Article

Temporal Lobe Dysfunction in Childhood Autism: A PET Study

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Objective: The nature of the underlying brain dysfunction of childhood autism, a life-long severe developmental disorder, is not well understood. Although researchers using functional brain imaging have attempted to contribute to this debate, previous studies have failed to report consistent localized neocortical brain dysfunction. The authors reasoned that early methods may have been insensitive to such dysfunction, which may now be detectable with improved technology.

Method: To test this hypothesis, regional cerebral blood flow was measured with positron emission tomography (PET) in 21 children with primary autism and in 10 nonautistic children with idiopathic mental retardation. Autistic and comparison groups were similar in average age and developmental quotients. The authors first searched for focal brain dysfunction in the autistic group by using a voxel-based whole brain analysis and then assessed the sensitivity of the method to detect the abnormality in individual children. An extension study was then performed in an additional group of 12 autistic children.

Results: The first autistic group had a highly significant hypoperfusion in both temporal lobes centered in associative auditory and adjacent multimodal cortex, which was detected in 76% of autistic children. Virtually identical results were found in the second autistic group in the extension study.

Conclusions: PET and voxel-based image analysis revealed a localized dysfunction of the temporal lobes in school-aged children with idiopathic autism. Further studies will clarify the relationships between these temporal abnormalities and the perceptive, cognitive, and emotional developmental abnormalities characteristic of this disorder.

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Childhood autism is a severe developmental disorder that impairs the acquisition of some of the most important skills in human life. Core clinical features include impaired social interactions, verbal and nonverbal communication deficiencies, limited activities and interest, and stereotypic patterns of behavior (1–3).

Progress in understanding the neural basis of childhood autism requires clear and reliable data indicating specific neuroanatomical or neurophysiological abnormalities. Localized structural and functional brain correlates of autism have yet to be established (4, 5). Previous brain imaging studies performed in autistic patients have reported abnormalities such as a larger total brain volume (6, 7), cerebellar abnormalities (8, 9), a smaller number of cortical metabolic correlations (10), and a delayed pattern of cortical metabolic maturation (11). Taken together these results are consistent with an anomalous pattern of brain organization in autism, but none of them fully account for the full range of autistic symptoms. Furthermore, most functional imaging studies have reported normal or near normal regional brain metabolism and cerebral blood flow (12–15). Yet, localized cerebral cortex abnormalities may have been overlooked with first-generation functional brain imaging techniques.

In the study reported here, we address this issue with up-to-date functional brain imaging methods. We used positron emission tomography (PET) and a voxel-based whole brain analysis to search for abnormalities in regional cerebral blood flow (rCBF), an indirect marker of neural activity, in children with primary autism. Twenty-one autistic children were compared to 10 nonautistic children. The results led us to perform an extension study in a separate group of 12 autistic children.

Method

Subject Selection

Two groups of children with primary autistic disorder (an initial group of 21 autistic children, including 17 boys and four girls, and an additional group of 12 autistic children, including 11 boys and one girl) were selected among patients attending a day-care child psychiatry unit of a university hospital. Infantile autism was diagnosed according to the DSM-IV criteria. Children who were 5–13 years of age were eligible for the study. The mean age of the initial autistic group was 8.4 years (SD=2.7), with nine children 5–7 years old and 12 children 8–13 years old. The mean age of the additional autistic group was 7.4 years (SD=1.7), with seven children 5–7 years old and five children 8–13 years old. We selected as a comparison group 10 nonautistic children with idiopathic mental retardation (eight boys and two girls). The diagnosis of mental

retardation conformed to DSM-IV criteria. No etiology was found after extensive clinical and laboratory investigations. This comparison group was chosen in order to detect abnormalities specifically related to autism, taking into account the fact that 75% of autistic children are also mentally retarded (2, 3). The mean age of the comparison group was 8.1 years (SD=2.1), with four children 5–7 years old and six children 8–13 years old. The severity of the mental retardation ranged from mild to severe (four children had mild mental retardation, four had moderate mental retardation, and two had severe mental retardation). The mean nonverbal development quotient was comparable between the autistic and comparison groups: 42.7 (SD=21.5) for the initial autistic group, 44.5 (SD=27.2) for the additional autistic group, and 50.8 (SD=17.8) for the comparison group. For both the autistic and mental retardation groups the following exclusion criteria were applied: 1) abnormal magnetic resonance imaging (MRI) result, 2) history of substantial medical or neurological disorder, 3) known infectious, metabolic, or chromosomal disease, 4) history of seizures, and 5) identifiable neurological syndrome. All children were free of psychotropic medication for at least 1 month before the rCBF study, and none of them had been taking long-term medication during the past year, except for one child with mental retardation who had been treated with thioridazine. The studies were performed after the approval of the ethical committee of Tours (France) public hospitals; written informed consent was obtained from subjects' parents before all studies.

Clinical Evaluation

All autistic and comparison children were assessed with a structured neurodevelopmental examination described in detail elsewhere (15, 16). Autistic behavior, mental retardation, language impairments, and neurological signs were assessed. Autistic behavior was evaluated by using the Behavior Summarized Evaluation scale (17, 18), a composite scale of 29 items for evaluation of autistic symptoms (aloneness, poor social interaction, abnormal eye contact, lack of initiative, echolalia, ritual use of objects) and associated features, including eating, sleep, and motor disorders. Items are scored from 1 to 5 (1=absent symptom, 5=severe symptom). The mental retardation score was related to the development quotient, which was evaluated by using the Brunet-Lézine developmental tests for infants and children (age-appropriated tests validated in a reference population in France [19, 20]). Development quotient values were classified into five levels of increasing severity: 1) development quotient >70, 2) 50–70, 3) 35–49, 4) 20–34, and 5) <20. Language impairments were evaluated with a complete speech scale of verbal and preverbal communication (21). This evaluation allowed the classification of speech disorder into five levels of increasing intensity: 1) appropriate and communicative speech, 2) minor speech abnormalities, 3) moderate speech abnormalities, 4) intense abnormalities of speech, and 5) no communicative speech. The three groups' mean scores for autistic behavior, mental retardation, language impairments, and neurological signs are shown in Table 1.

Brain Imaging Protocol

Relative rCBF was determined from the distribution of radioactivity measured with high-resolution PET cameras after bolus intravenous injections of $[^{15}O]H_2O$ (22). The first 16 PET scans (of 10 autistic children in the initial group and six comparison children) were obtained on a Siemens ECAT 953b tomograph (Knoxville, Tenn.). Attenuation-corrected data were reconstructed into 31 axial slices, with a resulting resolution of 7 mm full width at half maximum. The last 27 PET scans (of 11 autistic children in the initial group, 12 autistic children in the extension group, and four comparison subjects) were obtained on a Siemens ECAT Exact HR+ 962 camera (Knoxville, Tenn.). Attenuation-corrected data were reconstructed into 63 slices, with a resulting resolution of 5 mm full width at half maximum. Fifteen seconds before each scan, 7 mCi of $[^{15}O]H_2O$ were administrated by an intravenous bolus injection (22). Data were collected over a period of 80 seconds. In all autistic and comparison children, PET studies were performed at rest during sleep induced by premedication with 4 mg/kg of pentobarbital sodium. We have previously reported that this premedication has no effect on absolute rCBF values and regional distribution (15). A high-resolution MRI of the brain (General Electric 1.5-T Signa system, Milwaukee) was also obtained for all children.

TABLE 1. Ratings of Clinical Characteristics in Two Groups of Autistic Children and a Comparison Group of Nonautistic Children With Mental Retardation

	Autistic Group 1 (N=21)		Autistic Group 2 (N=12)		Comparison Group (N=10)	
Variable[a]	Mean	SD	Mean	SD	Mean	SD
Autistic behavior[b]	3.6	0.7	3.7	0.7	1.3	0.5
Mental retardation	3.3	1.0	3.2	1.5	2.7	1.1
Language impairment[c]	3.7	0.8	3.0	1.3	2.3	0.7
Neurological signs	1.5	0.6	1.4	0.5	1.9	0.6

[a] Severity was rated on standard scales (17–21) on which scores ranged from 1, normal development or absence of signs, to 5, severe mental retardation or maximal severity of signs.
[b] Significant difference between autistic group 1 and the comparison group ($t=9.77$, $df=29$, $p<0.001$) and between autistic group 2 and the comparison group ($t=9.50$, $df=20$, $p<0.001$).
[c] Significant difference between autistic group 1 and the comparison group ($t=4.67$, $df=29$, $p<0.001$).

Statistical Analyses

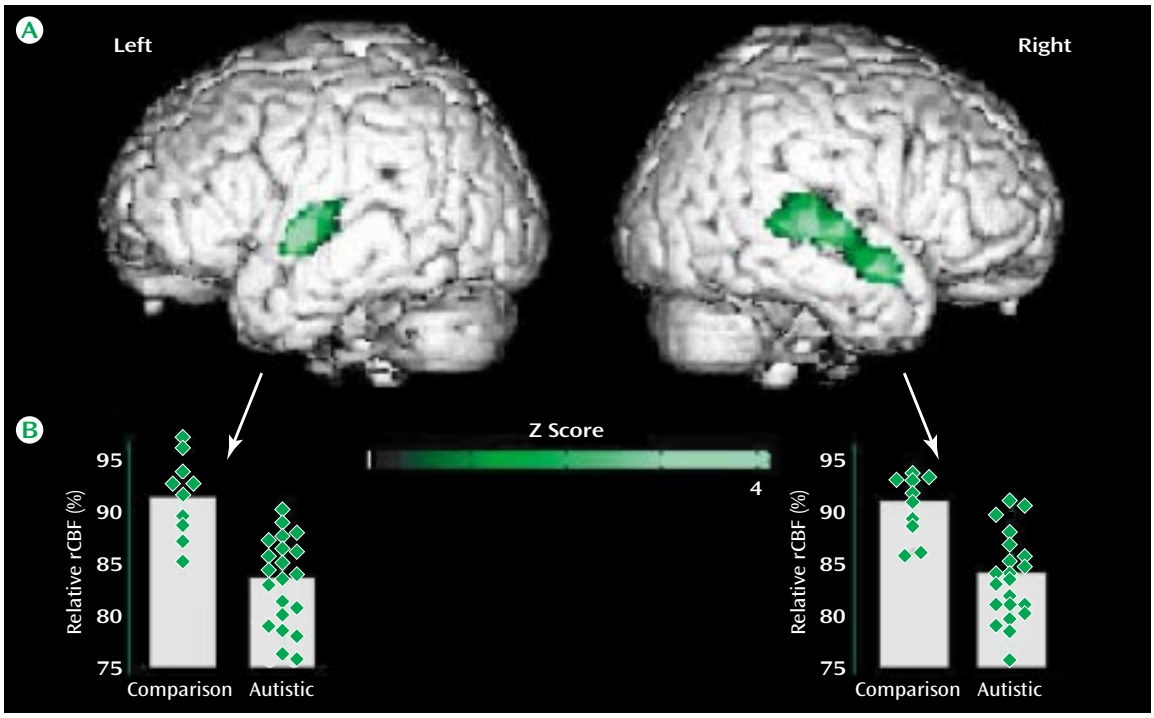
rCBF images were analyzed with the statistical parametric mapping (SPM) software (SPM 96, Wellcome Department of Cognitive Neurology, London) (23). The PET scan and MRI of each child were transformed into standard stereotactic space (24). PET images were smoothed with an isotropic Gaussian filter (full width at half maximum of 15 mm). Smoothed, normalized PET data were analyzed with the group comparison block design. Global intensity differences were corrected by using proportional scaling. Comparisons between groups were performed with the t statistic, further transformed into the Z statistic (SPM[Z]). MRI scans were combined to generate a mean anatomical image of each group that was used for the visualization and verification of the anatomical localization of the results.

Two statistical analyses were performed in the initial study: a group and an individual analysis. In the group analysis, the initial group of 21 autistic children were compared to the group of 10 nonautistic children. The resulting Z maps were thresholded at $p<.0001$. Clusters with spatial extend probability less than 5% (corrected for multiple comparisons) were reported. Since two PET scanners were used, we analyzed a possible confounding effect of the difference in scanners by decomposing the data set in principal components analysis to obtain eigenimages, or eigenvectors of the variance-covariance matrix, that best described the data set.

In the individual analysis, the scan data of each autistic child was compared to that of the comparison group as a whole, i.e., one image for each autistic child was compared with the 10 images of the comparison children. SPM maps were thresholded at $p<0.01$ ($Z>2.3$). To limit the risk of errors due to multiple region comparisons, we a priori restricted the analysis to the temporal regions that were abnormal in the group analysis. Individual abnormalities in extratemporal regions are also reported, but their analysis must be considered exploratory.

The same group and individual analyses were done in the extension study of the additional group of 12 autistic children. All statistical analyses performed with the SPM software were t tests.

FIGURE 1. Bilateral Temporal Hypoperfusion in Children with Autism (N=21), Compared With Nonautistic Children With Mental Retardation (N=10), and Relative Regional Cerebral Blood Flow (rCBF) in Area of Maximal Hypoperfusion[a]



[a] In part A, regions with significant hypoperfusion in autistic children, compared to nonautistic children, are superimposed on a rendering of T_1-weighted MRI anatomical template images of the left and right lateral surfaces in Talairach space. A statistical threshold of Z=3.09 (df=29, p<0.001, corrected for multiple comparisons) was used for display purposes. Part B shows relative rCBF for each group of children obtained on the peak of maximal hypoperfusion in autistic children. The green diamonds correspond to individual rCBF values. For the left side, the Z score is 4.17, and the coordinates in the Talairach space are x=–40, y=–14, z=4; for the right side, the Z score is 4.08, and the coordinates in the Talairach space are x=48, y=–28, and z=12.

TABLE 2. Brain Regions With Significant Hypoperfusion in Children with Autism (N=21) Compared With Nonautistic Children With Mental Retardation (N=10)

Brain Region	Z Score[a]	Coordinates in Talairach Stereotaxic Space[b] x	y	z
Right superior temporal sulcus (Brodmann's area 21)	3.86	44	4	–14
Right superior temporal gyrus (Brodmann's area 44/22)	4.08	48	–28	12
Right superior temporal gyrus (Brodmann's area 44/22)	3.62	40	–16	4
Left superior temporal gyrus (Brodmann's area 44/22)	4.17	–40	–14	4

[a] Only results with Z>3.09, which are significant at p<0.001, corrected, are reported.
[b] Coordinates in Talairach stereotaxic space (19) correspond to local extrema; x is the distance (mm) to the right (+) or left (–) of the midsagittal line; y, the distance anterior (+) or posterior (–) to a vertical plane through the anterior commissure; and z, the distance above (+) or below (–) the intercommissural (anterior and posterior commissures) plane.

Results

Initial Study—Group Analysis

SPM group analysis revealed a significant hypoperfusion (t=4.12–4.94, df=29, p<0.001; corrected p<0.05) in the autistic group in four foci localized in the temporal lobe, three in the right side, and one in the left (Figure 1). Regions of maximal hypoperfusion were centered in the left superior temporal gyrus (Brodmann's area 22/42), in the right superior temporal gyrus (Brodmann's area 22/42), and in the right superior temporal sulcus (Brodmann's area 21) (Table 2). We did not find any hypoperfused cerebral regions in the mentally retarded comparison group.

The principal components analysis showed that the group effect (autistic versus comparison children) explained much more of the total variance of the data set (49.2%) than the effect of the different scanners used in the study (10.0%). In addition, within-scanner comparisons yielded results similar to those of the global analysis, although less statistically significant.

Initial Study—Individual Analysis

A significant temporal hypoperfusion (t=2.84–5.40, df=9, p<0.01) was detected in 16 of 21 autistic children (76.2% positive individual detection). The temporal hypoperfusion was bilateral in seven of 16 autistic children and was located on the right side in nine autistic children. Figure 2 shows brain regions with significant hypoperfusion in an autistic child with bilateral temporal hypoperfusion. The exploratory analysis of extratemporal regions revealed abnormalities in five of the 21 autistic children: three of the

children had an abnormality in the frontal region, one in the frontocerebellar region, and one in the occipital region.

Extension Study—Group Analysis

We found the same pattern of bitemporal hypoperfusion that was observed in the initial study. Four foci of hypoperfusion (t=4.65–5.74, df=20, p<0.001; corrected p<0.05) were detected. They were localized in the left and right superior temporal gyrus and in the right superior temporal sulcus, within millimeters of those found in the initial study.

Extension Study—Individual Analysis

A significant temporal hypoperfusion (t=2.92–8.36, df=9, p<0.01) was detected in nine of the 12 autistic children (75.0% positive individual detection). The temporal hypoperfusion was bilateral in two of the nine autistic children and was located on the right side in the remaining seven autistic children. The exploratory analysis of extratemporal regions revealed abnormalities in four of the 12 autistic children: two children had an abnormality in the frontal region, one in the frontocerebellar region, and one in the occipital region.

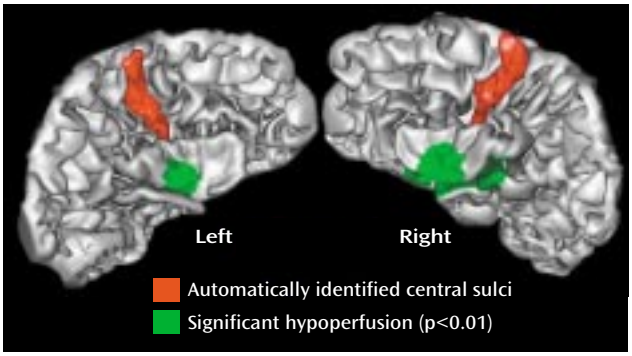
Clinical Correlations

To investigate the relationships between the pattern of temporal hypoperfusion and the clinical profile of the autistic children, we divided the autistic children into three groups: 1) those with a bilateral temporal hypoperfusion (N=9), 2) those with a right-side temporal hypoperfusion (N=16), and 3) those without temporal hypoperfusion (N=8). The mean age of these three subgroups was not significantly different. The three groups' mean scores for autistic behavior were also very similar (mean=3.6 [SD=0.7], mean=3.6 [SD=0.8], and mean=3.9 [SD=0.6], respectively), and no significant difference was observed in the three groups' scores for language impairments. The language score ranged from 1 (absence of impairment) to 5 (severe impairment) in the autistic group with bitemporal hypoperfusion, from 2 (minor deficits) to 5 in the group with right temporal hypoperfusion, and from 2 to 5 in the group without temporal hypoperfusion (mean=3.6 [SD=1.1], mean=3.1 [SD=0.9], and mean=3.9 [SD=1.1], respectively). The mental retardation score was also similar between the three groups (mean=3.1 [SD=1.3], mean=3.1 [SD=1.3], and mean=3.8 [SD=1], respectively).

Discussion

We found marked bilateral hypoperfusion in the temporal lobes, centered in associative auditory and adjacent multimodal temporal cortex, in a group of autistic children. These findings were confirmed in a second group of autistic children and thus provide the first robust evidence for a localized dysfunction of cerebral cortex in school-aged children with primary autism. The temporal hypoperfusion could be detected on an individual basis in nearly

FIGURE 2. Bilateral Temporal Hypoperfusion in an Individual Autistic Child[a]



[a] Regions with significant hypoperfusion (t=4.99, df=9, p<0.01) in one child with autism, compared to mean rCBF of 10 nonautistic children, are represented in green on a three-dimensional rendering of MRI images of the left and right surfaces of the lateral cortex viewed from inside. Central sulci, highlighted in red, are shown as reference points (25).

75% of the autistic children, with the current sensitivity of the imaging method.

These results contrast with those previously obtained with functional brain imaging in autistic patients at rest, most of which failed to find localized brain abnormalities in adult and school-aged autistic child (12–15). The differences could be explained by improvement in the spatial resolution of the imaging methods, roughly from 20 mm to 5 mm, between the current and earlier studies. In addition, the whole brain SPM analysis may be more appropriate than the region-of-interest method used in previous studies for detecting restricted foci of hypoperfusion in the temporal lobes.

Nevertheless, the results of the present study must be considered in the light of some methodological limitations. The first limitation is the lack, for ethical reasons, of rCBF values for normal children. Yet, inclusion of a comparison group of children with idiopathic mental retardation may be considered an advantage, since our findings cannot be attributed to the mental retardation associated with the autistic syndrome. Similarly, the findings cannot be attributed to language impairment, since temporal hypoperfusion was detected at a similar frequency in the autistic children with severe and mild language impairment. However, only 10 children were included in the comparison group, and our findings must be confirmed with a larger comparison group. The second limitation concerns the fact that rCBF measurements were performed during sleep. Since all subjects were studied under the same conditions, the findings reflect a true difference between autism and idiopathic mental retardation, but we cannot formally exclude that the possibility that the findings may have been different if measurements had been done when the subjects were awake. Finally, although the examinations were performed with two different PET scanners, the eigenimages of the principal components analysis con-

firmed that the difference between the autistic and nonautistic groups—and not the difference between scanners—accounted for most of the variance and explained the temporal hypoperfusion.

With these limitations in mind, we note that the finding of a bilateral temporal hypoperfusion extends to primary autism recent results suggesting a link between temporal lobe dysfunction and autistic behavior in children with neurological disorders. Indeed, autistic behavior has been associated with several clinical conditions resulting in temporal lobe pathology, such as epilepsy and herpes simplex encephalitis (26–30). Furthermore, two relatively recent neuroimaging studies have shown an association between temporal lobe abnormalities and the occurrence of secondary autism (29, 30). In children with infantile spasms, the early finding of a bilateral temporal hypometabolism is strongly associated with later emergence of an autistic-like disorder (29), whereas in children with tuberous sclerosis, there is a strong association between temporal lobe tubers and autistic syndrome (30). Thus, early anatomical or metabolic abnormalities of the temporal lobes may lead to secondary autism. In addition, nonhuman primate experimental data have shown that neonatal medial temporal lesions cause behavioral disturbances strikingly similar to those seen in autistic children (31).

A major challenge faced by all neurobiological theories of autism is to explain the variety of perceptive, cognitive, and affective deficits of autism. Although we do not currently have direct evidence, a theory based on temporal lobe dysfunction may address this challenge. First, autistic children have major sensory perceptual aberrations (5), and the temporal lobe is thought to be central to the processing of numerous environmental signals that enter the nervous system through visual and auditory sense organs and to the organization of these signals into the structured patterns of neuronal activity forming the substrate of experiences that confer meaning to the world around us (32). Furthermore, the temporal lobe dysfunction was centered in the auditory associative cortex and the superior temporal sulcus. Dysfunction of the auditory cortex may explain why young autistic child are so often initially misdiagnosed as deaf and why they often have severe communication impairments (2, 5). Dysfunction of the superior temporal sulcus may indirectly explain the emotional and cognitive components of autism, since this multimodal association region is strongly connected with frontoparietal and limbic regions (33, 34). These connections may also explain earlier brain imaging findings such as reduced functional parietofrontal connectivity and delayed frontal maturation (10, 11).

In summary, voxel-by-voxel image analysis and rCBF PET studies demonstrated a well-localized functional abnormality in autistic children located bilaterally in the superior temporal cortex. The temporal hypoperfusion could be detected in nearly 75% of the autistic children in the study. These results suggest that the idiopathic autistic syndrome is related to a dysfunction of both left and right superior temporal regions and may be useful for guiding future research in developmental disorders.

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