Abnormal cortical voice processing in autism

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Impairments in social interaction are a key feature of autism and are associated with atypical social information processing. Here we report functional magnetic resonance imaging (fMRI) results showing that individuals with autism failed to activate superior temporal sulcus (STS) voice-selective regions in response to vocal sounds, whereas they showed a normal activation pattern in response to nonvocal sounds. These findings suggest abnormal cortical processing of socially relevant auditory information in autism.

Autism is a complex neurodevelopmental disorder characterized by deficits in social interaction and communication[1,2]. One of the major hypotheses to explain social impairment in autism is a failure to acquire a 'theory of mind'[3], which refers to the ability to understand the mental states of other people. This ability relies on the perception of socially relevant material, called 'social perception'[4].

Voices and faces are key stimuli that provide relevant social information about others. Individuals with autism have abnormal face recognition and identification of facial expression[5] and have reduced or absent activation of the face-fusiform area (FFA) during tasks that require processing of faces[6–8]. In the auditory domain, voices, which can be thought of as 'auditory faces'[9], are at the center of human social interactions. Recent fMRI studies have identified voice-selective areas in normal adults, located along the upper bank of the STS bilaterally[9]. These voice-selective areas can be considered the auditory cortex counterpart of the FFA.

Individuals with autism have difficulties in voice perception, such as lack of a preference for their mother's voice[10] and impairment in the extraction of mental states from voices[11]. This suggests that abnormal cortical voice processing is a feature of autism.

To test this hypothesis, we used fMRI to study brain activation during voice processing in adults with autism. Five male adults with autism (25.8 ± 5.9 years) were compared to eight age-matched healthy adult male volunteers (27.1 ± 2.9 years). Autism was diagnosed according to DSM-IV criteria[1] and the Autism Diagnostic Interview–revised. Individual with autism were included only if they had developed speech abilities (see **Supplementary Table 1**). Written informed consent was obtained from all subjects or their parents.

The fMRI paradigm was the same as one previously used with normal subjects[9]. Subjects were scanned while passively listening to energy-matched blocs (20 s) composed of either only vocal sounds (21 blocs, 33% speech sounds and 67% nonspeech vocal sounds) or only nonvocal sounds (21 blocs, drawn from a variety of environmental sources), separated by 10-s intervals of silence. One series of 128 functional gradient-echo volumes was acquired using 1.5-Tesla magnetic resonance scanner. Brain volumes were acquired with a long inter-acquisition interval (TR = 10 s) to ensure minimal signal contamination by scanning noise artifacts[12]: hemodynamic changes induced by the noise had returned to near-baseline level when the next volume was acquired.

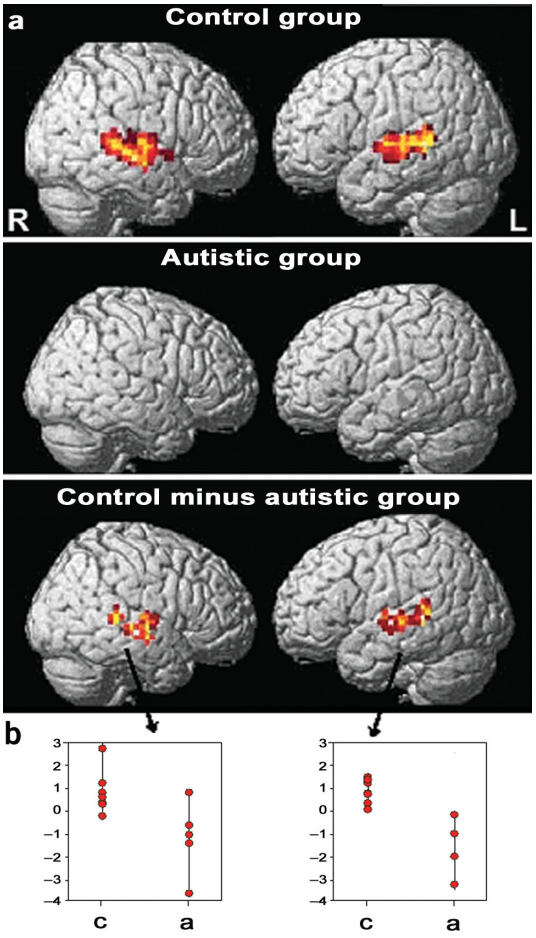

Figure 1 Voice versus non-voice—group analysis. (**a**) Location of activation peaks for the contrast 'voice' versus 'non-voice' in each group (controls and individuals with autism) and in the direct comparison between the two groups, at $P < 0.001$, in the fixed-effect model analysis, are shown in a lateral view of both hemispheres. (**b**) Plots illustrate the average voxel effect size for each subject of the two groups in the contrast 'voice' minus 'non-voice', extracted using the Marsbar SPM toolbox.

We compared cortical activation in normal adults and in adults with autism using statistical parametric mapping (SPM99) at both the individual and group levels. In each control subject, listening to voice stimuli elicited significantly greater activation along the upper bank of the STS than listening to non-voice stimuli ($P < 0.001$; see **Supplementary Table 1** and **Supplementary Fig. 1**), whereas no region showed greater activation in response to non-voice than to voice stimuli, thus replicating previous results[9].

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In individuals with autism, the activation maps elicited by the voice versus non-voice contrast were markedly different. In 4 of 5 individuals with autism, no significant STS activation was observed. Only one subject with autism showed a significant unilateral activation of the right STS and another presented a very restricted activation located outside STS (see **Supplementary Fig. 1** and **Supplementary Table 1**). Even if we conservatively consider the autistic subject with activation just outside the STS to be within the 'normal' range of variation, there is still a significant difference in the proportion of normal and autistic subjects who show any greater activation in this region in response to voices (8 of 8 for normal and 2 of 5 for autistic individuals; Fisher's exact test). No region showed greater activation during listening to non-voice as compared to voice stimuli.

At the group level, significantly greater activation was observed in the controls for voice as compared to non-voice stimuli, located along the upper bank of the STS bilaterally (random effect analysis, $P < 0.001$ corrected; **Fig. 1a**, upper). Conversely, group-average data in the autistic group did not reveal any region significantly more activated by voices (**Fig. 1a**); cortical activation was equivalent during voice and non-voice stimuli as compared to silence (see **Supplementary Table 2**).

This abnormal pattern of activation in response to voice stimuli in the autistic group was confirmed by the direct comparison between the two groups of images acquired during the voice stimulus. This comparison showed a significantly greater activation ($P < 0.001$ corrected) in the controls as compared to autistic individuals, located bilaterally along the upper bank of the STS as well as in right primary auditory cortex (**Fig. 1a**; see **Supplementary Table 3**). Notably, no significant difference was observed between the groups for the non-voice condition, suggesting that essentially normal processing of non-vocal sounds occurred in the autistic group. A region-of-interest analysis at the left and right peaks of STS activation in the contrast voice minus non-voice confirmed that the effect sizes were smaller in individuals with autism than in controls (**Fig. 1b**).

Just after scanning, subjects were asked to enumerate the sounds they had heard. The total number of recalled sounds was not significantly different between the two groups (11 ± 2.7 sounds in the control, 9.6 ± 8.4 sounds in the autistic group; see **Supplementary Table 1**). In contrast, the proportion of vocal sounds recalled was markedly different ($P < 0.001$): whereas the control group reported a similar proportion of vocal and non-vocal sounds (proportion vocal, 51%), the autistic group recalled a much smaller proportion of vocal sounds (proportion vocal, 8.5%). Moreover, whereas all control subjects but one reported a vocal sound in first position, three of the individuals with autism did not report any vocal sounds at all, and only one listed a vocal sound first; notably, this subject was the one who showed a right STS activation while listening to voices.

Thus, the autistic subjects, while showing normal cortical activation in response to non-vocal sounds, did not show the STS voice-selective activation observed in normal controls for vocal sounds; they also had a severe deficit in the recall of voice stimuli contrasting with a much better recall of non-voice stimuli (**Supplementary Table 1**). These results suggest that individuals with autism may be unable to process voice stimuli using the selective mechanisms activated by vocal sounds in normal controls. This is consistent with behavioral studies showing abnormal voice perception in autism as well as with findings relating to event-related potentials in children with autism that show a selective impairment in the attention to vocal-speech sounds[13]. One possible interpretation of these results is that autistic individuals could be characterized by an attentional bias towards non-vocal sounds, in line with recent findings of enhanced sensitivity to pitch in individuals with autism[14]; future studies will need to investigate whether this lack of salience of vocal stimuli causes, or is a consequence of, the abnormal pattern of cortical activation.

Abnormal processing of voice may be one of the factors underlying the social anomalies in autism. The marked similarity of the pattern of voice and face[6–8] processing deficits suggests common mechanisms underlying this abnormal processing of social information.

In conclusion, lack of activation of the STS in voice perception in autism could be part of the abnormal functioning of the entire social brain network[15]. The insensitivity to social stimuli seen in autism[2] may be associated with abnormal perceptual processing of socially relevant information.

Note: Supplementary information is available on the Nature Neuroscience website.

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COMPETING INTERESTS STATEMENT

The authors declare that they have no competing financial interests.

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