connectivity measures showed that both the low- and high-frequency components of the time courses contributed to the difference in connectivity between the groups.) Similar analyses into the basis for the underconnectivity were performed on another task in which the imaging data were acquired at a higher temporal resolution and hence provided more detail about the time course (TR = 1 s rather than the present TR = 3 s), and again similar results were obtained. The current analyses indicate that the decreased synchronization of activation between frontal and parietal areas is not due to some abnormality in the time course of the activation of either area, but in the time courses being less coordinated between regions.

There were no differences in the activation between autistic participants on medication and those not on medication in this sample or in our previous published fMRI studies of functional connectivity in different subject samples. From a theoretical perspective, functional connectivity likely relates to the quality of structural connections as well as the capacity to dynamically bring different systems online to address task demands. The effect of medications that reduce anxiety and enhance cognitive function, if they impact functional connectivity at all, might be expected to improve functional connectivity rather than reduce it. The medications would not be expected to impact structural connectivity.

Corpus Callosum Size

The normalized size of the 7 midsagittal subregions of the corpus callosum was compared between the 2 groups in a 2 (group) by 7 (segment) ANOVA. This analysis revealed a marginal main effect of group ($F_{1,34}$ = 4.05, $P < 0.1$), with a smaller mean segment size in autism (mean = 0.089, SE = 0.003) than in the control group (mean = 0.100, SE = 0.003) and a reliable group by segment interaction ($F_{6,204}$ = 2.55, $P < 0.05$). (There was also a main effect of segment, [$F_{6,204}$ = 425.05, $P < 0.0001$]). Tests of the simple main effect of group within each segment indicated that the genu (the most anterior region) and the

splenium (the most posterior region) were reliably smaller in the autism group than in the control group, as shown in Table 4. Genu fibers are presumed to connect prefrontal cortical areas (Witelson 1989) and hence are likely to be involved in frontal–parietal anatomical connectivity. These anatomical results are in general agreement with previous studies (Egaas and others 1995; Saitoh and others 1995; Piven and others 1997; Manes and others 1999; Hardan and others 2000), but here, the anatomical connection differences occur in the context of reduced functional connectivity between the relevant cortical regions in the autism group.

Relation between Functional Connectivity and Corpus Callosum Size

The results above establish that the group with autism had lower functional connectivity between frontal and parietal areas and also smaller corpus callosum areas. If the size of the corpus callosum imposes a constraint or upper bound on the functional connectivity between regions, one might predict that the autism group's (lower) functional connectivity measures in frontal–parietal ROI pairs would be positively correlated with their (smaller) genu sizes. There in fact was a reliable positive correlation between the frontal–parietal connectivity and the size of the genu in the group with autism ($r = 0.52$, $t_{16} = 2.47$, $P < 0.02$, 1-tailed test), as shown in Figure 5. In contrast, among control participants, there was no relationship between these measures, consistent with the idea that the size of the corpus callosum does not constrain their functional connectivity. Furthermore, there was a reliable difference between the correlations in the 2 groups ($z = 2.66$, $P < 0.01$). The pattern of correlations is suggestive of a constraint on functional connectivity in autism imposed by some anatomical property of the corpus callosum.

Relation between Functional Connectivity and ADOS Scores

If the decreased frontal–parietal connectivity in the group with autism is related to the severity of autism, one would predict a negative relationship between this measure and ADOS scores. Frontal–parietal functional connectivity was indeed negatively correlated with total ADOS scores among the participants with autism as expected ($r = -0.45$, $t_{14} = -1.91$, $P < 0.05$, 1-tailed test), as shown in Figure 6. (Two of the participants with autism whose ADOS-based diagnosis was obtained from a different site were excluded from the analysis because their precise ADOS scores could not be obtained.) The correlation indicates that autistic participants with lower frontal–parietal functional connectivity scores tend to have higher ADOS scores. Although ADOS scores are not intended to provide a measure of the severity of autism or to be used as a psychometric measure, it is intriguing to consider that a brain activation measure of functional connectivity may be related to the best current research-based measure of autism.

Table 4

Areas of the midsagittal slice of the corpus callosum normalized by the total gray plus white matter volume

Corpus callosum midsagittal slice area	Autism group	Control group	$F_{1,134}$
Rostrum	0.03	0.02	0.05
Genu	0.12	0.14	5.19*
Rostral body	0.10	0.12	3.62
Anterior midbody	0.08	0.08	0.09
Posterior midbody	0.07	0.08	0.60
Isthmus	0.05	0.06	0.87
Splenium	0.19	0.21	12.12*

Note: *F*-values are for tests of the simple main effect of group. Denominator degrees of freedom are adjusted using Satterthwaite's approximation. *$P < 0.05$.

Discussion

The central contributions of this study were to 1) document new evidence of functional underconnectivity in autism between frontal and parietal areas in an executive processing task; 2)

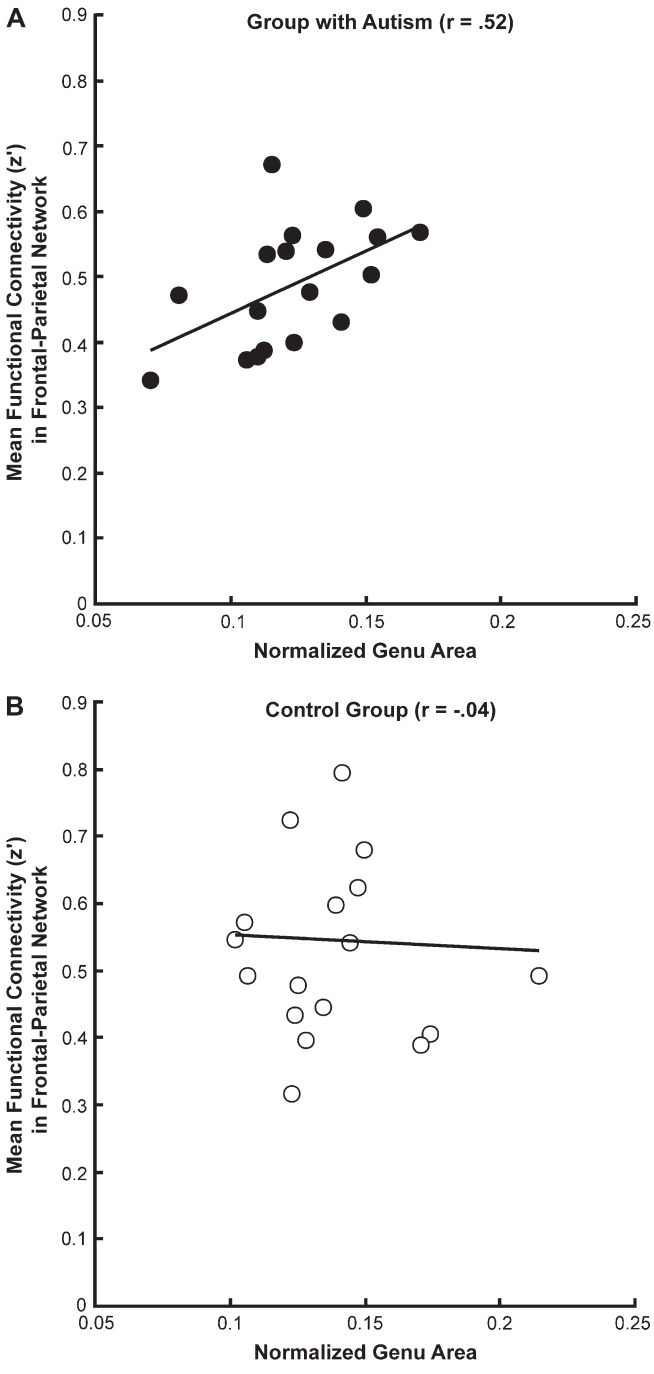

Figure 5. Correlation between the midsagittal area of the genu portion of the corpus callosum and the mean functional connectivity between frontal and parietal areas for the Autism Group (*A*) and the Control Group (*B*).

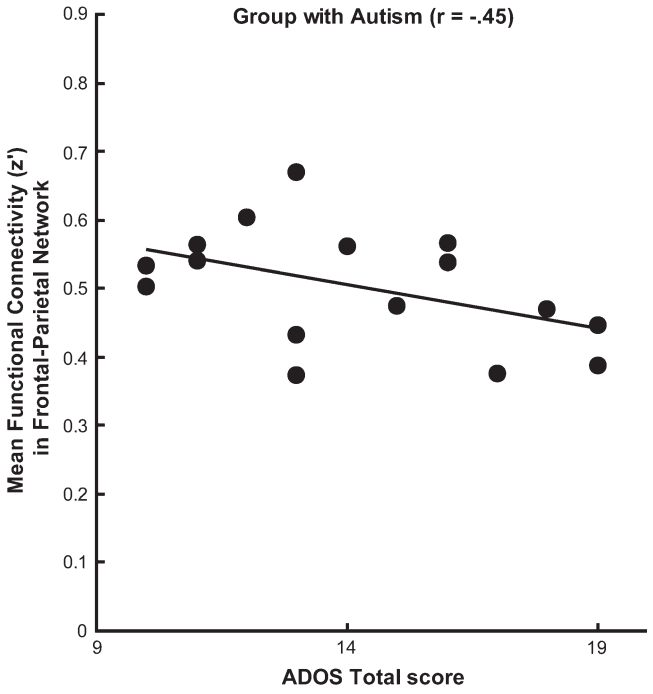

Figure 6. Correlation between the ADOS total score and the functional connectivity in the frontal–parietal network.

replicate previous findings of anatomically smaller corpus callosum sizes in autism; and 3) establish a relation between the functional and anatomical connectivity measures. These findings add support to the cortical underconnectivity theory of autism first proposed on the basis of similar evidence observed in an fMRI study of sentence comprehension (Just and others 2004) and more recently extended on the basis of results from a verbal working memory task (Koshino and others 2005). The frontal–parietal underconnectivity observed during the TOL task is provocative because a frontal–parietal network has been found to be involved not only in TOL problem solving (Newman and others 2003) but in many other executive function tasks (Schneider 1999). Thus, executive dysfunction in autism, which has been observed in a number of behavioral studies (Ozonoff and others 1991; Hughes and Russell 1993; Hughes and others 1994), might be the result of frontal–parietal underconnectivity. In this new perspective, executive dysfunction is just one of many possible consequences of cortical underconnectivity.

The lower functional connectivity in autism in an executive function task suggests that the communication between certain cortical areas is less effective in autism, affecting how the cortically distributed components of thinking are coordinated. The lowered functional connectivity can be thought of as a reduced interarea communication bandwidth. An underconnected system would be particularly disruptive to those complex or higher order psychological functions with a heavy dependence on the coordination of brain regions, such as social, language, and problem solving functions. These and other complex psychological functions require the concurrent coordination of many different types of information processing, explaining why symptomatic disruptions of such divergent psychological functions might co-occur in autism to form a syndrome. Underconnectivity theory is consistent with the broad yet circumscribed range of disruption of cognitive and social functioning in autism. Deficits in theory of mind (Baron-Cohen and others 1985), face processing (Critchley and others 2000; Schultz and others 2000; Pierce and others 2001), executive function (Ozonoff and others 1991; Hughes and Russell 1993; Hughes and others 1994), language (Just and others 2004; Harris and others 2006), and other seemingly unrelated deficits could all be the result of a deficit in integrating types of information processing. Even postural deficits have been reported in autism (Minshew and others 2004). Autism appears to be a neural systems disorder, and underconnectivity theory provides a framework for the accumulating empirical evidence concerning the nature of the disorder.

The newly discovered relationship between the lower functional connectivity and the reduced size of the genu in the group with autism opens new avenues of investigation. The smaller the genu was, the lower was the functional connectivity between the frontal and parietal regions. This correlation in the autism group may reflect a constraint on the functional connectivity imposed by anatomical properties of the corpus callosum. We interpret the reduced corpus callosum sizes in autism as an index of white matter abnormality, whose nature and impact are not currently understood. In control participants, by contrast, there was no such correlation and presumably no such constraint. Note that although the mean sizes of the genu and splenium tend to be smaller in autism, there is considerable overlap in the distributions of the 2 groups' regional measurements that probably fails to reflect larger underlying differences in microstructure and function.

The results suggest that abnormalities in major interhemispheric tracts such as the corpus callosum may contribute to diminished functional connectivity patterns in autism (Quigley and others 2001). The majority of callosal fibers are thought to originate from association cortices and subserve higher order functions (Innocenti 1986; Pandya and Seltzer 1986). A smaller corpus callosum in autism might reflect lower interhemispheric connectivity. Recent findings also indicate intrahemispheric white matter abnormalities in autism (see Courchesne and others 2001; Carper and others 2002; Herbert and others 2003, 2004; Chung and others 2004). Note that the white matter abnormalities in autism include not only smaller white matter volumes in some regions but also dysregulation and larger white matter volumes in other regions (Courchesne and others 2001; Herbert and others 2002). Moreover, our measure of white matter volume in the present study provided an index only of interhemispheric anatomical connectivity. (The results of the functional connectivity analyses provided no evidence that interhemispheric temporal synchronization of activation was more affected in autism than intrahemispheric synchronization.) It is important to keep in mind that it is not known how the white matter volume abnormalities in autism are related to the functioning of the white matter. Converging results from white matter analyses and from functional imaging results may establish the relation between white matter volume abnormalities and functional abnormalities. Our laboratory is currently collecting functional connectivity and diffusion tensor imaging data on the same participants with a goal of providing a converging measure of the relationship between functional connectivity and intrahemispheric and interhemispheric anatomical connectivity.

How General Is the Underconnectivity?

The newly reported cortical underconnectivity in executive processing raises the question of how general the

underconnectivity in autism might be. Does it occur in all tasks? Does it affect all pairs of regions? Does it occur in other special populations?

First, consider the generality over tasks. Functional underconnectivity has previously been observed in autism using fMRI in a sentence comprehension task (Just and others 2004) and in a letter n-back working memory task (Koshino and others 2005). Functional underconnectivity in autism (between occipital and temporoparietal regions) was also reported in a PET study (and hence measured at a more molar level) in a mental state attribution (Theory of Mind) task (Castelli and others 2002). In sensory tasks, electrophysiological studies have reported functional underconnectivity in autism (although with a measurement in a different time scale) among association areas but normal functional connectivity among sensory areas (Mottron and Burack 2001; Mottron and others 2003). The new TOL results demonstrate that reduced functional connectivity occurs in executive function tasks. There is thus a convergence of findings based on tasks involving reasoning, language, and social judgment, all the major symptom domains that define the syndrome of autism, supporting the idea of functional underconnectivity as a general characteristic of the neurobiology of neural systems in autism.

Second, consider whether the lower functional connectivity in autism applies to all pairs of cortical areas. The group difference in functional connectivity in the TOL was reliable only in the frontal–parietal network, namely, the network that constitutes the main neural underpinning of cognitive functioning in this task. The functional connectivity was lower in the autism group in other networks as well (such as the frontal–temporal and temporal–occipital networks, where the difference between groups in functional connectivity was marginally reliable). However, frontal–parietal networks are not necessarily the manifestation of underconnectivity in autism in other tasks. In some language tasks, the greatest degree of underconnectivity may occur in a frontal–temporal network. The generalization concerning localization to date is that underconnectivity affects connections between the association areas that are most activated in a task, particularly affecting connectivity with frontal areas. Further fMRI studies of a variety of tasks will determine how cortical underconnectivity is localized. It is important to keep in mind that functional connectivity is a dynamic property in which different regions become activated and coordinated on an as needed basis, depending on the task.

Third, it is interesting that autism is not the only disorder in which disconnection among brain areas has been observed or proposed. For example, Lawrie and others (2002) proposed a disconnection syndrome in schizophrenia. The symptoms of autism show considerable overlap with the negative symptoms of schizophrenia, suggesting corresponding overlap in the neural systems disruptions. (Not surprisingly, the term "autism" was borrowed from the schizophrenia literature and for decades autism was classified as a childhood psychosis, despite the absence of psychotic symptoms). It should not be surprising if a complex system like the brain consisting of interacting subsystems could be susceptible to disruption of the intersubsystem communication in more than one way. The lowered functional connectivity could vary in different pathologies, such as being limited to affecting the connections between particular brain regions (as has been proposed e.g., for dyslexia). It would be particularly interesting to examine functional connectivity in participants with complete or partial agenesis of the corpus callosum but who nevertheless show relatively unimpaired cognitive functioning to determine how callosal absence affects interhemispheric functional connectivity and presumably, the degree of coordination between hemispheres. Underconnectivity could be a part of several syndromes.

Previous Theories

The underconnectivity theory has a straightforward relation to predecessor approaches to autism that pointed in a similar direction. Major cognitive theories in autism such as the complex information processing theory (Minshew and others 1997) and the weak central coherence theory (Frith 1989) suggest the possibility of underdeveloped connections in the brain in autism. The information processing theory focused on autism as a disorder of processing complex information. This approach attributed the disorder to a fundamental abnormality in the handling of information in high-level tasks, particularly those requiring abstraction. Moreover, Minshew and Goldstein (1998) proposed that autism was a nonfocal, systemic disorder of the brain, a distributed neural systems disorder. Underconnectivity theory enriches Minshew's previous theory with the new findings from fMRI, linking the information processing abnormalities to a specific neurobiologic phenomenon, the brain connectivity itself. Frith's (1989) theory of weak central coherence deals with a tendency to focus on details at the expense of configural information, which has been proposed as a cognitive style in autism. According to this view, autistic individuals fail in integrated representation. This is consistent with the underconnectivity approach. In more recent work with her colleagues, particularly in neuroimaging research, Frith has attempted to apply the concept of weak central coherence to the brain activity level. Hill and Frith (2003) mentioned that the central coherence account referred to poor connectivity throughout the brain between more basic perceptual processes and top–down modulating processes, perhaps due to failure of pruning. Underconnectivity theory specifies a particular underlying biological mechanism and goes on to predict similar impairments in motor functions, memory, and expressive nonverbal language and to virtually all cortically mediated functions.

In summary, normal brain function has been construed here as a collaboration of a confederation of processing centers. The new fMRI and magnetic resonance imaging findings suggest that in autism, the confederation is loosened or underfunctioning. In this study, the underconnectivity theory is extended to new levels by linking it with white matter abnormalities. The new theory frames a number of research questions about the scope and nature of the underconnectivity in autism, which await investigation with converging methods.

Notes

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