Autism Severity and Temporal Lobe Functional Abnormalities

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Two independent studies[1,2] have described bilateral temporal hypoperfusion in autistic children. Temporal regions are implicated in social perception, language, and "theory-of-mind," abilities that are impaired in autism. We investigated a putative relationship between cerebral blood flow (rCBF) measured at rest and clinical profile of 45 autistic children (Autism Diagnostic Interview–Revised [ADI-R] scores). A whole-brain covariance analysis was performed. Significant negative correlation was observed between rCBF and ADI-R score in the left superior temporal gyrus. The more severe the autistic syndrome, the more rCBF is low in this region, suggesting that left superior temporal hypoperfusion is related to autistic behavior severity.

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Childhood autism, an early and severe developmental disorder, is defined by three main features: qualitative impairments in social interactions, verbal and nonverbal communication deficits, and limited and stereotyped activities and interests.[3] This clinical triad is associated with considerable variation in the degree of severity and associated symptoms. For example, 70% of the autistic children have mental retardation (intelligence quotient [IQ] <70), and 50% of them never develop verbal language. Therefore, capturing the clinical diversity of children sharing the same autistic core symptoms remains a challenge. One way is to use the Autism Diagnostic Interview (ADI) score.[4] The global ADI score may be considered as a quantitative index of autism severity along three main axes: impairment of social interaction, impairment of verbal and nonverbal communication, and severity of stereotyped activities. In this study, we tested the hypothesis that ADI scores may correlate with focal brain abnormalities as measured with positron emission tomography (PET). Although we[2] and others[1] have recently reported convergent results supporting a superior temporal lobe hypothesis of autism, consistent with the increasingly recognized "social brain" status of this area, we used a "voxel-by-voxel" *whole-brain* correlation approach without any a priori localization hypothesis.

Subjects and Methods

Subject Selection

Forty-five children with primary autistic disorder (37 boys) were selected from patients attending specialized autism consultation of a university hospital. Their mean age was 7.9 years (standard deviation [SD], 2.2). Their mean IQ or developmental quotient (DQ) was 44 (SD, 22). Fourteen of them had been included in a previous functional neuroimaging study.[2] Autism was diagnosed according to the Diagnostic and Statistical Manual of Mental States disorders–IV criteria[3] and confirmed by ADI scores. No cause was found after extensive clinical and laboratory investigations. All children were free of medication for at least 1 month before imaging. Written informed consent was obtained from all subjects' parents. The study was approved by the local ethics committee.

Clinical Variability Evaluation

The autistic syndrome variability was evaluated with the ADI-R algorithm. This is a semistructured investigator-based interview.[5] This questionnaire is based on three scores with diagnostic thresholds. Each score contains four items. Score B quantifies impairment in social interaction, score C quantifies impairment in communication with a verbal subscore (CV) and a non verbal subscore (CnV), and score D quantifies restricted, repetitive, and stereotyped patterns of behavior and interests. Because each item is scored from zero (the symptom is absent or cannot be assessed) to three (the symptom is strongly present), a child who does not speak at all (71% in this group) scores 0 on the CV score and earns a lower global ADI-R score (less severe autism) than a child able to speak with some verbal communication abnormalities. Therefore, our correlation analysis was based on a modified global ADI-R (mADI-R) score which excluded the CV subscore.

Brain Imaging Protocol

Cerebral blood flow (rCBF) was measured with PET (Siemens ECAT Exact HR+ 962) after intravenous injection of $H_2{}^{15}O$. Data were collected during a period of 80 seconds. In all autistic children, PET studies were performed during sleep induced by premedication with rectal pentobarbital (7–10mg/kg) to obtain perfect motionlessness. A previous study

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showed that sedation does not change either the global rCBF or local rCBF distribution.[6]

Images Analysis and Statistical Analysis

Images were analyzed with statistical parametric mapping software (SPM99). This software was used for image realignment, transformation into standard stereotactic anatomical Talairach space, smoothing, and statistical analysis.[7] SPM correlation analyses were performed to study univariate relationships between rCBF, ADI-R scores (ADI-R subscores and mADI-R global score), global IQ, and presence or absence of language.

Results

Detailed clinical data are shown in the Table. The mean mADI-R global score was 50 ± 13. The large range (26–85) illustrates the variability of the autistic syndrome. Although all of the 45 children reached the global ADI-R cutoff diagnosis score, three of them failed to reach the cutoff score at one ADI-R subscore (child 1: CnV = 4 [cutoff = 7]; child 2: D = 1 [cutoff = 3]; child 3: D = 2). They were not excluded because they meet the DSM-IV criteria for autism and were considered autistic children by their physicians. In addition, a larger range of clinical profiles was considered an advantage for the correlation analyses.

The correlation analysis with the mADI-R showed a single focus of significant negative correlation ($p < 0.005$, uncorrected; Talairach's x, y, z coordinates: −68, −28, +12) located in the left superior temporal gyrus (Fig); more severe autistic symptoms being associated with lower rCBF values. The D-score, which quantifies restricted, repetitive, and stereotyped patterns of behavior, was negatively correlated with rCBF in the same region of the left superior temporal gyrus ($p < 0.001$, uncorrected; Talairach's x, y, z coordinates: −68, −40, +12; see Fig). Because of this colocalization, we perform a posteriori a multiple regression of the mADI-R subscores versus rCBF values measured in a 5mm diameter spherical voice of interest (VOI) centered on the main left superior temporal focus (−68, −28, +12). The D-subscore was the only independent significant variable ($r = 0.461$, $p = 0.0014$).The B-score, describing the qualitative impairment in social interaction, was negatively correlated with rCBF in the right parietal region ($p < 0.005$, uncorrected; Talairach's x, y, z coordinates : +40, −40, +68). No correlation was found with the CnV score related to qualitative impairment in nonverbal communication, the global IQ, or the presence or absence of language. There were no positive correlation between ADI scores and rCBF distribution.

Table. Clinical Characteristics of the Group of 45 Autistic Children

Characteristic	Mean	SD	Range	Interquartile Range
Age (yr)	7.9	2.2	5–11.9	6.1–10.1
Global IQ	44	22	12–90	27–65
ADI-R	52	13	26–85	45–63
mADI-R	50	13	22–73	41–61
B	28	8	13–41	23–34
CnV	14	4	4–21	11–16
CV	8	2	4–12	7–9
D	9	4	1–18	6–12

SD = standard deviation; IQ = intellectual quotient; ADI-R = Autism Diagnostic Interview–Revised global score; mADI-R = modified ADI-R (CV score excluded); B = subscore describing impairment in social interaction; CV = subscore describing verbal communication abnormalities (obtained in 13 children); CnV = subscore describing nonverbal communication abnormalities; D = subscore describing repetitive and stereotyped patterns of behavior and interests.

Discussion

We found that mADI score, a global index of autism severity, correlated with rCBF decrease in the left superior temporal gyrus, as did the D-score, an index of stereotypes and repetitive behaviors. A post hoc multiple regression suggested that the mADI correlation could be mainly driven by the D-subscore values. This hypothesis needs to be validated in a prospective study. The B-score describing social interaction deficits correlated with the dysfunction of a region of the right parietal lobe. We did not find significant correlation in other brain regions. It is methodologically important to stress that these results were obtained by a *whole-brain analysis,* without a priori localization hypothesis.

Two independent studies previously reported bilateral temporal hypoperfusion at rest in autistic children.[1,2] More recently, temporal lobe abnormalities have also been described using anatomical magnetic resonance imaging (MRI) voxel-based morphometry[8,9] and functional MRI.[10]

These previous findings suggested a localized dysfunction of the superior temporal lobe in autism, but none of them reported correlation with the severity of the autistic symptoms. Furthermore, they all suffered from the use of either mentally retarded control groups or non-IQ matched normal children. These types of bias were absent in this study, which was based on a covariance analysis without any control group. It therefore is of interest to note that the left temporal foci correlating with autism severity are localized only approximately 15mm superoposteriorly to those previously described in the comparison of autistic and mentally retarded child as shown in the Figure.

The superior part of the temporal lobe in the dominant hemisphere performs language functions[11] and also recently has more been implicated in social perception of biological movement, including movements of the eyes, mouth, hands, and body.[12] The superior temporal sulcus is now considered a key component of the "social brain" and has also been implicated in "the-

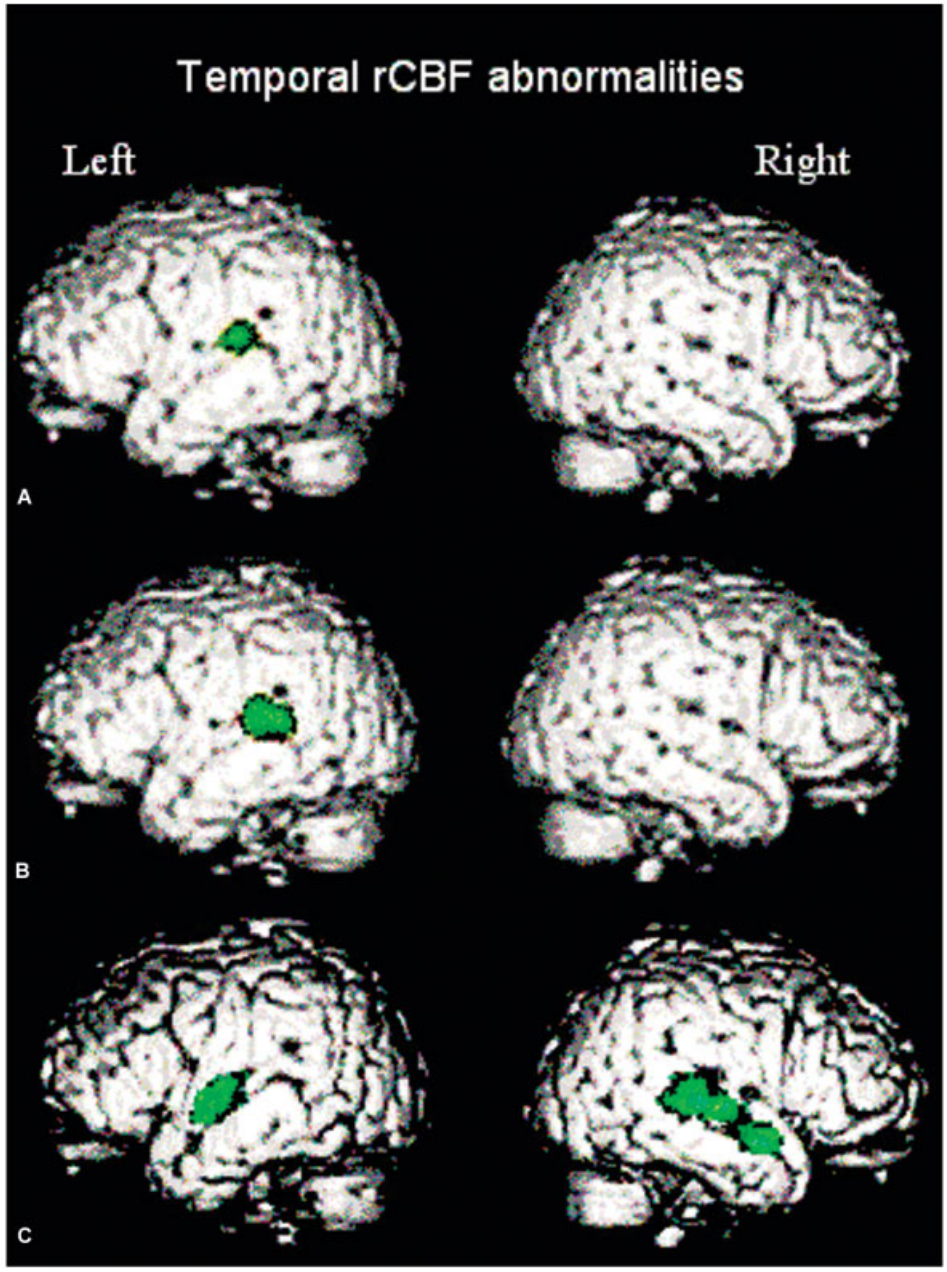

Fig. Significant negative correlation between cerebral blood flow (rCBF) distribution and Autism Diagnostic Interview (ADI) scores and previous group analysis showing bilateral temporal hypoperfusion. Results are superimposed on a rendering of T1-weighted magnetic resonance imaging anatomical template images of the left and right lateral surfaces in Talairach space. (A) Correlation between rCBF distribution and modified Autism Diagnostic Interview–Revised (mADI-R) score ($p < 0.005$ *uncorrected). Talairach coordinates (68, −28, +12). (B) Correlation between rCBF distribution and D-score* ($p < 0.001$ *uncorrected). Talairach coordinates are: (−68, −40, +12). (C) Bilateral hypoperfusion in 21 children with autism compared with 10 nonautistic children* ($p < 0.001$ *corrected).*[2] *Talairach coordinates are: (−40, −14, + 4), (+ 40, −16, + 4), (+ 48, −28, + 12), (+ 44, + 4, −14).*

ory of mind" abilities.[13] Therefore, our findings are consistent with autistic social impairments and may represent a brain correlate of the deficits in eye gaze perception, poor eye contact during communication, difficulties in recognizing or inferring the mental state of others,[14,15] and abnormal voice processing which are consistently described in autism.[16–18] In addition, the superior temporal sulcus has been implicated in motor imitation,[19] and the hypothesis of an early developmental failure of the mirror neuron system has been proposed in autism.[20]

An intriguing finding was that temporal lobe abnor-

malities in this study were localized in the left hemisphere, whereas previous comparison studies reported bilateral abnormalities. This may be caused by inadequate control groups in the previous studies. Alternatively, *right* temporal abnormalities may be nearly constant in autism, but the degree of *left* temporal hypoperfusion may underlie the severity of clinical symptoms as quantified by the ADI assessment. Further studies with larger data sets will be necessary to verify this hypothesis, which is consistent with the fact that clinical severity of autism is often related to the lack of language development.

Finally, the correlation between the B-score, an index of social impairment and a right parietal region was unexpected and needs further validation.

In summary, these findings support the hypothesis that childhood autism may be related to a dysfunction of superior temporal lobe structures. Further studies may unravel more specific correlations with social interaction, language, imitation behavior, and memory capacities. They are important because clinicoimaging studies may open new avenues for testing new therapeutics in autism.

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