Perception of Complex Sounds: Abnormal Pattern of Cortical Activation in Autism

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Objective: Bilateral temporal hypoperfusion at rest was recently described in autism. In normal adults, these regions are activated by listening to speech-like sounds. To investigate auditory cortical processing in autism, the authors performed a positron emission tomography activation study.

Method: Regional cerebral blood flow was measured in five autistic adults and eight comparison subjects during rest and while listening to speech-like sounds.

Results: Similar to the comparison subjects, autistic patients showed a bilateral activation of the superior temporal gyrus. However, an abnormal pattern of hemispheric activation was observed in the autistic group. The volume of activation was larger on the right side in the autistic patients, whereas the reverse pattern was found in the comparison group. The direct comparison between the two groups showed that the right middle frontal gyrus exhibited significantly greater activation in the autistic group. Conversely, the left temporal areas exhibited less activation in autistic patients.

Conclusions: These findings suggest that abnormal auditory cortical processing is implicated in the language impairments and the inadequate response to sounds typically seen in autism.


Autism is a severe pervasive developmental disorder characterized by impairments in reciprocal social relationships, verbal and nonverbal communication, and the ability to play and to develop interests outside of stereotypic preoccupations (1). Autism is also characterized by disturbances in the perception and modulation of sensory information, especially in the auditory domain. For example, young autistic children are often initially misdiagnosed as deaf (2). Two independent studies (3, 4) have reported bilateral hypoperfusion at rest in the temporal lobes of children with primary autism. In our study (3), abnormalities were centered on the multimodal superior temporal sulcus and in the auditory cortex of the superior temporal gyrus (3). However, up to now only two auditory functional brain imaging studies have been performed in autistic patients (5, 6). Thus, in the present positron emission tomography (PET) activation study, we further test auditory cortical processing in autism by using a passive listening task of complex speech-like auditory stimuli. We have previously shown in healthy subjects that these stimuli activate large areas of the superior temporal cortices (7), which are selectively involved in the initial "acoustic" stage of speech perception (8). These stimuli are never recognized as speech and are therefore unlikely to be explicitly processed by semantic language systems. Therefore, with this paradigm, the putative cortical activation differences between autistic patients and healthy subjects may reflect basic anomalies of cortical prelinguistic auditory processing rather than consequences of abnormal language development.
We used a subset of the synthetic speech-like auditory stimuli previously published elsewhere (7). Briefly, these stimuli contain spectral maxima (like speech formants) changing in time. They consist of complex sounds with a central 200-msec steady-state period surrounded by initial and final changes in frequency of the spectral maxima. Their acoustic structure was very similar to consonant-vowel-consonant, but as stated, normal volunteers never recognized them as speech sounds.

The rCBF images were analyzed with statistical parametric mapping software (SPM 96) used for image realignment, transformation into standard stereotactic anatomical space, smoothing (15 mm), and statistical analysis (11). State-dependent differences in global flow were covaried out by using proportional scaling. Comparisons across conditions were made with the t statistic subsequently transformed into the normally distributed z statistic by using a multistudy design. The resulting z maps were thresholded at $p < 0.001$ corrected at $p < 0.05$ for multiple comparisons.

Two statistical analyses of activation were performed: a within-group comparison of activation for listening to complex sounds versus the rest condition and a between-group comparison of activation.

**Results**

Passive listening to speech-like sounds versus the rest condition was assessed in each group independently. In the healthy comparison subjects, there was bilateral superior temporal cortex activation with a left-biased asymmetry ($z=3.09$, $df=22$, $p<0.001$). Five peaks of activation were detected along the left superior temporal cortex, whereas only two peaks were detected in the right superior temporal gyrus (Brodmann’s area 22). The volume of the activation was larger in the left hemisphere ($32 \text{ cm}^3$) than in the right ($20 \text{ cm}^3$). No peak of activation was detected outside the temporal lobes. This pattern of activation has been previously reported (7).

There was also bilateral superior temporal cortex activation in the autistic patients, but with a reverse right-biased asymmetry ($z=3.09$, $df=22$, $p<0.001$). Five peaks were detected in the right superior temporal cortex and three peaks in the left superior temporal gyrus. The volume of activation was larger in the right hemisphere ($55 \text{ cm}^3$) than in the left ($19 \text{ cm}^3$). In addition, six foci of activation were detected in the right frontal lobe and two in the left precentral gyrus.

The direct comparison showed a statistically significant difference between the autistic and the healthy comparison subjects in two brain areas ($z=3.09$, $df=22$, $p<0.001$). The right middle frontal gyrus (Brodmann’s areas 9, 9/46, and 10) exhibited significantly greater activation in the autistic patients than in the comparison subjects. In addition, the posterior part of the left middle and inferior temporal gyrus (Brodmann’s area 21) exhibited significantly less activation in the autistic patients than in the comparison subjects (Figure 1).

**Discussion**

In this study, we investigated auditory cortical processing in patients with autism by using stimuli designed to investigate early cortical stages of auditory speech processing. In healthy subjects, these stimuli induce bilateral...
activation of secondary auditory areas located in the lateral belt of the auditory cortex (7), which are selectively involved in the initial acoustic steps of language processing (8). In the present study, we observed an abnormal pattern of activation in the autistic patients. At the level of the auditory temporal cortex, our data suggest a reverse hemispheric dominance, since the volume of activation was larger in the right auditory cortex of autistic subjects, whereas the reverse pattern was found in the comparison subjects. It is of interest that the abnormal right dominance was confirmed by analysis of other brain areas. Autistic patients strongly activated the right middle frontal gyrus but not the comparison subjects, and the difference between both groups was statistically significant. Furthermore, the posterior part of the left middle temporal gyrus, a region that is involved in word processing (12), was significantly less activated in autistic patients than in the comparison group. This temporal region is also presumed to act as an interface between word perception and long-term representations of familiar words in memory (13).

These speech-like stimuli elicited an abnormal global cortical mapping in autistic patients characterized by hypoactivation of the left temporal word processing network and also by an emergence of an abnormal right frontotemporal network. Right-biased cortical processing has been previously reported in autism with other types of auditory stimuli (5, 6). In healthy subjects, the right middle frontal gyrus is activated by an auditory attentional task, i.e., discrimination of sound duration (14). Therefore, greater activation in the right middle frontal cortex, a region that integrates a cortical “attentional network,” may be implicated in the abnormal and often unexplained behavioral responses to sounds that are one of the most pronounced signs in autism.

The right shift of the global cortical mapping of auditory stimuli and reduced recruitment of the left temporal region in response to complex sounds in autism may be implicated in the abnormal behavioral responses to sounds and language acquisition impairment, both characteristic of autism. As auditory stimuli are perceived as strange electronic noises but never as speech, we speculate that the observed abnormal pattern of auditory activation in autism may reflect a fundamental alteration of the auditory cortical processing that leads to an abnormal early stage of language development rather than reflecting the consequences of abnormal language development. In addition, a similar right-shift pattern of activation was described by Muller et al. (6) in autistic men listening to human speech sounds. Our results are also in accordance with auditory evoked potential findings in autistic patients of a right hemispheric dominance in the processing of verbal and nonverbal auditory stimuli (15).

In conclusion, these preliminary results extend to the auditory domain previous findings of abnormal visual cortical pattern of activation in patients with autism (16–18), suggesting a disorganization in the establishment of global cortical networks.

References

A Prospective Study of Childhood Neurocognitive Functioning in Schizophrenic Patients and Their Siblings

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Objective: This study evaluated childhood cognitive functioning in individuals who later developed schizophrenia and in their unaffected siblings.

Method: Through the National Collaborative Perinatal Project, seven subtests of the Wechsler Intelligence Scale for Children were administered at age 7 to 32 individuals who developed schizophrenia in adulthood, 25 of their nonschizophrenic siblings, and 201 demographically similar nonpsychiatric comparison subjects. Mixed model analysis was used to examine between-group differences in standardized scores on the subtests.

Results: The probands and unaffected siblings had lower scores for picture arrangement, vocabulary, and coding than the comparison subjects but differed from each other only on the coding subtest.

Conclusions: Children who later developed schizophrenia and their siblings showed similar patterns of deficits involving spatial reasoning, verbal knowledge, perceptual-motor speed, and speeded processes of working memory. However, the probands exhibited more severe deficits in perceptual-motor speed and speeded processes of working memory than their unaffected siblings.

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Previous analyses of data from the National Collaborative Perinatal Project, a large population-based birth cohort, have revealed a general IQ deficit in the premorbid period of schizophrenia, before the onset of overt psychotic symptoms (1, 2). While these studies provide clear evidence for cognitive dysfunction in the premorbid period, the cognitive domains and developmental time points at which these deficits present themselves during the premorbid period are unclear. Previous research has shown that patients with schizophrenia and some of their healthy siblings exhibit greater deficits in executive function, attention, and verbal memory than in other functions (3, 4). In this study we primarily aimed to determine whether a similar profile of deficits is present during childhood in individuals diagnosed with schizophrenia as adults and to evaluate the degree to which such deficits are shared by their unaffected siblings.

Accordingly, we analyzed the profile of Wechsler Intelligence Scale for Children (WISC) subtest scores at age 7 for individuals from the Philadelphia cohort of the National Collaborative Perinatal Project who later developed schizophrenia and for their healthy siblings and demographically similar healthy comparison subjects.

Method

Data collection procedures, which were approved by the University of Pennsylvania institutional review board, have been described in detail previously (1, 5) and will only be summarized briefly. The original 9,239 individuals enrolled at the Philadelphia site of the National Collaborative Perinatal Project (6) were screened for contacts with public mental health facilities in Philadelphia from 1985 to 1995. This search yielded 72 individuals who received a DSM-IV diagnosis (confirmed by chart review) of...