Change detection in children with autism: An auditory event-related fMRI study

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Autism involves impairments in communication and social interaction, as well as high levels of repetitive, stereotypic, and ritualistic behaviours, and extreme resistance to change. This latter dimension, whilst required for a diagnosis, has received less research attention. We hypothesise that this extreme resistance to change in autism is rooted in atypical processing of unexpected stimuli. We tested this using auditory event-related fMRI to determine regional brain activity associated with passive detection of infrequently occurring frequency-deviant and complex novel sounds in a no-task condition. Participants were twelve 10- to 15-year-old children with autism and a group of 12 age- and sex-matched healthy controls. During deviance detection, significant activation common to both groups was located in the superior temporal and inferior frontal gyri. During 'novelty detection', both groups showed activity in the superior temporal gyrus, the temporo-parietal junction, the superior and inferior frontal gyri, and the cingulate gyrus. Children with autism showed reduced activation of the left anterior cingulate cortex during both deviance and novelty detection. During novelty detection, children with autism also showed reduced activation in the bilateral temporo-parietal region and in the right inferior and middle frontal areas. This study confirms previous evidence from ERP studies of atypical brain function related to automatic change detection in autism. Abnormalities involved a cortical network known to have a role in attention switching and attentional resource distribution. These results throw light on the neurophysiological processes underlying autistic 'resistance to change'.
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Introduction

The ability to detect unexpected new events is an essential part of normal adaptive behaviour which is critical in rapidly changing environments, particularly social situations. Autism is a neuro-developmental condition in which change processing may be atypical, possibly set at a too sensitive level. Autism involves significant social and communication difficulties, and this has received considerable research attention. A key characteristic of autism that may arise from atypical processing of irregular events is sometimes referred to as 'resistance to change'. This was initially described as a 'need for sameness' (Kanner, 1943). It may be expressed in terms of tantrums as a response to change, or in terms of restricted interests and repetitive or stereotyped behaviours, and is present at all ages (Kobayashi and Murata, 1998).

Resistance to change may also occur at the sensory level; individuals with autism – especially infants – display unusual behaviours in response to changes in sensory stimuli (Rogers et al., 2003; Malvy et al., 2004). This is especially the case in the auditory modality, where paradoxical responses to sounds, both hyper- and hypo-reactivity to noises, are reported (Wing, 2003). Finally, when left to their own devices, children with classic autism tend to compulsively create patterns, which may reflect a strong desire to impose control over changing events (Frith, 1970). Taken together, these clinical features suggest that people with autism may have a basic difficulty in automatically orientating to changing sensory stimuli. Although resistance to change is a main feature of autism, the brain processes underlying this aspect of the condition remain poorly understood.

The neural correlates of change detection are commonly studied through the *oddball* paradigm. This involves embedding infrequent acoustic changes in a sequence of repetitive ('standard') stimuli. The infrequent stimuli are either *slightly deviant* from the standard (e.g., tones of a higher pitch) or are *highly deviant* unique stimuli (unfamiliar sounds, designed to capture attention). In the oddball

paradigm, the slightly deviant stimuli are referred to as simply 'deviant', and the highly deviant unique stimuli are referred to as 'novel' and evoke distinct patterns of brain activation. These brain processes underlying pre-attentive auditory change detection have been investigated in typical populations largely using electro-physiological methods, particularly event-related potentials (ERPs).

The ERP response evoked by any deviant stimuli is called *mismatch negativity* (MMN). It is assumed to reflect a pre-attentional change detection process, and its recording does not require active participation from the subject. MMN is thought to reflect the automatic detection of a difference between the active sensory memory trace of the recent repetitive event (the standard) and an incoming deviant stimulus (Näätänen, 1992; Näätänen et al., 2005). Several studies using different methods have identified cortical generators of MMN (Picton et al., 2000). The main MMN component is generated bilaterally in the supratemporal part of the auditory cortex and might be associated with acoustic change detection (see Alho, 1995 for a review). An additional generator has been identified in the frontal region (Giard et al., 1990; Alho et al., 1994, Alain et al., 1998) which may be related to initiation of an involuntary attention switch toward the detected change (Giard et al., 1990; Näätänen, 1992; Schröger, 1996). MMN can be recorded early in development, and mechanisms underlying this response are assumed to be similar across the lifespan (Cheour-Luhtanen et al., 1996; Gomot et al., 2000).

A few studies on auditory change detection mechanism underlying MMN have been conducted with people with autism, and these have yielded contradictory findings. This is probably due to the variability in the populations studied and in the nature of the stimuli used. In response to tones, MMN amplitude has been found to be normal (Kemner et al., 1995; Ceponiene et al., 2003), reduced (Seri et al., 1999), or larger (Ferri et al., 2003) in autism than in controls. In order to understand the underlying neurophysiological processes, Gomot et al. (2002) used scalp potential and scalp current density mapping to study MMN in children with autism. Results showed that MMN topography in autism was characterised by atypical electrical activity (additional positive currents) recorded over left frontal sites. Although the precise location of the brain mechanisms underlying the abnormalities in the scalp-recorded ERPs remains to be clarified, this result suggests that cortical or subcortical sources located in the anterior part of the left hemisphere could be involved in the atypical processing of change in children with autism.

In addition to MMN, the ERP response typically elicited by any novel stimulus occurring in a sequence of repetitive sounds is the P3a or Novelty P3. This response is thought to be associated with involuntary switching of attention toward stimulus changes occurring outside the current focus of attention (Schröger, 1996; Escera et al., 1998, 2000). Several brain areas are assumed to participate in P3a generation. These include the dorsolateral prefrontal cortex, the temporo-parietal junction, the posterior hippocampal region (Knight, 1996), and the auditory cortex (Alho et al., 1998). Most studies carried out in autism on electrical responses associated with novelty processing have involved active novel-target detection. Results showed that the response is significantly smaller in children with autism compared to controls (Courchesne et al., 1984, 1985; Lincoln et al., 1993; Kemner et al., 1995). P3a in response to novel speech stimuli in a no-task condition has been shown to be reduced in autism (Ceponiene et al., 2003). These findings have been interpreted as

reflecting an atypical orientation to novel stimuli (Bomba and Pang, 2004).

Despite excellent temporal resolution, electrophysiological methods do not allow the precise localisation of the brain regions involved in atypical change detection in people with autism. fMRI offers the potential to identify the subcortical and cortical anatomical structures in which these effects occur. Automatic auditory change detection has recently been studied in typical adults using fMRI (Rinne et al., 2005, Molholm et al., 2005). Despite the contamination of the stimuli by the acoustic noise of fMRI, it is possible to carry out passive MMN-like paradigms as long as the physical features of the auditory stimuli differ sufficiently to allow detection (Opitz et al., 2002). Moreover, although fMRI noise alters sensory response in auditory cortex, it does not affect the change detection (MMN) response (Novitski et al., 2001). Various block design fMRI studies have been carried out to assess change detection using the classical passive oddball paradigm (Celsis et al., 1999; Opitz et al., 1999a; Liebenthal et al., 2003; Jääskeläinen et al., 2004; Sabri et al., 2004) or paradigms using multimodal transitions as the deviant event (Downar et al., 2000) or the noise produced by the scanner itself during gradient switching as the deviant stimulus (Mathiak et al., 2002). Most studies report bilateral activation of the superior temporal gyrus in response to the deviant stimuli but a few have highlighted the activation of the other brain regions which are known to be involved in the processing of infrequent sound changes. Using event-related fMRI, Opitz et al. (2002) and Doeller et al. (2003) found additional activation in the inferior frontal gyrus in response to deviant stimuli. Thus, even though the choice of the design used is crucial to capture deviance-related brain activity outside the auditory cortex (Schall et al., 2003), fMRI has proven to be a useful tool to investigate the cerebral basis of deviance detection.

Imaging of passive processing of novelty has not received much research attention. Some fMRI studies have addressed the brain regions associated with novelty detection in a no-task condition, and these have only been conducted with typical volunteers (Opitz et al., 1999b; Downar et al., 2002). These studies found bilateral activation of the superior temporal gyrus. The latter study also revealed activation of a common network across modalities involving the temporo-parietal junction, the inferior frontal region, the cingulate gyrus, and the insula.

The aims of the current study were (1) to test the hypothesis of atypical brain activation during automatic acoustic change detection in children with autism and (2) to determine if these activations differ according to the novelty of the stimuli. We used event-related fMRI to study the processing of unattended frequency-deviant and complex novel sounds and to highlight the brain regions underpinning these processes in children with and without autism. We predicted that in autism we would observe a perturbation of the cerebral network involved in involuntary attention switching during auditory change detection, including both the frontal and possibly the temporo-parietal region.

Method

Participants

Twelve male children with high-functioning autism (HFA) and twelve typically developing children matched for sex, age, and IQ

participated in the experiment. Children were aged 10 to 15 years (mean ± SD: autism 13.5 ± 1.6; control 13.8 ± 1) and were all right-handed. Participants with autism were diagnosed according to the DSM-IV-R criteria (APA, 2000) and using the ADI-R (Lord et al., 1994). Mean full-scale IQ scores based on the WASI (Wechsler Abbreviated Scale of Intelligence, 1999) did not differ between the autism group and the control group and were 116 ± 18 and 120 ± 7 respectively.

Participants with hearing abnormality (as assessed by a subjective audiometric task), infectious, metabolic, or neurological disorders, or contraindication for MRI were excluded. No child was on medication at the time of the scanning session, and all patients were free of psychotropic drugs for a period of at least 2 months before the study. The study was approved by the Addenbrooke's NHS Trust Local Research Ethics Committee. Written informed consent was obtained from the parents or guardians of the subjects, according to the Declaration of Helsinki, and from the children themselves.

Auditory stimuli and experimental paradigm

Change detection processes were studied through an oddball paradigm with three different types of stimuli, with an event-related fMRI design. Auditory sequences including 'Standard' (probability of occurrence: $P = 0.82$), 'Deviant' ($P = 0.09$), and 'Novel' sounds ($P = 0.09$) were delivered binaurally through non-ferromagnetic headphones. The Standard repetitive stimulus was a three-partial sound composed of 3 frequencies (sinusoids: 500 Hz, 1000 Hz, 1500 Hz) with the second and third components 3 and 6 dB respectively lower in intensity than the first component. The Deviant sound differed from the Standard by a 30% change in frequency of all partial components (components: 650 Hz, 1300 Hz, and 1950 Hz). The Standard and Deviant sounds were similar to those used in previous ERP and fMRI studies of deviance processing (Tervaniemi et al., 2000; Opitz et al., 2002). The Novel sounds differed from the Standard sounds with regard to their frequency composition, basic frequencies, and frequency transitions. They were originally sampled from a musician's keyboard and digitally prepared for stimulation purposes using the CoolEdit© sound editor. The resulting stimuli were always novel non-identifiable complex sounds, each of them comprising a different spectrum of frequency composition. These novel sounds were kindly provided by B. Müller (Müller et al., 2002). All sounds had an overall intensity level of 85 dB SPL and a duration of 80 ms (including 10 ms rise/fall). Stimuli were presented with a constant stimulus onset asynchrony (SOA) of 625 ms, in pseudo-random order with the following constraints: the five first stimuli were Standard sounds, each Deviant or Novel stimulus was preceded by at least 3 Standard sounds, and the last five stimuli were Standard sounds. The minimum time interval between two Deviant or Novel stimuli was thus 2500 ms. The total number of stimuli was 668, including 58 Deviants and 58 Novels. In order to control for tonotopic effect, the Deviant sound was swapped with the Standard sound halfway through the sequence. During the acquisition sequence, subjects were instructed to watch a video of bird migration. Six 'Resting' periods of 10 s each (involving video watching only with no auditory stimuli) were interspersed, including one at the beginning and one at the end of the auditory sequence.

fMRI procedure

Data acquisition

Magnetic resonance data were acquired on a 3 T whole body system consisting of a Bruker Medspec 30/100 spectrometer (Ettlingen, Germany) and a 910 mm bore whole body actively shielded magnet (Oxford Magnet Technology, Oxford, UK). Functional images were collected using T2*-weighted gradient-echo echo-planar imaging (EPI) with TR = 2.5 s, TE = 27.5 ms, and flip angle = 82°. The acquisition volume consisted of 20 oblique-axial slices with slice thickness = 4 mm and interslice gap = 1 mm. The matrix was 64 × 64 with a 20 cm field of view, yielding in an in-plane resolution of 3.125 × 3.125 mm. Two hundred volumes were acquired for each participant. The first five volumes acquired were discarded to allow for signal equilibration, giving a total of 195 volumes used in the analysis. In order to minimise the contamination of the auditory stimuli by the scanner noise, each stimulus was delivered exactly at the time when the scanner was the quietest, i.e., in the temporal gap between two slices. Hence, stimulus delivery was closely synchronised with the volume acquisition (Fig. 1).

Image pre-processing

fMRI data were analysed using statistical parametric mapping software (SPM2, Wellcome Department of Cognitive Neurology, London, http://www.fil.ion.ucl.ac.uk/spm). All functional volumes were time corrected, motion corrected by spatial realignment to the first volume, and normalised to the MNI reference brain (courtesy of the Montreal Neurological Institute). The normalised functional images were then spatially smoothed with an 8 mm full-width half-maximum Gaussian kernel to accommodate intersubject anatomical variability.

Statistical analysis

The statistical analysis of the variations of the BOLD signal was based on the application of the general linear model to time series of the task-related functional activations (Friston et al., 1995). Trials for all three events (Novel, Deviant, and Standard) were modelled separately by using a canonical haemodynamic response function (HRF) and its first-order temporal derivative (Friston et al., 1998). The three standard sounds following a 'Resting' period as well as the standard sounds following a rare stimulation (deviant or novel) were modelled as separate events. Contrast images (Novel-Standard and Deviant-Standard) consisting of statistical parametric maps (SPMs) of t statistics at each voxel were then produced for each individual. These SPM$\{t\}$ were entered into a second level group analysis to create an SPM$\{F\}$, permitting inferences about condition effects across subjects that generalise to the population (i.e., 'random effects analysis'). SPM$\{F\}$ statistics including both the HRF and its temporal derivative (corrected for non-sphericity) were thus computed for each contrast to examine areas of activation for the group as a whole (Control + Autism), with a threshold of $P < 0.01$ false discovery rate (FDR) corrected for multiple comparisons (Genovese et al., 2002). Differences between groups were evaluated in a similar manner by computing for each contrast the SPM$\{F\}$ statistics thresholded at $P < 0.001$ uncorrected. Thus, the only difference between the two analyses (group as a whole and between-groups comparison) was in the FDR correction which was applied for the population effects only. For each analysis, the F statistic was subsequently converted to a standard normal z statistic
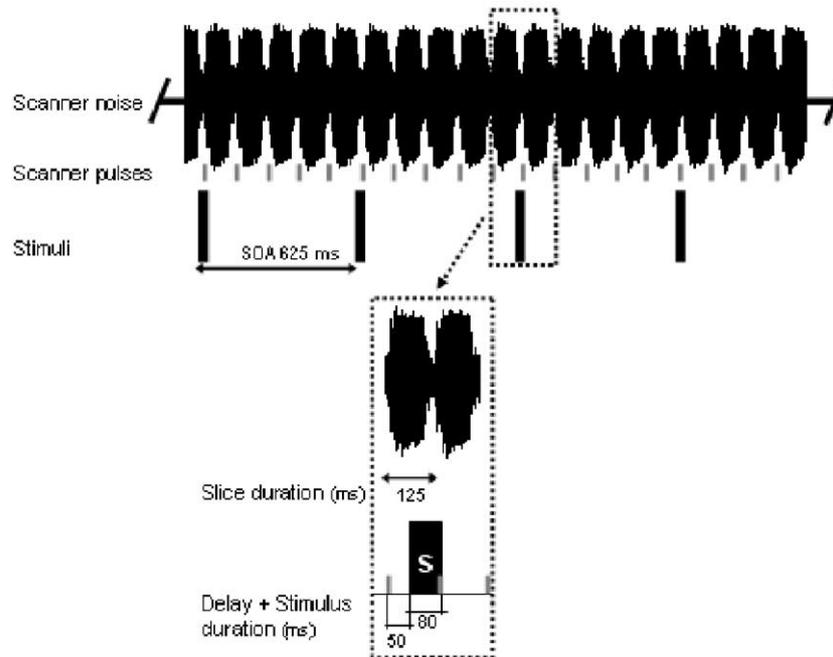
Fig. 1. Schematic illustration of the synchronisation between the sequence of acquisition and the sequence of stimulation. A pulse was sent by the scanner at every slice, and a stimulus was delivered every 5 pulses, after a delay of 50 ms. Auditory stimuli were thus delivered exactly in the 'silent' gap between the acquisitions of two slices.

for reporting. The locations of significant activations were expressed in Talairach coordinates (Talairach and Tournoux, 1988), using the nonlinear transformation procedure developed by M Brett (mni2tal: http://www.mrc-cbu.cam.ac.uk/Imaging/Common/mnispace.shtml).

Results

Deviance detection

Activation common to both groups

The contrast between Deviant and Standard sounds produced significant activation of multiple brain regions in an analysis of data from both groups combined (Table 1). Generically activated regions included bilateral superior temporal gyri (STG, approximate Brodmann area [BA] 22) and bilateral middle temporal gyri (BA 21), the extent of activation being greater in the right hemisphere (Fig. 2A). Activation was also observed in the right and left inferior frontal gyri (IFG, BA 44/45), the right inferior parietal lobules (IPL, BA 40), the right and left posterior cerebellum, the right medial dorsal thalamus and right head of the caudate, right cingulate gyrus, and right medial temporal region. In all these regions, the response to Deviant stimuli was greater than the response to Standard stimuli.

Activation differences between groups

The main group difference in response to deviant stimuli was found in the left anterior cingulate gyrus, which was more strongly activated by the control group than by children with autism (Table 2, Fig. 3A). To a lesser extent, the left medial orbitofrontal region and the left inferior frontal gyrus also demonstrated greater magnitude of activation in controls than in children with autism (Fig. 4A). No activation difference was found in the opposite

direction (i.e., greater activation in the autism group as compared to the controls). Further analysis was performed within each group by computing SPM{F} statistics for the Deviant minus Standard contrast in order to assess the activations in response to standard sounds and in response to deviant sounds in the anterior cingulate cortex. This showed that, whereas Deviant sounds enhanced activation of this region compared to the Standards in controls ($z = 3.25$; $P < 0.01$, uncorrected), children with autism showed the reverse pattern, with Deviant sounds showing less activation compared to the Standards ($z = 3.15$; $P < 0.01$, uncorrected). Notably, there was no evidence for any significant between-group difference in activation of auditory cortical regions.

Novelty detection

Activation common to both groups

The most salient focus of activation by Novel sounds compared to Standard sounds was in the bilateral STG (Table 1, Fig. 2B). This activation was more extensive in the right temporal cortex with additional significant signal increase in the right middle temporal gyrus (BA 21) and superior temporal pole (BA 38). Additional areas of activation were located in bilateral IFG (BA 44/45), bilateral tempoparietal junction (BA 40/22), cingulate gyrus, and right head of the caudate nucleus. In all these regions, the response to Novel stimuli was greater than the response to Standard stimuli.

Activation differences between groups

The main group differences in response to Novel stimuli were found in the left and right temporo-parietal junction (IPL and posterior STG), the right IFG and middle frontal gyrus, the left anterior cingulate gyrus, and the right anterior cerebellum (Table 2, Fig. 4B). In all these regions, differential response to Novel stimuli was significantly attenuated in children with autism compared to

Table 1
Activation common to both groups

Functional comparison	Cluster size (voxels)	Brain regions	BA	Talairach coordinates (*x, y, z*)	*Z* score
Dev > Sta	3040	R mid temporal gyrus	21	57, −22, −6	6.17
		R sup temporal gyrus	22	47, −33, 7	5.89
		R temporo-parietal junction	40	61, −34, 20	4.37
	2272	L sup temporal gyrus	22	−63, −23, 7	5.30
		L mid temporal gyrus	21	−48, −16, −9	4.87
		L inf parietal lobule	40	−46, −37, 35	4.65
	800	R cingulate	23	3, −28, 27	4.87
		R medial dorsal thalamus	NA	6, −13, 8	4.12
		R head of caudate	NA	18, −5, 13	4.05
	376	R inf parietal lobule	7	4, −60, 47	4.42
	287	R inf frontal gyrus	44	57, 16, 12	4.60
	231	R inf parietal lobule	40	38, −68, 37	4.72
	218	R medial temporal lobe	34	18, 1, −15	4.36
	82	R cerebellum	NA	34, −65, −20	4.51
	55	L cerebellum	NA	−28, −88, −12	4.60
	53	L inf frontal gyrus	45	−51, 33, 9	4.03
Nov > Sta	3209	R mid temporal gyrus	21	57, −20, −6	7.13
		R sup temporal gyrus	41	42, −36, 11	6.53
		R temporo-parietal junction/ sup temporal gyrus	40/22	65, −38, 22	5.61
	2582	L sup temporal gyrus	22	−63, −27, 7	6.22
		L sup temporal gyrus	22	−38, −38, 18	5.41
		L inf parietal lobule	40	−50, −34, 24	5.07
		L sup temporal gyrus	38	−57, 11, −11	3.59
	475	R cingulate	23	2, −26, 25	5.07
	385	R inf frontal gyrus	45/47	44, 33, 0	4.51
	231	R inf frontal gyrus	44	57, 16, 12	4.40
	140	R sup temporal gyrus	38	53, 13, −9	4.52
	45	R head of caudate	NA	11, 11, −4	4.02
	35	R medial dorsal thalamus	NA	8, −17, 8	4.00
	31	L ant cingulate	32	−12, 12, 44	4.20
	30	R temporo-parietal junction/ inf parietal lobule	40	40, −44, 48	4.00
	26	L inf frontal gyrus	45	−51, 33, 7	3.93
	20	L sup frontal gyrus	8	−12, 28, 52	4.01

Main regions demonstrating significant activation by Deviant sounds compared to Standard sounds, and Novel sounds compared to Standard sounds, in all subjects (*N* = 24; control + autism; *P* < 0.01, FDR-corrected). R = right; L = left; sup = superior; inf = inferior; mid = middle; ant = anterior.

controls. Further analysis in the anterior cingulate cortex did not show the reversed group patterns previously observed for deviance detection. It was again notable that there was no evidence for significant between-group difference in activation of auditory cortical regions.

Discussion

This study is the first attempt to address the brain processes involved in auditory deviance and novelty detection in typical children and in children with autism, using fMRI. As predicted, the results showed that, despite normal processing of infrequent acoustic changes at the level of the auditory cortex, regions involved in involuntary attention switching during change detection displayed atypical activation in autism. Specifically, lower activity was found in autism in the left anterior cingulate and the left inferior frontal region during deviance detection and in the left anterior cingulate, the bilateral temporo-parietal junction, and the right frontal cortex during novelty detection. Our results in typical children are consistent with those obtained in previous studies of

auditory change detection in adults. The findings in the autism group are congruent with our hypothesis of atypical change detection.

Deviance detection

Combining data from all volunteers, significant activation was seen in both the superior temporal gyrus and the inferior frontal gyrus during deviance detection, confirming previous findings from PET and fMRI studies in adults (Müller et al., 2002; Opitz et al., 2002; Doeller et al., 2003; Rinne et al., 2005). The current study also confirmed that additional brain regions are involved in deviance detection. Activation of the inferior parietal lobule and the temporo-parietal junction has been previously identified in an adult fMRI study (Celsis et al., 1999). Our findings of involvement of the right head of the caudate nucleus, the cingulate gyrus, and the cerebellum are consistent with PET data (Dittmann-Balcar et al., 2001), suggesting automatic subcortical processing of deviant auditory stimuli and may reflect cerebellar involvement in the pre-attentional processes of prediction and preparation (Allen et al., 1997).
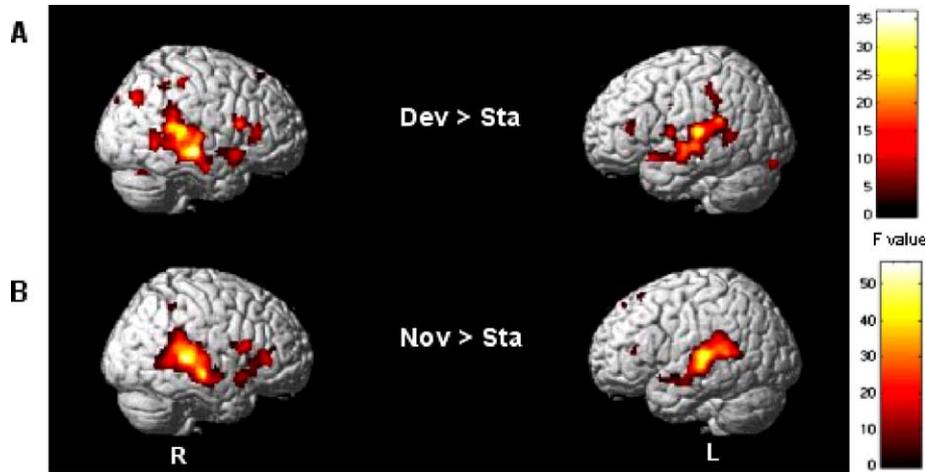
Fig. 2. Group activation map showing brain regions activated on average over all subjects (*N* = 24; Control + Autism) by processing of (A) Deviant sounds compared to Standard sounds and (B) Novel sounds compared to Standard sounds. Voxels with activation significant at *P* < 0.01 (*F* = 9.14), FDR-corrected for multiple comparisons, are shown; R = right hemisphere; L = left hemisphere.

The larger activation in the right more than in the left temporal region during deviance detection accords with previous electro-physiological (Giard et al., 1995) and magnetoencephalographic (MEG) findings (Levänen et al., 1996). These MEG results suggest that two dipoles are necessary to model MMN activity in the right hemisphere. The additional right generator is located in the inferior parietal lobule/temporo-parietal junction and would be involved in a more global and non-specific change detection process (Levänen et al., 1996). This finding of more general processing in the temporo-parietal junction has been confirmed in an fMRI study showing that the right posterior superior temporal gyrus is activated by brief periods of silence used as deviant events and thus plays a specific role in the integration of sequential auditory events rather than in the analysis of stimulus features (Mustovic et al., 2003).

Comparison of our data with results from other studies remains difficult since there have not yet been other fMRI studies of the oddball paradigm in children. Thus, we cannot establish clearly whether the highly significant activations found for the deviance contrast are related to the original paradigm we used (stimulus delivery in the 'silent' gap) or to the age of the population studied. rCBF has been shown to be elevated in children relative to adults in several developmental studies and is supposed to reach adult levels only between 15 and 19 years (Chiron et al., 1992; Takahashi et al., 1999). Slight variations in the BOLD response might thus be more clearly identified in younger populations. Moreover, deviance detection elicits larger brain electrical responses in children than in adults (Csepe, 1995; Gomot et al., 2000), and this age dependence is likely to be associated with larger BOLD responses in the corresponding cerebral regions (Logothetis et al., 2001). One possible extension to our study would be to scan a group of typical adults using our paradigm in order to address this age-related issue.

The direct group comparison during deviance detection showed a lower activation in the left anterior cingulate region in the autism group. This is an interesting finding as this area is thought to play a crucial role in stimulus evaluation (Bush et al., 2000). Anterior cingulate cortex is theorised to belong to a recency system that abandons older, stored information in order to capture new potentially relevant information (Ebmeier et al., 1995). The present results suggest that the hypo-activation in the left anterior cingulate cortex in children with autism compared to controls could actually reflect an inhibition of this region during deviance detection. This interpretation is consistent with a recent analogous result in the case of visual stimuli: children with autism deactivated the anterior

Table 2
Direct groups comparison Control > Autism

Functional comparison	Cluster size (voxels)	Brain region	BA	Talairach coordinates (*x, y, z*)	*Z* score
Dev > Sta	40	L ant cingulate	24/32	−13, 19, 23	4.25
	18	L mid orbitofrontal gyrus	11	−26, 50, −11	3.74
	16	L inf frontal gyrus	47/11	−31, 25, −3	3.27
Nov > Sta	91	L inf parietal lobule/ temporo-parietal junction	40/22	−43, −42, 20	4.11
	42	R cerebellum	NA	6, −49, −16	3.93
	33	R sup temporal gyrus	22	42, −40, 13	3.54
	24	R inf frontal gyrus	47	28, 32, −20	3.71
	20	L ant cingulate	24	−15, 17, 23	3.62
	20	R mid frontal gyrus	9	20, 50, 18	3.54

Brain locations of significant difference between groups in response to Deviant sounds and Novel (*N* = 12 in each group; *P* < 0.001, uncorrected).
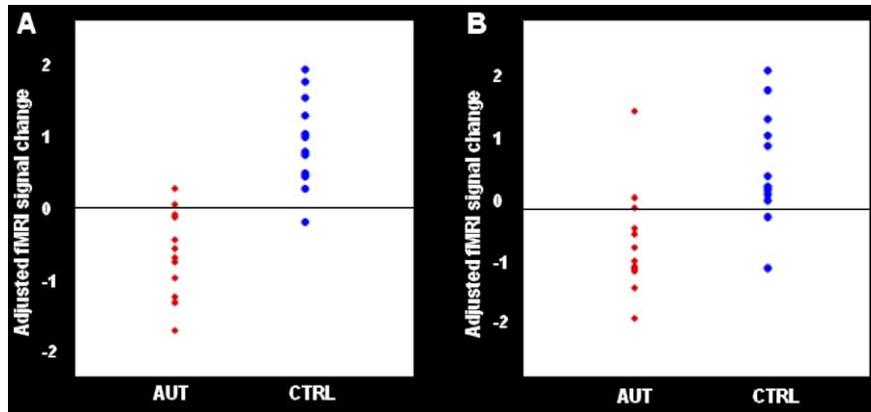
Fig. 3. Plots show adjusted fMRI activity (arbitrary units) in the left anterior cingulate for each child with autism (red rhombus) and for each healthy control (blue dot) in (A) the Deviant versus Standard contrast ($x = -13$, $y = 19$, $z = 23$) and in (B) the Novel versus Standard contrast ($x = -15$, $y = 17$, $z = 23$).

cingulate gyrus when processing visual distractors incongruent to a target stimulus as contrasted with congruent distractors (Belmonte and Baron-Cohen, 2004). Furthermore, inhibition of activity in this area could explain the lower activation that we found in the left prefrontal cortex in autism, given that these two regions have extensive connections. As the anterior cingulate is involved in detection of non-routine situations and is thought to trigger the lateral prefrontal cortex to engage further attentional top–down cognitive processes (Carter et al., 2000), atypical inhibitory mechanisms in this region could prevent appropriate allocation of pre-attentional processes to changing events.

Interestingly, the anterior cingulate region has been highlighted in autism in independent studies using entirely unrelated measurement techniques. Convergent findings from SPECT (Ohnishi et al., 2000), PET (Haznedar et al., 1997, 2000), ^{1}H-MRSI (Levitt et al., 2003), structural MRI (Abell et al., 1999; Haznedar et al., 2000), and post-mortem (Bauman and Kemper, 1994) studies support the idea that the cingulate gyrus displays both functional (hypoperfusion, hypometabolism) and anatomic (size reduction and increased

cell density) abnormalities in autism. Moreover, diffusion tensor imaging (DTI) has recently demonstrated a reduction of fractional anisotropy in the white matter adjacent to the anterior cingulate gyri, suggesting a disruption of neural connections between this region and other brain structures (Barnea-Goraly et al., 2004).

Additionally, the current data indicate lower activation in the left inferior frontal gyrus in the autism group during deviance detection. The frontal activity associated with the triggering of an attention switch during change detection is classically localised on the right hemisphere. However, evidence of the involvement of the left inferior frontal gyrus in the mismatch process has been provided by lesions studies (Alho et al., 1994; Alain et al., 1998) and fMRI studies (Doeller et al., 2003; Rinne et al., 2005), and in the present study, we also found activation in the left frontal region in the pattern common to both groups. This leads us to suggest that the left inferior frontal gyrus could also house an attention switch mechanism associated with deviance detection. Our results suggest that such mechanism that would enhance the automatic perception of potentially relevant deviant events is atypical in autism.
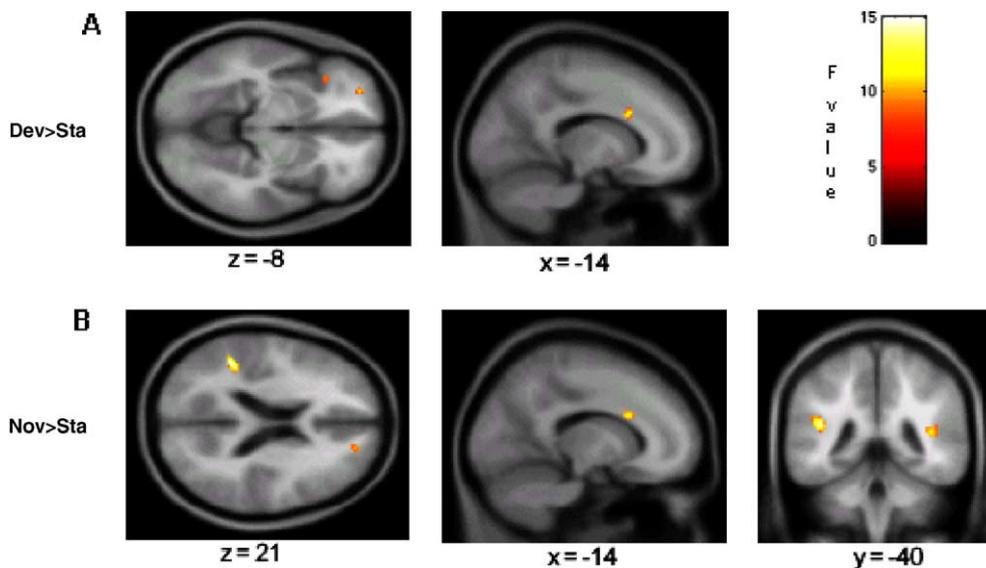

Fig. 4. Group difference map showing brain regions differentially activated between groups (Control > Autism; $N = 12$ in each group) by processing of (A) Deviant sounds compared to Standard sounds and (B) Novel sounds compared to Standard sounds. Voxels with activation significant at $P < 0.001$ ($F = 8.12$) are shown; R = right hemisphere; L = left hemisphere.

Novelty detection

Novelty detection processes are elicited by salient unexpected events, which are new each time. Our study reveals that the presentation of novel stimuli outside the focus of attention elicits significant functional activity in a network very similar to that involved in processing of deviant stimuli, both in controls and in children with autism. This network includes the superior temporal gyrus, the temporo-parietal junction, the superior and inferior frontal gyrus, the cingulate gyrus and the right medial dorsal thalamus and head of the caudate nucleus. However, the activations were slightly more widespread in response to novel stimuli compared to deviant stimuli in the right inferior frontal region, and additional activations were seen in the left superior frontal gyrus, these frontal activations perhaps being associated with involuntary switching of attention toward the novel stimulus.

In the current study, novelty detection (like deviance detection) was characterised by more extensive activation in the right hemisphere (with two separate anatomical foci and larger cluster size), confirming the findings of the PET study reported by Müller et al. (2002). This right dominance could be due to the frequency complexity of the sounds we used for both deviant and novel stimuli (no simple sinusoidal sounds), which is more likely to be processed within the right superior temporal cortex (Wessinger et al., 2001). However, this result is also consistent with the idea of right-hemisphere specialisation for the orienting of attention (Mesulam, 1998).

In individuals with autism, along with atypical activity in the left anterior cingulate gyrus, novelty detection elicited reduced activation in the left and right temporo-parietal region, and in the right inferior and middle frontal areas, compared to controls. These regions are described as belonging to the same novelty detection circuit and are assumed to have a major role in attention switching and in the distribution of attentional resources (Daffner et al., 2003). The temporo-parietal junction and the middle frontal region belong to the network of cerebral regions in which disruption of related white matter tracts has been demonstrated in autism using DTI (Barnea-Goraly et al., 2004). Moreover, measurement of cerebral glucose metabolism during rest demonstrates impairment in functional association between these two regions in autism (Horwitz et al., 1988).

In the current study, atypical activations within the novelty detection network in children with autism were particularly noteworthy in the temporo-parietal junction. This region is assumed to be involved in the pre-attentive gating mechanism that determines the extent to which unattended novel sounds enter awareness (Jääskeläinen et al., 2004). However, it has been shown that top–down attentional processes influence such pre-attentive mechanisms. Whilst habituation to repeated novel stimuli occurs in the frontal regions regardless of the focus of attention, it occurs in the parietal region when attention is directed away from the oddball stimuli (Cycowicz and Friedman, 1998). Thus, although all the volunteers in our experiment received the same instruction to focus on the video, one cannot exclude the possibility that people with autism were more absorbed in the movie they were watching and thus engaged fewer attentional resources in the processing of the auditory stimuli than the controls. Such a unimodal style of attention could have resulted in the lower responsiveness of the temporo-parietal region to novel auditory events in autism. The atypical activation in the temporo-parietal junction in autism suggests unusual reactivity of brain regions usually involved in

change detection, as if the autistic brain became 'hermetic' (or impenetrable) to novelty in one sensory modality whilst involved in a processing in another modality. Such a view if correct would be concordant with attention switching difficulties reported in clinical observations. Controlling for such attentional effects may be possible if a concurrent visual task was presented to the participants whilst the sound sequence is delivered.

The analysis of new events occurring outside the focus of attention is fundamental to adaptive functioning. Sensory events that are important for survival demand further analysis according to their relevance. The current results suggest that people with autism may have some difficulty in involuntary attention switching when processing unexpected infrequent stimuli. Mesulam's (1998) view of 'novelty seeking' provides an interesting framework for discussing these findings. According to this view, the bias for perceiving sameness and emitting automatic responses would represent 'a default mode' of brain function and would lead to behaviours that can be designated instinctual, stereotyped, or stimulus-bound. This mode would enhance efficiency and reliability but also increase premature closure, perseveration, and rigidity. Thus, one evolutionary improvement has been to develop specialised neural circuits dedicated to the rapid detection of unfamiliar events (Mesulam, 1998). The results discussed here suggest that these networks are atypical in autism. This could lead to a 'default mode' of brain functioning producing conservative and stereotyped behaviours. In this case, 'avoidance' of change would represent an adaptive behaviour by a brain aiming to keep the environment as predictable as possible and might be considered as a 'secondary dysfunction' of autism (Belmonte et al., 2004).

Conclusion

To summarise, our study found atypical activation of brain regions involved in involuntary attention switching associated with automatic detection of changing auditory events in children with autism. We demonstrated abnormalities in the cingulate gyrus regardless of the type of infrequent stimuli and an additional reduction of activation in temporo-parietal and frontal regions dedicated to novelty detection. This difficulty in modulating the processing of incoming new events may contribute to the clinical reports in autism of a tendency to ignore novel stimuli when they occur outside the focus of attention. This atypical response to changing events could play a role in the difficulty presented in people with autism in modifying expectancies in response to rare sensory information and may throw light on the neurophysiological process underlying 'resistance to change' in autism.

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