Deviant Functional Magnetic Resonance Imaging Patterns of Brain Activity to Speech in 2–3-Year-Old Children with Autism Spectrum Disorder

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Background: A failure to develop normal language is one of the most common first signs that a toddler might be at risk for autism. Currently the neural bases underlying this failure to develop language are unknown.

Methods: In this study, functional magnetic resonance imaging (fMRI) was used to identify the brain regions involved in speech perception in 12 2–3-year-old children with autism spectrum disorder (ASD) during natural sleep. We also recorded fMRI data from two typically developing control groups: a mental age-matched (MA) ($n = 11$) and a chronological age-matched (CA) ($n = 12$) group. During fMRI data acquisition, forward and backward speech stimuli were presented with intervening periods of no sound presentation.

Results: Direct statistical comparison between groups revealed significant differences in regions recruited to process speech. In comparison with their MA-matched control subjects, the ASD group showed reduced activity in an extended network of brain regions, which are recruited in typical early language acquisition. In comparison with their CA-matched control subjects, ASD participants showed greater activation primarily within right and medial frontal regions. Laterality analyses revealed a trend toward greater recruitment of right hemisphere regions in the ASD group and left hemisphere regions in the CA group during the forward speech condition. Furthermore, correlation analyses revealed a significant positive relationship between right hemisphere frontal and temporal activity to forward speech and receptive language skill.

Conclusions: These findings suggest that at 2–3 years, children with ASD might be on a deviant developmental trajectory characterized by a greater recruitment of right hemisphere regions during speech perception.

Key Words: Development, fMRI, language, laterality, pediatric, sleep

A striking disparity in language development between autistic and typical children is seen by the second year of life (1). In fact, a delay in language is often one of the first warning signs to parents and clinicians that a child might be at risk for autism (2,3). Language impairments in autism can be severe with approximately 50% percent of individuals never acquiring functional language (4). Those autistic children who do develop functional language commonly show impairments in semantic and pragmatic aspects of language, such as use of prosody, pronoun, or inferring intentions of the speaker, whereas structural aspects, such as syntax and grammar, more often seem relatively less impaired (5), although more recent evidence suggests some children with autism do show structural impairments as well (6). Although much research has elucidated the behavioral characteristics of language impairments (for review see [7]), remarkably little is known about the neural bases of language abnormalities in autism, particularly at young ages.

The extant functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) studies examining the neural bases of language processing in autism have all been conducted with relatively high-functioning older children and adults (8–13), except one in which sedation was used with children 4–10 years of age (14). In general, these studies reveal an abnormal frontal and/or temporal response during language processing in autism, and some show a pattern of reduced or reversed laterality in frontal cortex (8–11). Although these studies have advanced our understanding of brain abnormalities underlying language processing at a middle or end point of development, the findings might not reflect the initial brain abnormalities at the time of the emergence of the disorder or brain abnormalities of children on the lower-functioning end of the autism spectrum. Much evidence suggests that deviant patterns of brain structure are not only greater at younger ages but might also be different than at older ages in autism (15–21). For example, whereas amygdala volume and neuron number is normal or reduced at older ages, amygdala volume is increased at younger ages (19,22–26), suggesting neurobiological processes in the initial phase of autism might be unique.

Only one study has examined the neural correlates of linguistic processing in children as young as 3 years of age with autism spectrum disorder (ASD) (27). In that study, presentation of deviant phonemes failed to elicit an event-related potential (ERP) index of sound discrimination, the mismatch negativity (MMN), in children with autism. Interestingly, studies of older children with autism revealed an intact MMN response to phonemes but reduced P3a amplitude as compared with typical children (28–30). In sum, limited functional evidence from very young children with ASD also suggests that the neural bases of autism need to be addressed from a developmental perspective, because brain activation patterns from the older child and adult with autism might not necessarily reflect those of the younger child. Electrophysiological studies lack the whole brain resolution afforded by fMRI methods. Thus, a critical question remains: what are the specific neural structures underlying language impairments in autism at the time the disorder is first reliably identified and diagnosed, namely at 2–3 years of age?

The paucity of functional neuroimaging from very young children with autism is likely due to the difficulty in acquiring

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Received September 10, 2007; revised May 1, 2008; accepted May 24, 2008

0006-3223/08/$34.00
doi:10.1016/j.biopsych.2008.05.020

Table 1. Participant Information

ID	Gender	Age (mo)	Receptive Language Age Equivalent	Visual Reception Age Equivalent	Composite Score	Receptive Language T-Score	Visual Reception T-Score
			ASD Group				
ASD1	M	25.7	10	13	54	20	20
ASD2	M	26.5	10	17	54	20	27
ASD3	M	29.7	18	25	75	29	43
ASD4	M	30.3	14	23	68	20	34
ASD5	M	30.3	5	18	45	<20	20
ASD6	M	31.8	6	15	54	<20	20
ASD7	M	32.1	10	15	30	<20	20
ASD8	M	36.2	9	17	44	<20	20
ASD9	M	41.0	18	25	60	<20	20
ASD10	M	41.9	23	21	51	20	24
ASD11	M	46.5	25	25	54	<20	20
ASD12	M	46.9	36	33	68	35	27
n = 12	12M	34.9 (7.4)	15.3 (9.1)	20.6 (5.8)	54.8 (12.2)	24.0 (6.5)	24.6 (7.3)
			MA Group				
MA1	M	13.1	9	12	89	35	46
MA2	M	14.5	8	12	80	31	46
MA3	M	14.3	23	26	90	47	56
MA4	M	16.3	24	18	134	72	57
MA5	F	20.3	14	19	107	54	53
MA6	M	21.2	23	16	87	56	36
MA7	M	22.5	28	24	124	65	56
MA8	M	22.9	25	21	105	58	47
MA9	F	22.9	28	31	110	59	65
MA10	M	23.8	18	27	85	32	55
MA11	M	23.9	23	21	91	47	43
n = 11	9M 2F	19.6 (4.2)	20.3 (7.1)	20.6 (6.1)	100.2 (17.3)	50.6 (13.5)	50.9 (8.1)
			CA Group				
CA1	F	24.8	30	21	105	63	43
CA2	F	30.5	30	26	92	49	42
CA3	M	31.1	31	39	103	49	63
CA4	M	34.0	39	52	121	56	77
CA5	M	35.2	39	41	111	56	60
CA6	M	36.4	47	39	123	68	56
CA7	M	35.4	39	46	118	56	67
CA8	M	36.9	36	27	82	47	29
CA9	F	38.0	44	43	121	58	58
CA10	M	38.9	36	45	125	57	72
CA11	M	41.5	62	50	132	76	63
CA12	F	44.7	[a]	[a]	[a]	[a]	[a]
n = 12	8M 4F	35.7 (5.3)	39.4 (9.3)	39.0 (10.2)	112.1 (15.2)	57.3 (14.2)	55.3 (13.3)

Mean and SD are given for each of the three groups separately. T-scores and Age equivalent scores are taken from the subscales Mullen Scales of Early Learning. Composite score reflects the composite of the four subtests of the Mullen: Visual Reception, Fine Motor, Receptive and Expressive Language. The standardized mean is 100.

ASD, autism spectrum disorder; MA-matched, mental age-matched control; CA-matched, chronological age-matched control.

[a]Behavioral testing was not available from CA12 with 2 months of fMRI acquisition.

such data. Previous work by our group (31,32) and others (33–35) have identified reliable fMRI activation patterns during presentation of auditory stimuli during natural sleep in infants, toddlers, and very young children. In a previous fMRI study we identified age-related changes in the Blood Oxygenated Level Dependent (BOLD) response between typically developing toddlers and 3-year-old children during presentation of text passages in sleep (31). In that study, the 3-year-old group used primarily bilateral superior temporal and parietal regions to process forward speech as compared with no sound presentation, whereas the toddler group recruited a large number of cortical and subcortical brain regions. We suggest that these regions might be part of an extended network of brain activation here and in our previous paper (31), although the extent to which these regions are functioning as a network has not been directly tested. We raised the possibility that this hypothesized network of regions in toddlers might reflect the state of a young brain that has not yet become specialized for language but rather

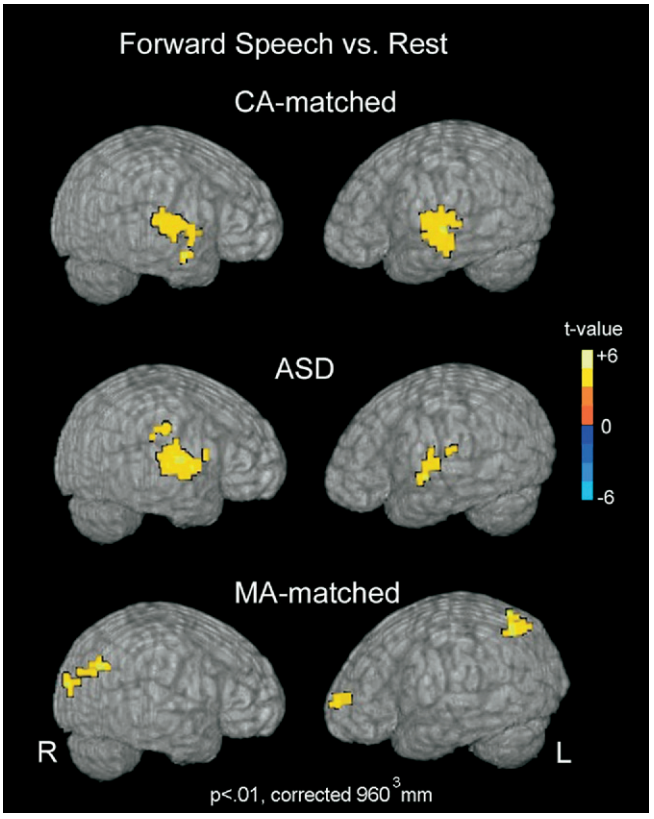

Figure 1. Forward speech versus rest. Group activation maps for the forward speech as compared with rest conditions are shown for each group. Activation maps are projected onto the surface of a rendered brain from a single representative subject. Data are presented at an intensity of $p < .01$ and voxel-wise cluster correction of 960 mm^3. CA-matched, chronological age-matched; ASD, autism spectrum disorder; MA-matched, mental age-matched; R, right; L, left.

is poised and ready to acquire language through social, attention, and other systems that are available.

In this study, we presented the same speech paradigm used in the Redcay *et al.* study (31) to 2–3-year-old children with a provisional diagnosis of ASD during sleep. The design contained both a mental age-matched typically developing control group (MA) to control for the effects of language skill and a chronological age-matched (CA) typically developing control group to control for the effects of maturation. These control groups largely overlapped with the toddler and 3-year old groups in our previous report (31). The goal of the study was to determine whether the ASD group would show an extended network pattern of brain activation like their MA-matched control subjects or whether activity would be specialized to superior temporal regions like that seen in the CA-matched control subjects.

Methods and Materials

Participants

Twenty-three children between 2 and 3 years of age with a provisional diagnosis of ASD participated in the current study. Children with ASD were recruited from the San Diego Regional Center, Rady Children's Hospital toddler school, online advertisements and parent groups, the University of California at San Diego (UCSD) autism research program, and flyers. For details on diagnostic information for the ASD group see text and Table 1 in Supplement 1.

Of the 23 children, 8 were unable to fall or stay asleep in the scanner, even after 3 separate nights of repeated attempts. Thus, functional and structural MRI data were acquired from 15 children with provisional ASD. Of these 15, 1 child's data were discarded due to motion artifacts and 2 children did not meet criteria for autistic disorder or ASD on the Autism Diagnostic Interview–Revised on follow-up assessments at 3 years of age. In sum, reliable fMRI data were acquired from a total of 12 participants with ASD (11 autism disorder, 1 ASD) (Table 1).

Two control groups of typically developing children were recruited: a chronological age-matched group (CA) and a mental age-matched group (MA). The chronological age-matched group was matched to the autism group on the basis of mean chronological age. The mental age-matched group was younger than the ASD group. In this way, the mean mental age, as determined by the receptive language (RL) age equivalent score from the Mullen Scales of Early Learning, was similar in both groups (Table 1). Mental age-matching was done as the best approximation of language level, because the very low language skill of one-half the autism group (T score < 20) makes the measure of receptive language age-equivalent less reliable. For both control groups, a portion of the subjects were included in our prior publication examining speech perception in typical development with the same paradigm and protocol as the current study (31). Data from six additional control participants were included in the present study to provide closer matching in chronological age and mental age for the CA and MA groups, respectively.

All participants received behavioral assessments including the Mullen Scales of Early Learning and the Vineland Adaptive Behavior Scales. Additionally, several parent-report questionnaires were obtained, including the MacArthur-Bates Communicative Developmental Inventory (CDI) and a family medical history questionnaire. The Institutional Review Board of Children's Hospital and the University of California, San Diego approved this study. Informed written consent was obtained from the parents, and they were compensated monetarily for participation.

Stimuli and Design

Participants were presented with the same auditory stimuli in the same design as in our previous study (31). These stimuli consisted of three stimulus conditions: 1) Forward speech, simple (F:s); 2) Forward speech, complex (F:c); and 3) Backward speech (B). For details see text in Supplement 1. Stimuli were presented in a block design in which each condition was presented for 20 sec and followed by 20 sec of "rest" (no auditory stimulus presented).

Data Acquisition

Images were acquired on a 1.5 Siemens Symphony scanner at the UCSD Hillcrest Medical center. Whole brain axial slices were collected with a gradient recalled echo planar sequence (EPI) (repetition time = 2500 msec; echo time = 35 msec; flip angle = 90°; field of view = 25.6 mm; 64 × 64 matrix [4 × 4 mm in-plane resolution], number of slices = 30; slice thickness = 4 mm; 154 volumes acquired). A T1-weighted anatomical image in the coronal plane with an magnetization-prepared rapid gradient-echo sequence was collected before fMRI scanning for co-registration with the functional images (field-of-view = 22.8 mm; matrix = 256 × 256; 128 slices; .89 × .89 mm in-plane resolution; slice thickness = 1.5 mm).

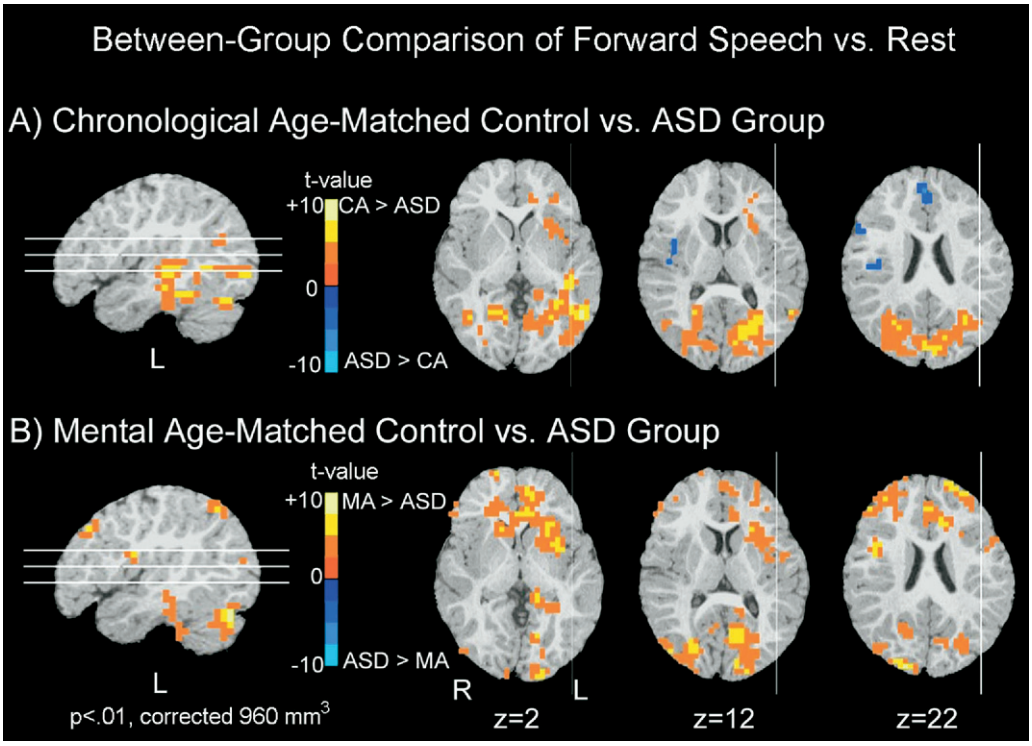

Figure 2. Between-group comparison of forward speech versus rest. Significant differences in activation to forward speech versus rest between the ASD group and the two control groups (MA-matched and CA-matched) are shown. Regions in blue depict regions in which the ASD group showed significantly greater activity than either the CA (**A**) or MA (**B**) control groups. Conversely, regions shown in red are ones in which either the MA or CA group showed greater activation than the ASD group. In comparison with the CA-matched group, the ASD group recruited medial and right frontal regions to a greater extent, whereas the CA-matched group recruited greater left frontal, temporal, and bilateral posterior regions than the ASD group. In comparison with the MA-matched group, the ASD group showed reduced activity in a number of brain regions. Data are represented on a brain image from a single subject. Abbreviations as in Figure 1.

Data Analyses

All analyses were performed with the Analysis of Functional NeuroImages (AFNI) software (36). Several pre-processing steps were performed before individual general linear model analyses. Each dataset was time shifted to account for slice time-offsets in volume acquisitions. Motion correction was performed with an automated volume alignment program that registered each volume to a specified volume in the time series with an iterative time series. The middle volume of the run was chosen as the reference volume unless signal outliers or motion were detected within the middle volume. Data points not correctable by head motion were censored from the analyses (see Supplement 1). Images were spatially smoothed with a smoothing kernel of 6 mm at full-width-at-half-maximal (FWHM).

A general linear model analyses was conducted to fit the individual time series to an ideal hemodynamic response function (γ variate). The first two volumes in each data series were removed to compensate for T1 equilibration effects. Motion covariates were included in the general linear model to model noise due to movement in three rotational (x, y, z) and three translational (roll, pitch, yaw) planes. The mean and linear trends were included in the general linear model. A general linear test was included to obtain a main effect of forward speech (F) by modeling the amplitude response to both F:s and F:c. A general linear test was also included to contrast forward and backward speech. For this report, discussion of forward speech will refer to the collapsed "F" condition rather than the separate F:s and F:c analyses. The linear contrast coefficient for each condition was converted to percent signal change by calculating the percent difference from the baseline model.

Before group analyses, each individual's data from the general linear model analyses were registered into standard Talairach space through a 6-parameter affine transformation based on landmarks identified from the high-resolution anatomical image. Because brain anatomy differs in young children from an adult template, we conducted pilot studies to determine the fidelity of anatomical co-registration for two anatomical landmarks in a group of typical toddlers, 3-year-old children, and adults as well as autistic 2–3-year-old children. See Supplement 1 for discussion.

Group analyses were conducted both within group and between groups with repeated measures analyses of variance (ANOVAs). For within-subject group analyses, a one-way ANOVA was run for each group separately with condition as the repeated measure. For the between-group analyses, a repeated-measure ANOVA was run with the ANOVA program in the AFNI Matlab package. Contrasts were run within each group (ASD, CA, MA) to contrast percent signal change values between the forward (F) and backward (B) speech conditions. Additionally, contrasts were run to identify differences between the ASD group and the two control groups (MA and CA) separately for both the forward and backward speech conditions.

To directly test whether hemispheric asymmetries were present during processing of forward speech, a whole-brain, voxel-wise, paired *t* test was performed within each group. The *t* test compared percent signal value in the forward speech

Table 2. Between Group Comparisons

Region	Side	BA	Talairach Coords (x,y,z)	*t* Value
MA > ASD				
Frontal				
Anterior Cingulate Cortex	L	24	(−6,31,3)	5.93
Anterior Cingulate Cortex	R	24	(14,34,−1)	4.40
Medial Frontal Cortex	L	32	(−11,46,8)	5.12
Medial Frontal Cortex	R	32/9	(2,36,23)	4.23
Superior Frontal Gyrus	R	9	(29,38,28)	5.52
Superior Frontal Gyrus	L	9	(−28,43,26)	5.07
Superior Frontal Gyrus	R	6	(18,−3,55)	4.61
Superior Frontal Gyrus	R	10	(18,62,14)	4.29
Cingulate Gyrus	R/L	31	(2,7,31)	4.61
Orbitofrontal Gyrus	L	11	(−19,23,−16)	5.65
Orbitofrontal Gyrus	R	11	(22,27,−18)	4.79
Middle Frontal Gyrus	R	10	(38,47,16)	3.74
Inferior Frontal Gyrus	R	46	(50,34,11)	3.22
Precentral Gyrus	R	4	(41,−1,27)	4.98
Precentral Gyrus	L	4	(−43,−6,19)	4.19
Insula	L		(−33,2,3)	4.43
Temporal				
Parahippocampal Gyrus	R	35	(33,−24,−13)	3.53
Parahippocampal Gyrus	L	30	(−22,−42,−1)	4.53
Inferior Temporal Gyrus	L	20	(−46,−33,−20)	4.39
Parietal				
Superior Parietal Lobule	L	7	(−9,−42,43)	3.55
Superior Parietal Lobule	R	7	(9,−41,43)	4.95
Angular Gyrus	L	39	(−35,−73,38)	4.11
Precuneus	L	7	(−8,−62,35)	4.04
Precuneus	R	7	(15,−88,31)	3.51
Occipital				
Cuneus	R	19	(18,−89,26)	6.27
Cuneus	L	18	(−5,−69,14)	5.45
Lingual Gyrus	L	18	(−15,−86,−5)	4.88
Subcortical				
Cerebellum	L		(−37,−70,−20)	8.20
Cerebellum	R		(34,−51,−29)	3.99
Caudate	R		(13,19,−1)	4.45
CA > ASD				
Frontal				
Anterior Cingulate Cortex	L	24	(−10,28,–6)	4.71
Middle Frontal Gyrus	L	10	(−29,39,3)	3.52
Insula	L		(−30,12,0)	4.57
Temporal				
Superior Temporal Gyrus	L	22	(−43,−30,2)	5.66
Middle Temporal Gyrus	L	37	(−50,−55,3)	6.03
Fusiform Gyrus	L	37	(−42,−38,−13)	5.22
Parahippocampal Gyrus	L	36	(−28,−45,3)	4.79
Inferior Temporal Gyrus	R	20	(43,−33,−12)	4.70
Inferior Temporal Gyrus	L	37	(−45,57,−16)	4.25
Parietal				
Superior Parietal Lobule	R	7	(25,−73,39)	6.14
Superior Parietal Lobule	L	7	(−28,−57,42)	6.40
Posterior Cingulate	L	30	(−22,−65,11)	5.68
Inferior Parietal Lobule	R	40	(33,−47,43)	4.47
Cingulate Gyrus	L	31	(−11,−29,44)	5.29
Occipital				
Lingual Gyrus	R	19	(17,−54,−1)	5.08
Cuneus	L	18	(−10,−82,16)	5.63
Cuneus	L	19	(−10,−81,35)	5.68
Subcortical				
Cerebellum	R		(33,−54,−21)	5.25
Cerebellum	L		(−33,−65,−16)	7.65
ASD > MA				
Parietal				
Postcentral Gyrus	R	3	(38,−29,56)	−3.69
Postcentral Gyrus	L	3	(−38,−32,52)	−3.93
ASD > CA				
Frontal				
Medial Frontal Gyrus	R	32/9	(2,45,19)	−4.67
Inferior Frontal Gyrus	R	44/9	(49,15,31)	−4.31
Insula	R		(37,−9,15)	−4.50
Parietal				
Postcentral Gyrus	R	43	(41,−18,28)	−3.88

The peak *t* value and Talairach coordinate is given for each region or Brodmann Araa (BA) showing significant activity. Coords, coordinates; other abbreviations as in Table 1.

condition of each voxel in one hemisphere with that of the corresponding voxel in the contralateral hemisphere. This analysis revealed voxels in which the response to forward speech was significantly greater in one hemisphere than the other across the group. This analysis was conducted for the ASD and CA groups separately.

Due to the large variability in behavioral and clinical measures in the ASD group, exploratory correlations were run with the ASD group to determine whether the response to forward speech varied by behavioral and clinical measures. These measures included the receptive language age-equivalent (RL age) measures from the Mullen Scales of Early Learning and autism severity score from the Childhood Autism Rating Scale (CARS).

Results

Response to Forward Speech

The group-averaged BOLD response to forward speech as compared with no sound presentation is shown in Figure 1 for each of the 3 groups at $p < .01$, corrected at 960 mm^3. For details, see Supplement 1.

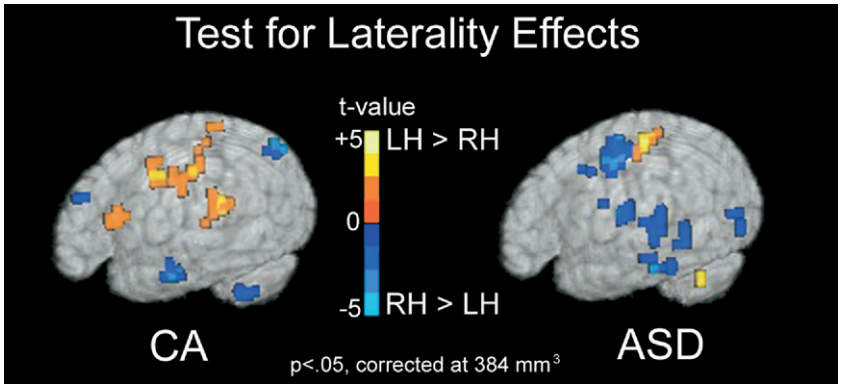

Figure 3. Test for laterality effects. Regions showing a trend toward hemispheric asymmetry in response to forward speech are shown for both the chronological age-matched (CA) and autism spectrum disorder (ASD) groups separately. Regions in red are those in which the left hemisphere (LH) voxels were significantly > the right. Regions in blue are those in which voxels in the right hemisphere (RH) were significantly > the left. In the ASD group, a number of regions show a trend toward greater right than LH activation (blue). The CA group shows a trend toward greater left than right hemisphere activation (red) in inferior frontal and superior temporal regions. Maps are show at an intensity threshold of $p < .05$ and a cluster threshold of 384 mm^3 and displayed on a single subject's rendered brain image.

ASD Versus MA-Matched Response to Forward Speech

In direct statistical comparison with the MA group, the ASD group showed reduced activity within an extended number of brain regions, including regions within bilateral frontal, temporal, parietal, and occipital lobes, cerebellar cortex, and right caudate (Figure 2, Table 2). The only regions showing a greater response to forward speech in the ASD than the MA group were bilateral postcentral gyri.

ASD Versus CA-Matched Response to Forward Speech

In comparison with the CA-matched group, the ASD group recruited a greater number of right hemisphere (RH) frontal and parietal regions [frontal: right medial frontal gyrus, $t = 4.67$; right inferior frontal gyrus, $t = 4.31$; right insula, $t = -4.5$; parietal: right postcentral gyrus, $t = 3.88$]. In direct statistical comparison with the ASD group, the CA-matched control group recruited a greater number of both left hemisphere (LH) frontal and temporal regions [frontal: left anterior cingulate, $t = 4.71$; left middle frontal gyrus, $t = 3.52$; temporal: left superior temporal gyrus, $t = 5.66$; left middle temporal gyrus, $t = 6.03$; left fusiform gyrus, $t = 5.22$]. The CA-matched group additionally recruited greater bilateral posterior regions within parietal, extrastriate, and cerebellar cortices (Figure 2, Table 2) in comparison with the ASD group.

Laterality Analyses for ASD and CA Groups

To directly test whether differences in laterality are found within the ASD and CA groups, we ran a paired t test between hemispheres within the ASD and CA groups for the response to forward speech as compared with rest. The results reported were significant at a trend level ($p < .05$, corrected at 384 mm^3). For the ASD group, there was a trend toward greater RH than LH activation within a number of frontal, temporal, occipital, and parietal regions as well as the caudate nucleus. There was a trend for the CA-group to show overall greater LH than RH activation within frontal, temporal, and parietal regions (Figure 3, Table 3).

Speech-Specific Response

The ASD group showed a greater response to forward as compared with backward speech within bilateral superior temporal gyri and right precentral gyrus (Figure 4, Supplement 1). The CA group also recruited superior temporal regions to a greater extent during forward speech presentation than backward speech (Figure 4, Supplement 1). However, activations in the left superior temporal regions did not reach significance at a cluster volume of 960 mm^3 in the CA group. The MA group recruited a number of regions throughout cortical and subcortical regions. For a full list see Supplement 1.

It is interesting to note that whereas the CA group recruited robust bilateral superior temporal regions during presentation of backward speech as compared with rest, the MA and ASD groups did not (Supplement 1). This difference could account for the reduced discrimination between forward and backward speech in the CA group. See text in Supplement 1 for further discussion.

Correlation Analyses

Because the ASD group had a wide range of language skill and autism severity, whole-brain correlations with percent signal data from the forward speech condition and two clinical variables (RL age-equivalent score and CARS autism severity score) were run to examine individual differences in the response to forward speech in the ASD group. Correlation analyses revealed that as receptive language age increased so did activity in RH frontal and temporal regions (i.e., medial and inferior frontal gyri and superior temporal sulcus/middle temporal gyrus). Similarly, as autism severity decreased, increased activity was seen in RH inferior and medial frontal cortex as well as right superior temporal sulcus and middle temporal gyrus. Left hemisphere frontal (superior and middle frontal) and temporal (superior temporal gyrus/superior temporal sulcus and middle temporal gyrus) activity also showed a significant negative correlation with autism severity (Figure 5) (Table 2 in Supplement 1).

Discussion

In this first fMRI study of 2–3-year-old children with ASD, we identified a pattern of neural response to speech that differed in children with ASD from both their chronological age- and mental age-matched typically developing control subjects. In comparison with MA-matched control subjects, the ASD group showed reduced activity in an extended number of brain regions in response to speech. In comparison with their CA-matched control subjects, the ASD group showed both a delayed and deviant pattern of brain response to speech, characterized by a greater recruitment of RH frontal regions.

A deviant pattern of laterality in ASD in response to speech versus rest was identified in three separate analyses. First, in comparison with their CA-matched control subjects, the ASD group recruited greater right frontal regions (Figure 2). Second, in a paired hemispheric comparison, the ASD group showed a trend toward greater recruitment of RH frontal and temporal regions during the forward speech condition, whereas the CA group showed a trend toward greater LH recruitment in a number of brain regions (Figure 3). Third, correlations with receptive language age revealed a greater reliance on primarily RH frontal and temporal regions with increasing language abilities and decreasing autism severity (Figure 5). Autism severity, however, was also correlated with a similar pattern in the LH. These findings suggest that not only is the RH recruited to a

Table 3. Laterality Effects

Left > Right (red)				Right > Left (blue)			
Region	BA	Talairach Coords (x,y,z)	*t* Value	Region	BA	Talairach Coords (x,y,z)	*t* Value
CA Group							
Frontal				Frontal			
Inferior Frontal Gyrus	44/45	(−41,16,11)	3.91	Middle Frontal Gyrus	9	(−37,26,24)	4.05
Precentral Gyrus	6	(−56,−2,39)	3.63	Temporal			
Middle Frontal Gyrus	10	(−30,44,−1)	3.89	Middle Temporal Gyrus	21	(−55,−8,−17)	3.87
Medial Frontal Cortex	32	(−4,39,14)	2.54	Parietal			
Anterior Cingulate Cortex	32	(−4,22,−6)	3.64	Angular Gyrus	39	(−39,−65,38)	3.84
Superior Medial Frontal Gyrus	8/9	(−2,43,36)	3.73	Subcortical			
Temporal				Cerebellum		(−14,−66,−22)	3.17
Transverse Temporal Gyrus	41	(−38,−25,7)	3.60				
Superior Temporal Gyrus	42	(−45,−37,11)	3.05				
Parahippocampal Gyrus	18	(−25,−56,3)	2.97				
Parietal							
Postcentral Gyrus	3	(−59,−22,40)	3.31				
Cingulate Gyrus	31	(−18,−21,31).	2.92				
ASD Group							
Temporal				Frontal			
Superior Temporal Gyrus	38	(−38,−6,−9)	2.88	Superior Frontal Gyrus	10	(−26,43,19)	3.90
Parietal				Cingulate Gyrus	31	(−10,−2,42)	4.51
Postcentral Gyrus	1/2	(−50,−26,51)	5.62	Inferior Frontal Gyrus	47	(−31,26,−13)	4.13
Subcortical				Precentral Gyrus	6	(−45,−14,10)	3.24
Cerebellum		(−31,−53,−29)	3.93	Insula	13	(−33,−9,18)	2.78
				Temporal			
				Superior Temporal Gyrus	21/22	(−43,−33,1)	2.34
				Middle Temporal Gyrus	21	(−43,−46,−1)	2.73
				Inferior Temporal Gyrus	20	(−46,−29,−22)	3.12
				Fusiform Gyrus	20	(−39,−25,−18)	3.74
				Occipital			
				Middle Occipital Gyrus	19	(−42,−74,3)	2.97
				Parietal			
				Inferior Parietal Lobule	40	(−35,−54,31)	4.38
				Paracentral Lobule	4	(−18,−33,55)	3.46
				Subcortical			
				Caudate		(−6,12,14)	2.40

The peak *t* value and Talairach coordinate is given for each region or Brodmann Area (BA) showing significant effects of laterality. Coords, coordinates; other abbreviations as in Table 1.

greater extent in autism than in control subjects at 2–3 years of age but also that early RH recruitment might be predictive of a better language outcome in autism.

In comparison with their MA-matched control subjects, the ASD group showed reduced activity in an extended network of brain regions. In a previous report (31), we hypothesized that an extended network of brain regions including frontal, occipital, and cerebellar regions might be recruited at the cusp of the rapid burst in language skills seen in the second year of life. This hypothesis is additionally supported by ERP studies in which the response to known words progresses from widespread to more focal patterns with increasing language skill in typically developing 20-month-old children (37–39). In addition to reduced activity in a number of frontal, occipital, and cerebellar regions, the ASD group also showed deviant patterns of right and medial frontal activation in comparison with their CA-matched control subjects. Taken together, these findings reveal that the pattern of activity in ASD is both reduced and deviant as compared with the pattern recruited in the MA-matched control subjects. The reduced and deviant activation in the ASD group could reflect a failure to engage the full network of brain regions that might facilitate language learning. Studies of 1–2-year-old children with provisional ASD will be needed to determine whether a typical extended network is ever recruited or whether evidence of a deviant developmental trajectory is already present at even younger ages.

This pattern of deviant lateralization and immature frontal recruitment in autism as compared with control subjects suggests a possible lack of specialization for language systems in autism by 2–3 years of age. Previous studies of the older child and adult have identified patterns of reduced or reversed laterality in frontal and/or temporal cortex in structural studies (40–43) and functional studies using ERP (44,45), PET (8,10), fMRI (9,11,46), and magnetoencephalography (MEG) (47). However, this is the first study to suggest abnormal laterality in children with ASD as young as 2–3 years of age. Furthermore, the significant correlation of RH frontal and temporal activation to speech with receptive language skill in autism suggests that, by 2–3 years of

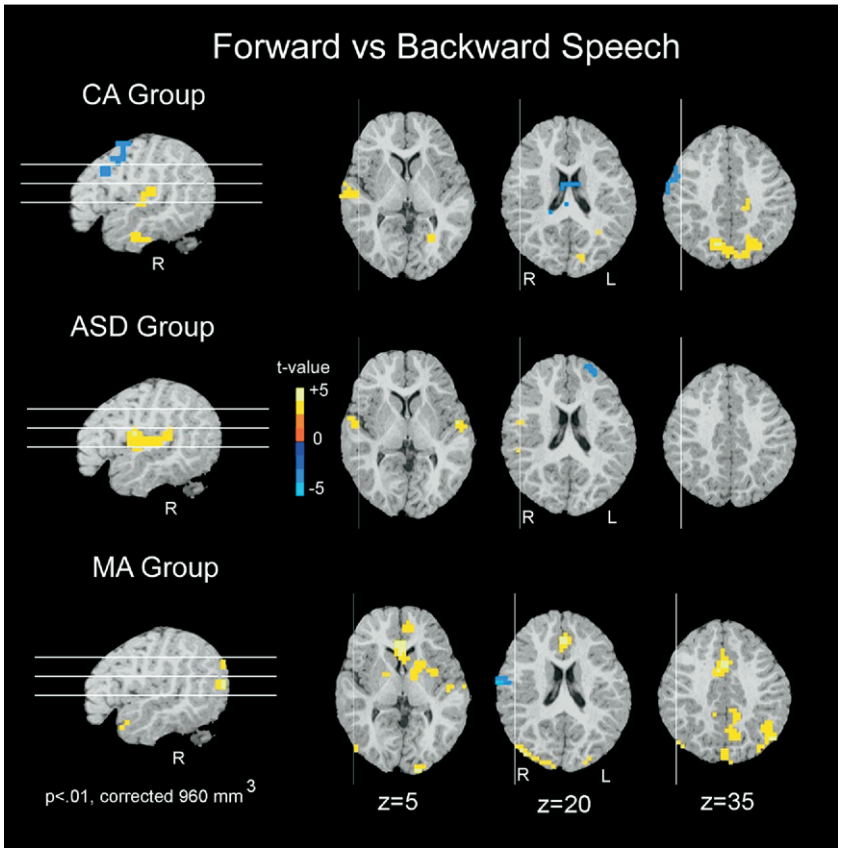

Figure 4. Speech-specific response within each group. For each of the three groups separately, regions in which forward speech elicited greater activation than backward speech are shown in red. Regions in which backward speech elicited greater activation than forward speech are shown in blue. All three groups showed a differential response between forward and backward speech; however, this difference is primarily within superior temporal and parietal regions for the CA and ASD groups. Data are represented on a brain image from a single subject. Abbreviations as in Figure 1.

age, children with autism might already be on a deviant developmental trajectory characterized by RH recruitment for language.

The cause of this deviant developmental trajectory can only be speculated. Some evidence suggests that recruitment of RH regions might be a compensatory mechanism to account for the more effortful processing required to process language in autism (9). However, the current study was conducted during natural sleep, suggesting cognitive strategies alone cannot account for the reversed asymmetries seen in the autism group. Structural MRI studies have revealed that a number of structures that showed evidence of deviance in functional laterality at 2–3 years of age in the current study (e.g., inferior frontal and posterior temporal regions) also show greater rightward asymmetry at 5–11 years of age in ASD (42,43,48), suggesting a possible structural bias underlying the deviant functional patterns. However, it is not possible to disentangle whether this structural asymmetry is a cause or consequence of aberrant functional patterns early in life. Some evidence suggests brain volume in right temporal and frontal regions is strongly dependent on genetic factors, whereas LH regions are more influenced by experience (49) and develop more slowly than the right (50). It is possible that a combination of both genetic and experiential factors very early in life results in a greater reliance on RH regions and possible reduced development of LH regions for language processing. Given the differing rates of development within each hemisphere, the timing of brain insults could be particularly important in altering hemispheric asymmetries.

Three limitations of the current study warrant discussion, because they might have potential implications for the interpretation of the findings. First, although the ASD group contained only male subjects, both control groups contained a small number of female subjects (4 of 12 in the CA group, and 2 of 11 in the MA group). This limitation is addressed in information in Supplement 1 through a post hoc analysis with a male-only control sample and in text in Supplement 1 (Figure 1 and Table 4 in Supplement 1).

Second, although this study contained two typical control groups for the ASD sample (one chronological age-matched group and one language-age–matched group), it did not contain a contrast group of children with developmental language disorder (DLD) or specific language impairment (SLI). Evidence suggests some overlap in language profiles (6) and anatomical asymmetries (43,48) between children with autism and those with language-impairments but not autism. Thus, the inclusion of this third contrast group could elucidate functional activation patterns that might be specific to autism and not due to language impairments alone.

A third limitation of the current study is that data were recorded during natural sleep without monitoring sleep stage. As discussed in our previous report (31), rapid eye movement (REM) onset latency differs between 1- and 3-year-old typical children; however, for both ages mean REM onset latency is reported to be approximately 60 min or greater (51,52). These data were recorded approximately 45 min into sleep, and thus a systematic difference in sleep stage is not expected between groups. In studies of older children and adolescents with autism, REM onset latency was not significantly different between autism and control groups (53,54). Thus, although sleep stage could affect patterns of brain activation, between group differences are not expected to be due to sleep stage differences alone. However, further studies would benefit from polysomnographic

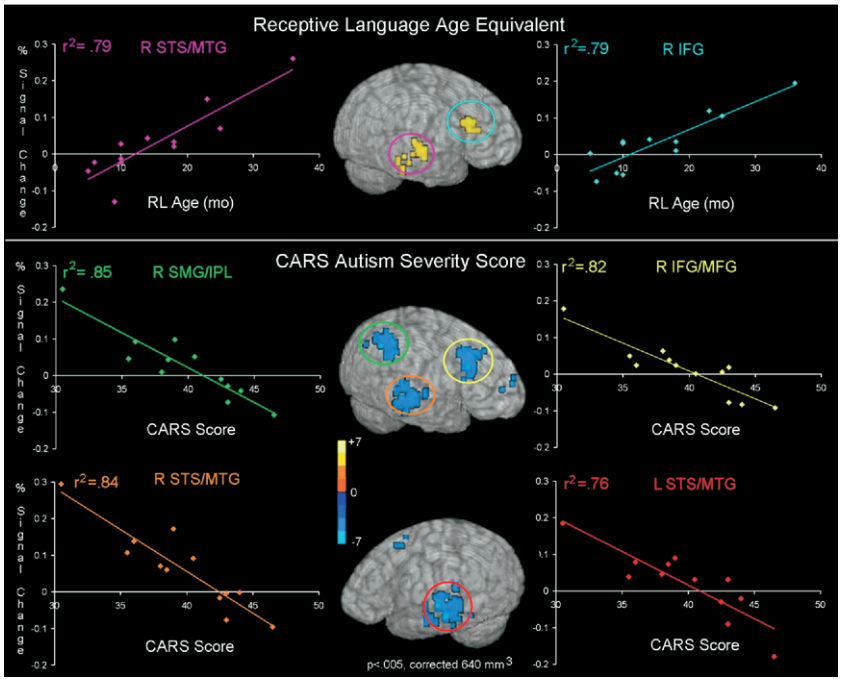

Figure 5. Individual differences in the ASD group. Regions showing a significant correlation between percent signal change in the forward speech condition and receptive language age (top row) or autism severity (bottom row) are shown on a single rendered brain. Individual data were extracted from these regions and plotted to obtain the R^2 correlation coefficient. The color of the circled region corresponds to the color of the plot of the behavioral measure and the mean percent signal change for that region. Right superior temporal sulcus (STS) and right inferior frontal gyrus (IFG) both show significant correlations with receptive language age and autism severity. CARS, Childhood Autism Rating Scale; MFG, middle frontal gyrus.

recording, because much variability is often seen in latency to REM onset (51,52).

The use of fMRI during natural sleep poses a number of advantages. First, fMRI data can be acquired from infants, toddlers, and young children with minimal motion artifact. Second, children across a broad range of cognitive and behavioral function can be studied. Functional MRI studies of awake and performing older children and adults inherently require high-functioning participants with ASD: a narrow subset of the autism population. Third, effects of arousal, anxiety, or attentional state that typically can confound fMRI studies of patient populations are not present. Thus, sleep fMRI might be a valuable tool in understanding the biological bases of autism. Identification of specific structures and networks showing functional abnormalities at the time of emergence of autism could give clues for where to look for microstructural differences or gene candidates (e.g., those involved in hemispheric patterning) in autism.

This research was supported by the National Institutes of Health MH-36840 Grant and a gift from the Donald C. and Elizabeth M. Dickinson Foundation awarded to EC.

We are grateful to the parents and children who participated in this study. We are also grateful to members of our research team who performed clinical testing (Dr. Cindy Carter and Dr. Natacha Akshoomoff) and assisted with data collection (Anna Bajo, Anne Erickson, Vera Grindell, Cindy Hsu, Grace Kim, Doreen Nguyen, Lindsey Schubert, Randy Wu, and Weifang Zhou). We also thank Dr. Ruth Carper, Graham Wideman, and Dr. Natalia Kleinhans for their contributions to the Talairach validation study discussed in Supplementary Information.

The authors reported no biomedical financial interests or potential conflicts of interest.

Supplementary material cited in this article is available online.

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