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# Cortical activation and synchronization during sentence comprehension in high-functioning autism: evidence of underconnectivity

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## Summary

**The brain activation of a group of high-functioning autistic participants was measured using functional MRI during sentence comprehension and the results compared with those of a Verbal IQ-matched control group. The groups differed in the distribution of activation in two of the key language areas. The autism group produced reliably more activation than the control group in Wernicke's (left latero-superior temporal) area and reliably less activation than the control group in Broca's (left inferior frontal gyrus) area. Furthermore, the functional connectivity, i.e. the degree of synchronization or correlation of the time series of the activation, between the various participating cortical areas was consistently lower for the autistic than the control participants. These findings suggest that the neural basis of disordered language in autism entails a lower degree of information integration and synchronization across the large-scale cortical network for language processing. The article presents a theoretical account of the findings, related to neurobiological foundations of underconnectivity in autism.**

**Keywords**: autism; sentence comprehension; functional MRI

**Abbreviations**: fMRI = functional magnetic resonance imaging; DLPFC = dorsolateral prefrontal cortex; LIFG = left inferior frontal gyrus; LSTG = left posterior superior and middle temporal gyrus; ROI = region of interest

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## Introduction

One of the enigmas of autism in high-functioning individuals is the juxtaposition of some domains of preserved or even enhanced cognitive function, coupled with domains of deficit. In particular, previous behavioural studies of the processing of language in high-functioning autistic individuals have reported a preserved or even enhanced ability in the narrower-scope task of reading individual words, coupled with a deficit in the broader-scope task of processing grammatically complex verbal instructions (in the Detroit Test of Oral Directions) (Goldstein *et al*., 1994), thus epitomizing in microcosm the enigma of autism.

In our study we examined brain activation during sentence comprehension using functional MRI (fMRI), comparing the activation of high functioning autistic individuals and control participants. Our goal was to compare the activation, not simply in terms of which cortical areas became active, but also in terms of the distribution of the activation across some of the key language areas and in terms of the synchronization of the activation across cortical areas.

Previous functional neuroimaging studies in normal individuals have identified a number of cortical areas that become activated during sentence comprehension, providing a point of departure for the investigation of language processing in autism. In a number of previous studies (reviewed by Bookheimer, 2002), LIFG (left inferior frontal gyrus) or, more informally, Broca's area, was involved in a number of processes that could play an integrating role in sentence comprehension, such as syntactic processing (Just *et al*., 1996; Caplan *et al*., 1998, 1999; Friederici *et al*., 2000; Ni *et al*., 2000; Keller *et al*., 2001; Röder *et al*., 2002), semantic processing (Fiez, 1997; Fiez and Petersen, 1998; Gabrieli *et al*., 1998), and working memory functions (D'Esposito *et al*., 1999). Moreover, it has become possible to associate a sub-region of LIFG, pars triangularis, with a set of language-related functions, such as

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semantic and syntactic analysis and working memory, that contribute to the integration of the meaning components of a sentence (Petersen *et al*., 1989, 1990; Fiez, 1997; Fiez and Petersen, 1998; Gabrieli *et al*., 1998; Michael *et al*., 2001). A second key area in sentence comprehension is the more posterior LSTG (left superior and middle temporal gyrus), or more informally, Wernicke's area, which has particularly been associated with lexical processing (Howard *et al*., 1992). In particular, the area immediately surrounding the posterior left superior temporal sulcus (including the superior temporal and middle gyri) has been shown to be strongly involved in sentence comprehension (Just *et al*., 1996; Röder *et al*., 2002).

Neuroimaging studies during sentence comprehension in autism have made initial forays into the neural basis of language comprehension in autism. A PET study of sentence listening in five high-functioning autistic participants showed less left-lateralization (compared with the control group) in the perisylvian and temporal areas (Müller *et al*., 1999). Moreover, a morphometric study has shown that these two areas, LIFG and the posterior LSTG, show a reversal of the usual left–right size asymmetry in high-functioning autistic boys (ages 7–11 years), in whom the left-hemisphere homologue is smaller than the right (Herbert *et al*., 2002). Thus a number of converging neuroimaging studies in normal participants and a few studies of autism suggest that the brain activation in LIFG and LSTG may play a central role in accounting for the language comprehension abnormalities in autism.

Our analysis compared the relative amounts of activation in these two areas between the autistic and the control participants. We examined the hypothesis that autistic participants may rely more on an enhanced word-processing ability (which would be indicated by more-than-normal activation in Wernicke's area), and rely less on integrating processes that bring the words of a sentence together into an integrated syntactic and semantic structure (indicated by less-than-normal activation in Broca's area). These predicted findings of abnormal brain activation in autism during sentence comprehension would converge with the previously reported behavioural differences in complex comprehension (Goldstein *et al*., 1994).

Our second main focus was on the synchronization of the activation between cortical areas. The theoretical rationale for this focus is that it is becoming clear that thinking is an emergent property of a large-scale network of collaborating cortical areas. Thus, to characterize neural functioning in autism, it may be necessary to examine the cortical activation at a system level rather than at the level of a single area. The proposal of an interactive large-scale network arose long before the days of functional neuroimaging, in the theories of neurologists such as Luria (1980) and Mesulam (1990), who were seeking to explain why patients with focal lesions usually displayed non-focal cognitive deficits. Anatomical pathways between potentially collaborating cortical areas (cortical-cortical intrahemispheric pathways or interhemispheric pathways such as the corpus callosum as well as indirect pathways through subcortical areas such as the thalamus) provide the communication infrastructure for the proposed collaborative nature of the processing. The early increase in brain growth and increase in grey and white matter volume provide supporting evidence for abnormalities in these pathways (e.g. Courchesne *et al*., 2001; Aylward *et al*., 2002; Sparks *et al*., 2002; Herbert *et al*., 2003).

The view we advocate and test with our fMRI studies is that cognitive tasks are subserved by large-scale cortical networks that consist of spatially separate computational centres that collaborate pervasively to perform complex cognitive processing. The activation in a set of cortical areas should be synchronized, indicating collaboration among areas. One way to measure the synchronization is to compute the correlation (Friston, 1994) or covariance (Horwitz *et al*., 1998) between the activation levels in two activated areas. In particular, functional connectivity as defined by Friston (1994), and as we will use it, refers to the correlation between the activation time series data of two brain areas. This measure generally shows systematic synchronization between areas, modulated by a number of variables. The synchronization is taken as evidence of 'functional connectivity'.

In the context of brain imaging, functional connectivity refers to indirect evidence of communication or collaboration between various brain areas. Early measures of functional connectivity examined whether the activation levels of a pair of regions of interest (ROIs) were correlated with each other, across the participants in a study. This is the main way that functional connectivity can be measured with PET. One functional connectivity finding in autism that used this PET-based correlation of activation levels between two ROIs across the participants in the study showed a lower level of functional connectivity among autistic participants during a theory of mind task (Castelli *et al*., 2002). Two older functional imaging studies using coarser-grain measures (e.g. Horwitz *et al*., 1988; Zilbovicius *et al*., 1995) implicated lower inter-regional brain connectivity in autism. The study of Horwitz and colleagues used a resting state PET study to demonstrate reduced intra- and interhemispheric correlations with frontal and parietal cortices. Using a SPECT (single photon emission computed tomography) study, Zilbovicius and colleagues demonstrated delayed maturation of frontal circuitry in 4–5 year olds with autism compared with controls.

fMRI can provide a finer grain measure of functional connectivity than PET. Functional connectivity in fMRI data can be based on the correlation of the activation time series between voxels in different areas. The time series in our study included an observation every 3 s [i.e. a repetition time (TR) of 3 s] while participants were performing the sentence comprehension task. The general assumption is that the functioning of voxels whose activation levels rise and fall together is coordinated. The measures of functional connectivity are difficult to interpret in any absolute sense, but they typically make excellent sense when interpreted relatively, by making comparisons across experimental conditions, across different pairs of areas, or across different populations of participants.

We measured the functional connectivity between some of the key areas involved in sentence comprehension, and compared these measures between the autistic and control participants. We hypothesized a lower level of functional connectivity among the autistic participants, because a difficulty in the integrative aspects of understanding a complex sentence could well stem from a lower level of coordination and synchronization among cortical areas. This hypothesis is part of a broader theoretical proposal that autism is a cognitive and neurobiological disorder of integrative circuits and processes which results in a deficit of integration of information at the neural and cognitive levels. The underconnectivity theory, described in more detail in the Discussion, provides an integrating framework for the new findings, and also provides useful extensions to previous theories of autism.

## Methods

### *Participants*

Seventeen high-functioning autistic and 17 healthy normal participants were included in the study, all with Full Scale and Verbal IQ scores of 80 or above. The diagnosis of autism was established using the Autism Diagnostic Interview (ADI) (Lord *et al*., 1994), the Autism Diagnostic Observation Schedule (ADOS) (Lord *et al*., 2000) and expert clinical diagnosis. The autistic participants met criteria for autism on all three assessments and on both the social and communication domains of the ADOS. Medically healthy control participants were recruited using group matching. Potential autistic participants were excluded if they had an associated disorder such as fragile-X syndrome or tuberous sclerosis. Potential autistic participants were also excluded in the presence of evidence of birth asphyxia, head injury or a seizure disorder. Exclusions were based on neurological history and examination, chromosomal analysis and, if indicated, metabolic testing.

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. Potential control participants were screened by questionnaire, telephone, face-to-face interview, and observation during screening psychometric tests. Exclusionary criteria, evaluated through these procedures included current or past psychiatric and neurological 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. 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 neurological or psychiatric disorder thought to have a genetic component. All participants were Caucasian.

There were no statistically reliable differences between the autistic and control participants in age or IQ. Handedness was determined with the Lateral Dominance Examination from the Halstead–Reitan Neuropsychological Test Battery (Reitan, 1985), revealing three autistic and one control participants who were left-handed (but who were all nevertheless clearly left-dominant in their cortical activation during sentence comprehension). The brain activation data from these left-handers were clearly similar to each of their groups and the data were not further separated by handedness. Six of the participants were taking medication (primarily serotonin reuptake inhibitors) but their data were qualitatively very similar to (and not statistically different from) the presented data of the autistic participants without medication. Written informed consent was obtained from participants or their guardians, using procedures approved by the University of Pittsburgh Medical Center Institutional Review Board.

### *Materials*

The comprehension task was to read an active or passive sentence and respond to a probe (displayed on a separate line) identifying either the agent or the recipient of the action by pressing the left or right hand response button that was on the same side as the correct response, such as:

The cook thanked the father.

Who was thanked? cook – father

(An example of a passive sentence and probe is The editor was saved by the secretary. Who was saving?)

Sentences of the same type were presented in epochs of five items. There were seven randomly distributed epochs of each type, and eight 24-s fixation epochs (in which the participant fixated an asterisk). Inter-epoch intervals not filled by a fixation epoch were filled by a 6-s rest interval.

### *fMRI data acquisition and processing*

Each testing session consisted of a structural spoiled gradient recalled (SPGR) scan and a functional echo-planar scan acquired during the comprehension task, using a GE Medical Systems 3.0 or 1.5 T scanner at the University of Pittsburgh Magnetic Resonance Research Center. An echo planar pulse sequence with TR = 3000 ms, echo time (TE) = 25 ms (50 ms at 1.5 T), a 90° flip angle, and an acquisition matrix size of 128 × 64 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 × 256, 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 two scanners were pooled. Maximum head motion did not exceed 0.7 mm. A small and similar number of participants from the autism and control groups without clear left-lateralization in this task [with lateralization defined as substantially more left-hemisphere activation in IFG, STG and dorsolateral prefrontal cortex (DLPFC)] was excluded from further analysis.

### *Data analyses*

#### *Distribution of activation*

To compare the participating groups in terms of the distribution of activation, the data were analysed using 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 *et al*., 1995). Group analyses were performed using a random-effects model. Statistical maps were superimposed on normalized T1-weighted images. The data from the two scanners and the two experimental conditions (active and passive sentences) were combined into a single 'Sentence' condition that was contrasted with the fixation condition. An uncorrected height threshold of $T = 2.92$ ($P = 0.005$) and an extent threshold of 50.8-mm$^3$ voxels was used.

### *Functional connectivity*

Functional connectivity was computed for each participant as a correlation between the average time course of all the activated voxels in each member of a pair of anatomically defined ROIs. Thirty-five cortical ROIs, which included the association areas most likely to activate in a sentence comprehension task, were defined for each participant using a conventional cortical parcellation scheme (Rademacher *et al*., 1992; Caviness *et al*., 1996). These ROIs are defined with high reliability and have provided excellent coverage of activation in previous fMRI research (e.g. Just *et al*., 2001, 2004). Voxels (3.125 × 3.125 × 5 mm, in this analysis) were identified as activated in the original image space separately for each participant in terms of their *t*-value (passive condition versus fixation baseline). This *t*-threshold was set individually for each participant so as to yield exactly 35 activated voxels in the sum of three key ROIs (LIFG, LSTG and LDLPFC), such that the number of activated voxels whose time course was averaged was similar across participants. To ensure some minimum amount of activation in each ROI involved in a functional connectivity computation, a minimum activation volume of 3 voxels was required in each member of the ROI pair before the functional connectivity was considered 'measurable'. The average number of images included for each condition was approximately equated across all participants by truncating the longest epochs. The time courses included all of the images acquired during the specific experimental condition, including two additional images (6 s) after the end of each epoch (to take advantage of the gradual decrease in signal due to the delayed haemodynamic response). All other images corresponding to any fixation or rest conditions were excluded, so the measure focuses on the correlation during task performance, rather than focusing on the alternation between task performance and fixation. Fisher's *Z*-transformation was applied to the resulting set of correlations. ROI pairs that did not have measurable connectivity for at least 50% of the participants in both groups were excluded from consideration. The functional connectivities for the active and passive conditions were treated as repeated measures in the analyses of variance (ANOVAs). Two control participants with extremely high functional connectivities were considered outliers and were excluded from the functional connectivity analysis. Had these two participants been included, the difference in mean functional connectivity between the autistic and control groups reported below would have been even greater.

## Results

### *Distribution of activation*

One of the main results was a large systematic difference between the autistic and control groups in the distribution of their brain activation among the key cortical components of the language network, namely Wernicke's and Broca's areas. Although both groups showed activation in Wernicke's area [consisting of the posterior left superior and middle temporal gyri (BA 21, 22)], the extent of activation in this posterior area was greater in the group with autism, as shown in Table 1 and

**Table 1** *Areas of activation (and Brodmann areas) for the contrast of sentence comprehension with fixation for the autistic and normal groups*

| Cortical regions (Brodmann areas) | Cluster size | *Z* score | Talairach coordinates | | |
|---|---|---|---|---|---|
| | | | *x* | *y* | *z* |
| Participants with autism | | | | | |
| Left superior and middle temporal gyri (21, 22) | **562** | 3.98 | −53 | −50 | 10 |
| Left inferior frontal gyrus (45, 47) | **201** | 4.16 | −32 | 29 | −1 |
| Left precentral, middle frontal, and inferior frontal gyri (6, 8, 9, 44, 45) | **1676** | 5.41 | −53 | 20 | 21 |
| Left angular, supramarginal, superior occipital gyri and cuneus (39, 40, 19) | 1167 | 4.52 | −30 | −60 | 36 |
| Left parahippocampal gyrus (27, 28) | 183 | 5.36 | −24 | −27 | −5 |
| Right inferior frontal gyrus (45, 47) | 60 | 2.98 | 34 | 25 | 2 |
| Right angular gyrus (39) | 399 | 3.99 | 36 | −60 | 36 |
| Right parahippocampal gyrus (27, 28) | 145 | 4.41 | 24 | −25 | −4 |
| Bilateral superior/medial frontal gyri (6, 8) | 798 | 4.34 | −4 | 14 | 45 |
| Bilateral lingual, fusiform, and middle occipital gyri (17, 18, 19, 37) | 972 | 4.24 | −12 | −84 | −8 |
| Normal control participants | | | | | |
| Left superior/middle temporal gyri (21, 22) | **265** | 4.52 | −57 | −31 | 0 |
| Left inferior frontal gyrus (45, 47) | **1018** | 4.94 | −48 | 25 | −5 |
| Left precentral, middle frontal, and inferior frontal gyri (6, 9, 46, 44, 45) | **2762** | 4.89 | −50 | 6 | 44 |
| Left supramarginal/postcentral gyri (40, 2) | 50 | 3.02 | −50 | −31 | 42 |
| Right inferior frontal gyrus (47) | 408 | 3.65 | 34 | 25 | −5 |
| Right middle frontal gyrus (9) | 80 | 3.2 | 42 | 13 | 27 |
| Bilateral superior/medial frontal gyri (6, 8) | 1419 | 4.58 | 6 | 14 | 49 |
| Bilateral intraparietal sulcus, precuneus, cuneus and middle occipital/lingual gyri (7, 40, 17, 18, 19) | 5887 | 5.23 | −34 | −76 | −10 |

The threshold for significant activation was $P < 0.005$ for a spatial extent of at least 50 voxels, uncorrected for multiple comparisons. Region labels and Brodmann areas apply to the entire extent of the cluster. *Z* scores and Talairach coordinates are for the peak activated voxel in each cluster only. Clusters in bold are the circled areas shown in Fig. 1.

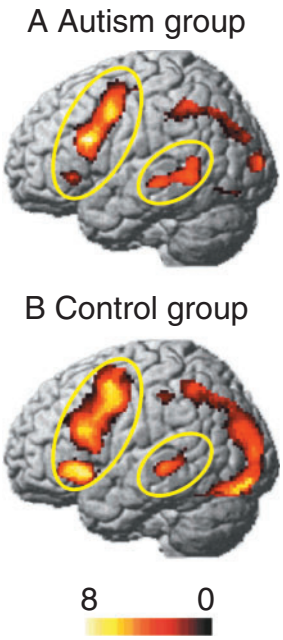


**Fig. 1** Brain activation of autistic (**A**) and control (**B**) groups (Sentence versus Fixation contrast). Autistic participants show less activation in the left inferior frontal gyrus (LIFG) than the control group, but more activation in the left posterior superior temporal gyrus (LSTG) than the control group. Circled areas indicate the first three clusters for each group listed in Table 1.

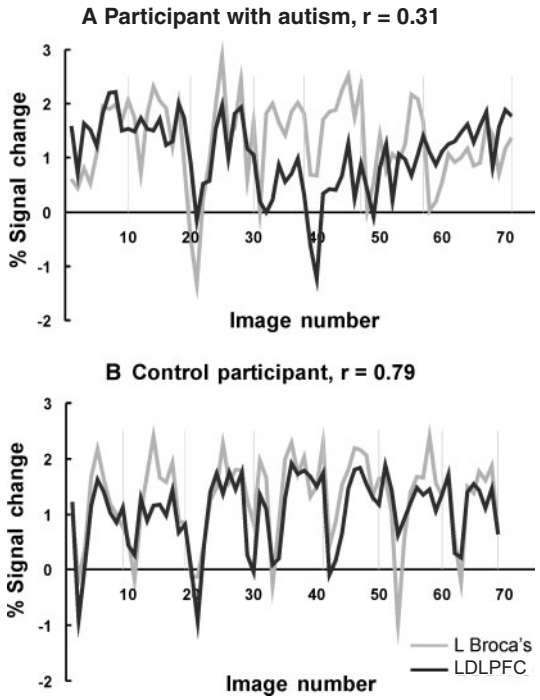


**Fig. 2** Examples of functional connectivity between LDLPFC and LIFG (Broca's area) in individual participants, shown as the activation time series in the two brain regions, with vertical bars indicating boundaries between seven epochs of sentences of the same type. (**A**) Autistic participant with low functional connectivity, $r = 0.31$, where the two time series do not closely track each other. (**B**) Control participant with high functional connectivity, $r = 0.79$, where the activation time series in the two regions is highly similar.

Fig. 1. (These analyses contrast sentence comprehension with the fixation baseline.) By contrast, in Broca's area (BA 44 and 45), it was the control group that showed more activation. This group difference in the left prefrontal area applied not only to Broca's area proper, but also to other adjacent areas, namely BA 47 (at the inferior portion of the left prefrontal activation) and in the middle frontal gyrus and precentral sulcus (at the superior portion of the prefrontal activation). When the comparison of the activation was restricted to Wernicke's and Broca's areas proper (by masking to grey matter within those areas), the autistic participants showed more activation (244 voxels) in Wernicke's than the control group (154 voxels). By contrast, in Broca's area, the autistic participants showed less activation (171 voxels) than the control participants (236 voxels). These differences in the distribution of activation between Wernicke's and Broca's areas between the groups were also verified in the direct group contrast. In this group comparison, there was an area in LSTG that was reliably more active in the autistic group than the control group but no area that was more active in the control group than the autistic group [$T(32) = 2.74$, $P < 0.005$]. Conversely, there was an area in LIFG that was reliably less active in the autistic group than the control group but no area that was less active in the control group than the autistic group [$T(32) = 2.74$, $P < 0.005$]. Thus the results reflect a difference between the two groups in the *distribution* of activation in Broca's area (and adjacent portions of LIFG) and Wernicke's area (left posterior STG and MTG).

With regard to activation in other areas, the two groups generally activated the same areas, with some exceptions, as shown in Table 1. Most notably, the control group showed more activation in secondary visual areas, encompassing bilateral occipitoparietal and occipitotemporal areas, such that the activation appears as one large cluster for this group. Two additional differences were that the control group showed larger clusters of activation in superior/medial frontal and right inferior frontal areas and only the autistic group showed activation of the left and right parahippocampal gyrus.

## *Functional connectivity*

The functional connectivity between pairs of ROIs was lower for the autistic participants than for the control group, as indicated by several types of statistical analyses. To illustrate the type of data on which the functional connectivity correlations are based, Fig. 2 shows the activation time series data for one autistic and one control participant for one pair of regions, showing that the time courses in the two regions are less similar to each other for the autistic as compared with the control participant.

When the functional connectivities of the two groups were compared in each ROI pair separately, every single one of the 10 reliable ($P < 0.05$) differences (out of 186 comparisons) showed a lower functional connectivity in the autistic group, as shown in Fig. 3. Although about nine differences might be

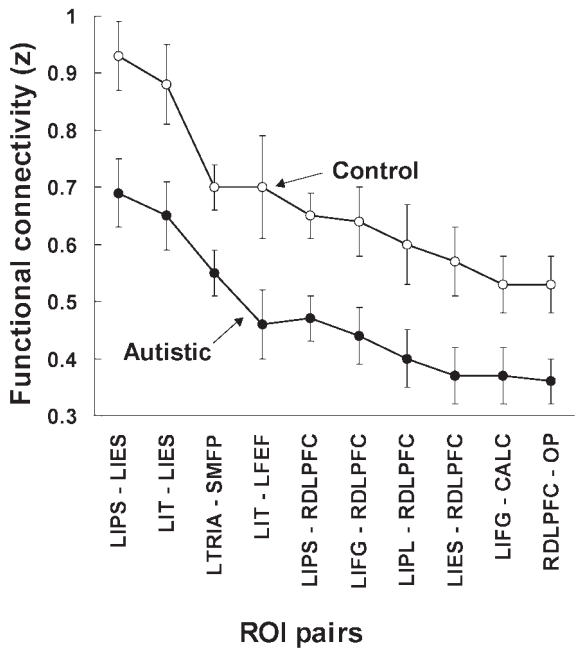


**Fig. 3** Functional connectivity for autistic and control participants in the 10 ROI pairs with a reliable ($P < 0.05$) difference between autistic and control participants (presented in descending order of mean connectivity). The pattern of functional connectivities across these 10 ROI pairs is very similar for the two groups ($r = 0.98$). Error bars represent the standard error of the mean. L = left; R = right; CALC = calcarine fissure; DLPFC = dorsolateral prefrontal cortex; FEF = frontal eye field; IES = inferior extrastriate; IFG = inferior frontal gyrus; IPL = inferior parietal lobe; IPS = intraparietal sulcus; IT = inferior temporal; TRIA = triangularis; OP = occipital pole; SMFP = superior medial frontal paracingulate.

expected to be reliable by chance, the uniform direction of difference is not expected by chance. The same uniform direction of difference (lower functional connectivity among the autistic participants) is also true for an additional 13 marginally reliably different ($0.05 < P < 0.075$) ROI pairs. Out of all 186 pairs, 147 (79%) showed this same direction of the difference in functional connectivity. When the functional connectivities of the two groups were compared with an ANOVA that included all ROI pairs as items, the autistic participants had a reliably lower mean connectivity (0.58) than control participants (0.61) [$F(1, 231) = 14.39$, $P < 0.01$]. Despite the lower inter-region functional connectivities in the autistic participants, the two participant groups nevertheless had a similar ordering ($r = 0.98$) of functional connectivities across the 10 reliably different ROI pairs, as shown in Fig. 3. (The correlation across all 186 pairs was 0.73.) The correlations indicate systematicity in the synchronization of both the autistic and control participants, but the levels of synchronization are lower in the autistic group.

Note that our analysis shows that the activation between two areas is less synchronized in the autistic group specifically at the time that they are doing the sentence comprehension and not in their alternation between comprehension and fixation. Note also that the lower functional connectivities (time series correlations) in the autistic group cannot be attributed to this group having a lower variance. The variance across time points (i.e. in the data on which the correlations were computed) was not globally or even locally lower for the autistic group. In fact, in a few ROIs, the autistic group had a slightly and generally non-reliably greater variance than the control group. The functional connectivity difference reflects the type of synchronization difference illustrated in Fig. 3.

### *Behavioural performance*

The behavioural results suggest that the autistic group performed the task faster and less accurately. The autistic participants had mean reaction times of 2456 and 2803 ms for the active and passive sentences, respectively. Control participants took reliably longer [$F(1,32) = 4.36$, $P < 0.05$] (3061 and 3447 ms). Error rates were 8 and 13% for the autistic group, which is slightly but not reliably higher than those of the control group (5 and 7%). These data are consistent with the interpretation that the group with autism is less proficient at semantically and syntactically integrating the words of a sentence, resulting in more errors for the more complex passive sentences.

## Discussion

This study showed systematic group differences between autistic and control participants with respect to the distribution of brain activation across the main language areas, and differences in functional connectivity between brain areas. The autistic participants showed significantly more activation in LSTG and significantly less activation in LIFG, as compared with control participants. A plausible interpretation of this finding is that, compared with controls, the autistic participants engage in more extensive processing of the meanings of the individual words that comprise a sentence, manifested as more LSTG (Wernicke's areas) activation, which is consistent with their hyperlexicality or unusual strength in processing single words (Goldstein *et al.*, 1994). At the same time, the autistic participants showed less activation in LIFG than the control group. LIFG (and pars triangularis in particular) is associated with semantic, syntactic and working memory processes (Petersen *et al.*, 1989, 1990; Fiez, 1997; Fiez and Petersen, 1998; Gabrieli *et al.*, 1998; Michael *et al.*, 2001), all of which serve to integrate the meanings of individual words into a coherent conceptual and syntactic structure. The reduced activation in this region is consistent with the finding that high-functioning autistic participants are impaired in their ability to process the meaning of complex sentences (Goldstein *et al.*, 1994). The autistic group's lower activation in yet another region, the occipito-parietal area, may also be consistent with this account, if this group engaged in less use of mental imagery of the event the sentence described. The use of mental imagery during sentence comprehension might be yet another way to form an integrated representation of the

meaning of a sentence (Just *et al*., 2004). In general, the results suggest that the brain in high functioning autistic individuals engages less in the integrative aspects of sentence processing than the brain in control participants.

The second main finding of this study was that the functional connectivity was lower throughout the cortical language system among the autistic participants than in the control participants, suggesting that the coordination and communication between cortical areas is lower in the autistic group. In another study that is currently being prepared for publication, a similar finding of lower functional connectivity in the autism group was obtained in a non-language task, namely in solving Tower of London problems. Thus, the functional connectivity finding is unlikely to be specific to language tasks but rather a general phenomenon of those neural systems affected in autism. Moreover, there are reports of similar lowered functional connectivity in schizophrenia (the disconnection hypothesis) (Lawrie *et al*., 2002).

The findings here entail a reduction in the integrative processing and an excessive focus on lower level lexical processing, as well as a reduced level of synchronization. This interpretation can account for the encapsulated cognitive strengths in autism observed in certain focused tasks, such as hyperlexic word reading, which may require relatively less coordination among cortical areas, as well as the poorer performance in tasks like sentence and story comprehension, which require larger-scale integration of cortical function. Specifically, the findings suggest that autism entails preservation and possibly enhancement of the function of individual cortical centres, but at the same time entails poorer integration of information at higher levels of processing that require more coordination among cortical centres. The dissociation between intact or enhanced simple abilities and impaired higher order abilities is a recurring profile across cognitive and neurological domains in autism including the motor, memory, language, abstract reasoning and probably also sensory domains (Minshew *et al*., 1997).

## *Underconnectivity theory*

We use the term 'underconnectivity' theory as a shorthand to refer to the underfunctioning of integrative circuitry and emergent cognitive, perceptual, and motor abilities in autism. We propose that autism is a cognitive and neurobiological disorder marked and caused by underfunctioning integrative circuitry that results in a deficit of integration of information at the neural and cognitive levels. The cognitive deficit in autism is most likely to arise when the task requires integrative processing (i.e. an emergent process) at a high level, regardless of the domain of the task. The theory predicts that any facet of psychological or neurological function that is dependent on the *coordination* or *integration* of brain regions is susceptible to disruption, particularly when the computational demand of the coordination is large.

The underconnectivity framework can account for the social symptoms of autism. Social interactions place large (if not the largest) demands on information integration. This model attributes social abnormalities in autism to a deficit in integrative processing. Abnormalities may arise in integrating the perceptual and affective processing of social stimuli such as face affect and prosody with language with the concurrent theory of mind processing to determine the social partner's intentions. The rapidly changing dynamics of social interaction, frequently involving several people, could put enough strain on the integrative processing to compromise both the quality of the interaction as well as concurrent cognitive processing. The deficit in theory of mind that occurs in autism (Baron-Cohen *et al*., 1985) could itself be the outcome of such a deficit in integrating social and cognitive processing. In addition, having a theory of someone else's mind requires a high level abstraction (computing a second world-view besides one's own), which could impose a large demand on high level integration processes on its own. Thus, the underconnectivity theory can extend to the entire cognitive and social profile in autism.

The underconnectivity could explain the difficulty in novel cognitive tasks wherever inter-regional coordination is critical. A novel task requires the underpinning brain regions to dynamically configure themselves into an appropriate network, and the poorer connectivity in autism impairs this dynamic ability. (The compensatory strategy that often arises in autism under such circumstances is a reversion to relying on a previously learned rule-based system.)

Another example of a larger role of inter-regional coordination might occur where a change or shift in strategy is required, such that control of processing has to shift from one network organization to another. A third example where inter-regional coordination would be important is one in which a new, overt strategy or plan has to be formulated, such that the prefrontal executive area flexibly controls a network of brain regions.

The cognitive deficit in autism is most likely to arise when the task requires integrative processing or abstraction at a high level, regardless of the domain of the task. The theory predicts that any facet of psychological function that is dependent on the *coordination* or *integration* of brain regions is susceptible to disruption, particularly when the computational demand of the coordination is large. Tasks that require a large contribution from integrating, frontal regions might be particularly susceptible in autism. At the same time, it is possible for a person with autism to attain excellent and even extraordinary cognitive successes. In such cases, underconnectivity theory would predict normal or higher functional connectivity than for control participants, and with less reliance on frontal, integrating centres.

## *Related neurobiological indices*

The proximal biological cause(s) of the altered levels of brain activation and functional underconnectivity could be either in grey or white matter or both. In the grey matter, there may simultaneously be a disruption of local and distant circuit organization in highly specialized grey matter, leading to

abnormal specializations. The underfunctioning or disorganization of white matter tracts could be accompanied by underfunctioning of the inter-regional communication processes that make use of these tracts. All of these postulated abnormalities may arise together, and there is no current consensus on which if any of them is central or causal. The most visible behavioural consequence of the altered brain activation and functional underconnectivity is a swath of cognitive and social deficits in those processes that especially depend on inter-regional coordination and integration. Below, we offer some speculations of how the underconnectivity might be related to abnormalities observed at a more granular neurological level.

At the neurobiological level, a number of findings of brain growth dysregulation in autism have been reported that could be the basis of the altered pattern of fMRI activity and functional underconnectivity. This was initially apparent in the increased occurrence of megalencephaly and the increased mean head circumference for autistic children. Subsequently, Courchesne *et al*. (2001) found that by 2–4 years of age, total brain volume was larger than normal in the MRI scans of autistic boys. [In a recent study of head circumferences rather than brain volume, Courchesne *et al*. (2003) reported a below average head circumference at birth and two phases of accelerated brain growth one between 1 and 2 months of age and a second between 6 and 14 months of age.] The volume increase affected cerebral grey matter (12%), cerebral white matter (18%) and cerebellar white matter (39%). Sparks *et al*. (2002) similarly found an increase in total brain volume in 3–4-year-old children with autism spectrum disorder relative to typically developing and developmentally delayed children but measurements of grey and white matter volumes were not reported. Aylward *et al*. (2002), studying 8–47 year olds, found that larger brain volume of the children with autism eventually 'normalized' when their brain growth reached a plateau, whereas the growth in the normal controls continued. Herbert *et al*. (2003) found the same trend in white matter increase in older autistic boys, aged 7–11 years, but found a reduction in cerebral grey matter volume. They also found regional differences in volume relationships with cerebral cortex and hippocampus and amygdala as one (reduced in size), white matter as a second (increased in size), and basal ganglia, cerebellum and diencephalons as a third (no change). The relevance of such volume difference findings is that 'The altered relationship between volumes of regions . . . suggests compromise in the optimality of connectivity in these autistic brains' (Herbert *et al*., 2003).

It is not known whether the white matter abnormalities in autism arise from a growth dysregulation or excessive preservation of unneeded connections. Most of the knowledge about white matter dysfunction comes from acquired damage such as cerebral palsy or disorders such as multiple sclerosis. The relationship of developmental abnormalities such as those seen in autism to abnormalities in cerebral cortex and information processing patterns have yet to be understood. Casanova *et al*. (2002) has reported abnormalities in the unit of vertical organization in the cerebral cortex in which there is an increase in the number and packing density of the minicolumns. He hypothesizes that this would lead to an increase in white matter both locally and over distance to maintain connectivity between these neuronal units.

The abnormal activity observed in fMRI is located in cortex and is presumed to reflect alterations in neuronal function. These alterations have now been observed in autism with language processing in this study, face processing (Schultz *et al*., 2000) and theory of mind studies (Castelli *et al*., 2002) representing multiple areas of cortex and reliance on interconnecting regions. Until the report of Casanova *et al*. (2002), there were no reports of neuroanatomic abnormalities in the cerebral cortex in autism, though functional evidence from seizures, executive dysfunction, language dysfunction and mental retardation are relied on in neurology as typical though not exclusive signs of grey matter dysfunction.

## *Relationships to other theories*

The most closely related other theory of autism is Frith's theory of weak central coherence (Frith, 1989). Below we point out the continuity with this and other theories, and describe the added contributions of underconnectivity theory and their potential value.

Frith's central coherence theory (Frith, 1989) proposed a compelling analogy between the flow of thought and the flow of a river which imposes coherence among contributing streams or inputs, with autism having weaker central coherence. One of the reasons that central coherence theory has been so influential is that it made sense of the focus on details at the expense of developing a more integrated representation, which we have seen is consistent with the underconnectivity view.

Although central coherence theory provided a useful framework in its time, it was (and remains) fundamentally an analogy between mental processes and phenomena in a hydraulic system. The excellence of the analogy distracts from the theory's absence of a plausible underlying mechanism. By contrast, underconnectivity theory squarely targets underlying biological structures and processes, and links them, albeit somewhat loosely, to psychological processes. Note that underconnectivity also predicts weak coherence among ongoing processes, by virtue of poorer communication and collaboration among them.

Many of Frith's elaborations or assumptions that accompany her theory go beyond the analogy, and some of these elaborations can be contrasted with underconnectivity theory. One of her assumptions is that in normal people, the high level (central) processes impose coherence on lower level (peripheral) processes. More specifically, the attribute of coherence is assumed to be imposed and monitored by some central part of the system. By contrast, underconnectivity theory treats the coherence as an emergent property of the collaboration among brain centres. The coherence arises by virtue of the coordination among the processes, and does not have to be imposed by

an external mechanism. To use an analogy, central coherence theory construes thought as the product of a symphony conducted by a conductor, and the conductor does a poor job in the case of autism. By contrast, underconnectivity theory construes thought as a product of a jam session, and the communication (say, the ability to hear each other) among musicians is poorer in the case of autism. One caveat is that even underconnectivity acknowledges the possible conductor role of the prefrontal executive system in some strategically controlled forms of thought. Furthermore, underconnectivity theory is much more than an analogy in its proposal that the inter-centre communication is impaired in autism.

Another difference is that central coherence theory does not explicitly decompose the cognitive system into its components and furthermore implies that, in autism, the components are normal except for the weak coherence among them. By contrast, underconnectivity theory postulates that the components of the cognitive system correspond to cortical centres, each with a set of specializations, and furthermore, that in autism, the specializations are abnormal in that they are tuned to more autonomous and less collaborative inter-centre processing. In other words, the underconnectivity is presumed to foster the development of a less integrated, more autonomous set of processing centres.

In more recent work with her neuroimaging colleagues, Frith has attempted to apply the concept of weak central coherence to the brain activity level. In very recent articles (Castelli *et al*., 2002), for example, Frith and her colleagues say that the lack of coherence is seen between brain regions and is expressed in reduced connectivity and synchrony. Castelli and colleagues show that the correlation between the activity level of two involved brain regions is correlated across participants to a lower degree across autistic than control participants. Although we agree with the prediction, it is difficult to relate it to any mechanism arising from the river analogy. The result is entirely consistent with underconnectivity theory.

Underconnectivity theory goes on to predict impairments in motor function, memory, and expressive nonverbal language (such as hand gestures and facial expressions), and to virtually all cortically mediated functions. Wherever inter-region connectivity and coordination come into play, an underconnected system can manifest impairments, particularly when there is a large load on the system. It is difficult to see how abnormal prosody, facial expression and motor function can be explained in terms of central coherence. Frith describes these phenomena in terms of a communication shortcoming that fails to take a conversation partner's perspective into account. Although we agree with elements of that description, we have proposed how the phenomena could arise out of underconnectivity, but it is more difficult to meaningfully relate them to central coherence theory.

In summary, central coherence theory provided a useful organizing analogy that was applicable to a broad range of phenomena in autism. Underconnectivity theory makes the same clinical sense as weak central coherence, but additionally proposes a set of underlying neurobiological mechanisms that relate the biological and psychological levels, providing the theory with substantial generative and integrative power.

The new fMRI functional connectivity data provide a link from brain activity to Minshew *et al*.'s theory of autism (Minshew *et al*., 1997) as a disruption of complex information processing. This model attributed the disorder to a fundamental abnormality in the handling of information in high level tasks, particularly those requiring abstraction. Abstraction refers to generating a representation at a level higher than a previous one, and that abstraction presumably required the increased involvement of additional brain areas. Moreover, Minshew *et al*. (1989) proposed that autism was a non-focal, systemic disorder of the brain that affected a wide range of high level tasks, including motor function, memory, language and abstraction, which all made a high demand on information processing resources.

Underconnectivity theory enriches Minshew's previous statements of the theory with the new findings from fMRI, thus linking the information processing abnormalities to a specific neurobiological phenomenon, the brain connectivity itself. This new view of the basis of autism stands on the shoulders of previous proposals. It makes sense of some of the lack of convergence of many previous findings, makes good contact with clinical observations, and provides a link between cognition and brain function.

We conclude with a comment relating theories of autism with theories of normal brain function. Brain function has sometimes been construed as a collaboration of a confederation of processing centres. These fMRI findings suggest that, in autism, the confederation is loosened or underdeveloped. This construal can account for the observations that autism can entail mastery of detail, narrow attentional focus, and difficulty in higher-level abstraction of many types of information. The impairment in social interaction in autism may, for example, be an outcome of a lack of integration of different types of information at a high level (e.g. facial expression, personal intent, social games, and so on).

The abnormal specialization of the neocortical processing centres could be due to excessive preservation of elementary circuitry (an intra-centre disturbance) in combination with a deficiency in the development of integrative circuitry (an inter-centre disturbance). These are maturational processes that normally develop in tandem, and the explanation of the disturbance is likely to be found in developmental neurobiological processes. A processing centre that has inadequate connectivity to another centre with which it would normally collaborate might develop processing algorithms that are less dependent on collaborative input and hence might become 'hyperspecialized'. The causality of the deficit could also be in the opposite direction, such that centres that inherently develop more self-reliant algorithms might also develop weaker connections to other centres. In either case, the outcome is manifested as deficient higher order cognitive processes, reduced fMRI activation of regions performing integrative processing during

complex tasks, reduced synchronization, and a local processing approach to cognitive challenges.

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