fMRI investigation of visual change detection in adults with autism

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People with autism spectrum disorders (ASD) may show unusual reactions to unexpected changes that appear in their environment. Although several studies have highlighted atypical auditory change processing in ASD, little is known in this disorder about the brain processes involved in visual automatic change detection. The present fMRI study was designed to localize brain activity elicted by unexpected visual changing stimuli in adults with ASD compared to controls. Twelve patients with ASD and 17 healthy adults participated in the experiment in which subjects were presented with a visual oddball sequence while performing a concurrent target detection task. Combined results across participants highlight the involvement of both occipital (BA 18/19) and frontal (BA 6/8) regions during visual change detection. However, adults with ASD display greater activity in the bilateral occipital cortex and in the anterior cingulate cortex (ACC) associated with smaller activation in the superior and middle frontal gyri than controls. A psychophysiological interaction (PPI) analysis was performed with ACC as the seed region and revealed greater functionally connectivity to sensory regions in ASD than in controls, but less connectivity to prefrontal and orbitofrontal cortices. Thus, compared to controls, larger sensory activation associated with reduced frontal activation was seen in ASD during automatic visual change detection. Atypical psychophysiological interactions between frontal and occipital regions were also found, congruent with the idea of atypical connectivity between these regions in ASD. The atypical involvement of the ACC in visual change detection can be related to abnormalities previously observed in the auditory modality, thus supporting the hypothesis of an altered general mechanism of change detection in patients with ASD that would underlie their unusual reaction to change.

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Behavioral studies of change detection have shown that the ability to detect targets increased with increasing developmental level for typical children, but remained constant over the same developmental range for children with ASD, pointing to an atypical developmental trajectory for change-detection in ASD (for review see Simmons et al., 2009). Atypical abnormalities have been proposed to contribute to atypical reactions to change in autism: increased distractibility might generate heightened reactivity to seemingly meaningless stimuli, while overly focused attention might contribute to the development of restricted pattern of interests or activities (Allen and Courchesne, 2001; Goldstein et al., 2001; Keehn et al., 2012; Lovaas et al., 1979; Simons and Rensink, 2005). Although attentional abnormalities have been shown to be involved in RBB in ASD, the pre-attentional processing involved in automatic change detection that initiates the orientation of attention towards relevant events, has not been determined in the visual modality.

A popular means to study the neural correlates of automatic change detection is the use of an oddball paradigm where a sequence of repetitive standard stimuli is presented with infrequent unpredictable deviant stimuli. Classically, in the auditory modality, electrophysiological and fMRI studies report that generators of automatic change detection are located bilaterally in the supratemporal part of the auditory cortex with additional generators in the prefrontal cortex (Celsius et al., 1999; Doeller et al., 2003; Garrido et al., 2009; Gomot et al., 2006; Moehring et al., 2005; Opitz et al., 2002; Rinne et al., 2005; Schall et al., 2003; Schonwiesner et al., 2007). Atypical auditory change processing in ASD has been described, in both electrophysiological and fMRI studies (Gomot et al., 2002; Gomot et al., 2006) highlighting normal activity in the auditory cortex but unusual activation in the ACC, a region known to be involved in attention switching and in the distribution of attentional resources (Daffner et al., 2003). The ACC is involved in the detection of non-routine situations and is thought to trigger the lateral prefrontal cortices to engage further attention-top-down cognitive processes (Carter, 2000). Gomot et al. (2006) suggested that atypical activation of the ACC could prevent appropriate allocation of pre-attentional processes to changing events. The normal activity in the sensory cortices associated with the abnormal involvement of non-specific regions such as the ACC in ASD suggested the existence of atypical change processing that would operate independent of the sensory modality.

Visual change detection process has been investigated in several electrophysiological studies in control participants using various deviants such as colors (Czigler et al., 2004), form (Maekawa et al., 2005), motion (Kremlacek et al., 2006; Urban et al., 2008), spatial frequency (Kimura et al., 2006; Sulykos and Czigler, 2011) and orientation (Astikainen et al., 2008; Kimura et al., 2010; Sulykos and Czigler, 2011). Previous fMRI (Yucel et al., 2007) and electrophysiological studies showed the main contribution of the occipital areas (Kimura et al., 2010; Urakawa et al., 2010), associated with prefrontal areas (Clery et al., 2012; Czigler et al., 2004; Heslenfeld, 2003; Urakawa et al., 2010) in automatic visual change processing. Other electrophysiological studies have further revealed sources in prefrontal regions. Kimura et al. (2010, 2011) performed source analysis of responses to visual changes and showed generators of vMMN in the visual extra-striate region (BA19) and in the medial, lateral and ventro-lateral prefrontal cortex (right orbitofrontal region (BA47 and BA11)). Concordant with these findings, the prefrontal area has been described as one of the multimodal cortical areas sensitive to sensory changes in fMRI (Downar et al., 2000) and MEG (Tanaka et al., 2009) studies.

To date, no study has reported brain correlates of automatic visual change process in ASD. The present work investigated brain activations elicited by visual change in adults with ASD to determine whether there are abnormalities comparable to those reported in the auditory modality, and thus whether unusual reactions to change might be underlain by atypical general change processing independent of sensory modality. To localize brain activations elicited by unattended visual change in healthy adults, we designed an fMRI study using a passive three-stimulus oddball paradigm, adapted from Besle et al. (2005). Stimuli consisted of the dynamic deformation of a circle into an ellipse either horizontally or vertically, resulting in two different shapes and thus involving two visual dimensions: object shape and motion direction. Based on previous electrophysiological, magnetoencephalographical and functional neuroimaging studies reviewed above, a region of interest (ROI) analysis approach was selected. We expected larger activity in the following regions in response to deviant and novel stimuli compared to standard stimuli: BA 17/18/19 (occipital visual region), BA 39/40 (temporo-parietal junction), BA 6/8 (dorsolateral prefrontal cortex), and BA 11 (orbitofrontal cortex). The dynamic stimuli used are expected to elicit activation along the two visual pathways, thus ROIs in BA 7 (dorsal stream) and BA 20 (ventral stream) were included. Finally, the ACC has been repeatedly found to be involved in novelty processing (Clark et al., 2000; Kiehl et al., 2001), and atypical involvement of this region has been described during change detection in the auditory modality (Gomot et al., 2006). Therefore, we also examined the BA 32/24 during automatic detection of novel and deviant stimuli.

To further investigate ACC involvement during automatic change detection, a psychophysiological interaction analysis was done with ACC as the seed region.

2. Materials and methods

2.1. Participants

Twelve adults with high functioning autism or Asperger syndrome aged (mean age (years) ± SD: 28 ± 7; 11 males and 1 female) participated in the experiment. Diagnosis was made according to DSM-IV-R criteria (APA, 2000) and by using the Autism Diagnostic Observation Schedule-Generic (ADOS-G, fourth module) (Lord et al., 2000) (social interaction + communication scores mean ± SD: 10 ± 4; threshold for ASD = 7). Diagnosis was complemented by the Autism Spectrum Quotient (AQ) (Baron-Cohen et al., 2001) (mean ± SD: 38 ± 7; threshold for ASD = 32). Intellectual quotients (IQ) were assessed by the Wechsler Adult Intelligence Scale (WAIS-III) (Wechsler, 1997), which provided overall intellectual (mean ± SD: IQ: 114 ± 21), verbal (VIQ: 119 ± 18) and performance (PIQ: 101 ± 22) quotients. Adults with ASD were age matched with seventeen healthy volunteer adults (mean age (years) ± SD: 27 ± 6; 15 males and 2 females), none of whom had a previous history of neurological or psychiatric problems. All participants had normal or corrected-to-normal vision and none were receiving psychotropic medication. The Ethics Committee of the University Hospital of Tours approved the protocol. Written informed consent from all participants was obtained.

2.2. Stimuli and experimental design

Change detection process was studied through an oddball paradigm with three different types of stimuli, using an event-related fMRI paradigm. The stimuli consisted of the deformation of a circle into an ellipse either horizontally (Standard) or vertically (Deviant) or into another, always novel, non-meaningful shape (Novel), adapted from Besle et al. (2005) (Fig. 1). The amount of deformation in either direction relative to the diameter was 33% and lasted 140 ms. Between each deformation, the circle remained present on the screen. Each stimulus was constituted of seven successive images presented in 140 ms (i.e. 20 ms per image) which resulted in apparent motions in the stimulus. Sequences included ‘Standard’, ‘Deviant’ (probability of occurrence...
P = 0.03) and ‘Novel’ (probability of occurrence P = 0.03) stimuli. The total number of stimuli was 1395. To control for effects related to the stimulus features, 2 runs were performed in which Standards and Deviants were counterbalanced. In order to present the visual stimuli outside the focus of attention, a primary task was required. Subjects were asked to fixate at a central cross and to respond to its disappearance (target stimuli: 7% of the trials) by pressing a button with the right thumb as quickly as possible. This disappearance had a duration of 120 ms and occurred unpredictably within a standard trial, was desynchronized relative to the standard onset and could not occur during a standard preceding a deviant trial. Visual stimuli were presented with a constant interstimulus interval of 650 ms. Three resting periods of 15 s each (involving a black screen watching) were presented at the beginning, at the middle and at the end of the sequence.

2.3. Behavioral responses

For each subject, the reaction times (in ms) and response accuracy were measured by taking into account the rates of hits, false alarms to non-target stimuli and missed targets, according to the formula: (targets – missed targets) × 100/(targets + false alarms).

2.4. fMRI procedure

2.4.1. Data acquisition

Magnetic resonance data were acquired on a 1.5-T Siemens Magnetom scanner (Siemens AG, Erlangen, Germany). Structural image were a 3-D anatomical T1-weighted sequence (repetition time: 1970 ms; echo time: 3.93 ms; inversion time = 1100 ms; FOV: 256; matrix size: 256 voxel size: 1 × 1 × 1 mm³). Data were acquired in the sagittal plane. Functional images were collected using a T2*-weighted gradient-echo EPI sequence with TR = 2.5 s, TE = 50 ms, and flip angle = 90°. The acquisition volume consisted of 29 interleaved axial (AC/PC) slices with slice thickness = 4 mm and interslice gap = 0 mm. The matrix was 64 × 64 with a 220 cm field of view, yielding an in-plane resolution of 3.4 × 3.4 mm.

2.4.2. Image pre-processing

Image preprocessing was performed using statistical parametric mapping software (SPM5, Wellcome Department of Cognitive Neurology, London, http://www.fil.ion.ucl.ac.uk/spm). Functional volumes were first time corrected, motion corrected by spatial realignment to the first volume and then normalized to the MNI reference brain (courtesy of the Montreal Neurological Institute).

The normalized functional images were finally spatially smoothed with an 8 mm FWHM (full-width half-maximum) Gaussian kernel. The six estimated movement parameters were included as covariates in the design matrix.

2.4.3. Statistical analyses

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 events (Target, Standard, Deviant, Novel, Rest) were modeled separately by a canonical hemodynamic response function and its first-order temporal derivative. The three standard stimuli following a resting period as well as the standard stimulus following a rare stimulus (deviant stimulus, novel stimulus or target) were modeled as separate events. Contrast images (Standard–Rest, Deviant–Standard and Novel–Standard) consisting of statistical parametric maps (SPMs) of t statistics at each voxel were then produced for each individual.

Analyses were completed using different methods. A whole brain analysis was used for the standard minus rest contrast. Individual SPM(t) were entered into a second level group analysis permitting inferences about condition effects across subjects that generalize to the population (i.e., random effects analysis). SPM(t) statistics were computed for this 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).

For the Deviant–Standard and Novel–Standard contrasts analyses were performed by investigating a priori regions of interest (ROIs) using the WFU PickAtlas toolbox (version 2.4, Maldjian et al., 2003) within SPM5. We based our regions of interests (ROIs) on findings from previous studies that localized generators of visual automatic change detection process. BA 17–18–19 (occipital cortex), BA 39–40 (posterior parietal cortex), BA 6–8 (anterior premotor cortex), BA 11 (orbitofrontal cortex), BA 20 (ventral stream) and BA 7 (dorsal stream) and the ACC were examined (BA 32/24). These ROIs were defined in MNI space. The locations of significant activations were expressed in Talairach coordinates (Talairach and Tournoux, 1988), using a non-linear transformation, as implemented in the WFU PickAtlas and based on the method developed by Matthew Brett (http://www.imaging.mrc-cbu.cam.ac.uk/imaging/Mni2Talairach). The differences between the two groups were evaluated by computing for each contrasts the SPM(t) using a two sample Student’s t. Statistical threshold was set at P < 0.05 with small volume correction (Worsley et al., 1996).

2.4.4. Psychophysiological interaction analysis

The PPI analysis is a seed-region-based measure that establishes predictive linkages of neural activity in one cortical area based on the activity in the chosen seed region within the experimental or psychological context (Friston et al., 1997). PPI can reveal the interactive effect between the experimental condition and the predictive activity from the seed region. Although PPI analysis cannot provide detailed information about mutual modulatory facilitations among multiple cortical regions, it nevertheless provides data on how the activities in one region influence those in other brain regions, which served to test the specific hypothesis of the present study. We conducted a PPI analysis to estimate dynamic coupling between ACC and the other ROIs previously defined during visual deviance detection. For each participant, the ACC time-series was derived by extracting the first eigenvariate time series (“volumes of interest” within SPM5) from a sphere of 8 mm radius centered in the seed coordinates obtained in the ROI analysis for the deviant minus standard contrast. These time series were mean-corrected and high-pass filtered to remove low-frequency signal drifts. PPI analyses were then carried out for each subject by creating a design matrix with the interaction term, the psychological factor, and the physiological factor as
regressors. For each subject, voxel-wise PPI effects were estimated, and statistical parametric maps (SPMs) were produced for the PPI term. The resulting contrast images were used in a second-level PPI group analysis, comparing the PPI contrast images between adults with ASD and controls in a two-sample t-test. Statistical threshold was set at P<0.05 with small volume correction (Worsley and Friston, 1995). The locations of significant activations were expressed in Talairach coordinates (Talairach and Tournoux, 1988), using a non-linear transformation, as implemented in the WFU PickAtlas.

3. Results

3.1. Behavioral results

Both groups performed the distraction task well, indicating that they looked at the screen and perceived the visual stimuli; no significant between groups difference was found, neither in response accuracy (Ctrl: 98.4%±1.2; ASD: 96.2%±6.4; n.s) nor in reaction times (Ctrl: 453 ms±78; ASD: 459 ms±62; n.s).

3.2. fMRI results

3.2.1. Activations common to both groups

3.2.1.1. Standard stimuli. Combining data from all control and ASD participants, the whole brain analysis of the contrast between standard and rest conditions produced significant activation of posterior brain regions (P<0.01, FDR corrected). Left and right middle occipital gyri (BA 18, left: x=−28, y=−99, z=3 and right: x=26, y=−93, z=0) were more activated in the standard condition than during rest.

3.2.1.2. Deviance detection. Main findings from the ROI analysis of brain activation elicited by deviant stimuli compared to standard stimuli in both groups combined (Controls+ASD) are listed in Table 1 (with P levels after small volume corrections) and illustrated in Fig. 2. Generically activated regions mainly included the left anterior premotor cortex (BA 6/8). Left-lateralized activation was also seen in the orbital cortex (BA 11) and the left posterior parietal cortex (BA 7). Finally, activations of the left posterior parietal cortex (BA 7) were elicited by visual deviant stimuli.

3.2.1.3. Novelty detection. Table 1 also shows the main findings from the ROI analysis of brain activations elicited by novel stimuli compared to standard stimuli in both groups combined. Significant bilateral activations were revealed in the occipital cortex (BA 19) and in orbitofrontal cortex (BA 11). Left-lateralized activations were found in the middle frontal gyrus (BA 6/8). Finally, only the visual dorsal stream displayed significant activation (BA 7) (Fig. 2).

3.2.1.4. Salience effect. Although brain activity elicited by visual deviant and novel stimuli appeared very comparable, a degree-of-deviance effect was observed (Fig. 2); compared to deviant stimuli, novel stimuli elicited greater activity in bilateral occipital regions (BA 19) and in orbitofrontal cortex (BA 11).

3.2.2. Activation differences between groups

3.2.2.1. Standard stimuli. ROI analysis was performed using the WFU PickAtlas toolbox (version 2.4, Maldjian et al., 2003) within SPM5. Two spheres were drawn centered around the peaks of activation common to both groups but no significant between groups differences were found for the standard vs. rest contrast.

3.2.2.2. Deviant and novel stimuli. The same between group differences were observed in response to deviant and novel stimuli (Table 2, Fig. 3). Compared to adults with ASD, controls revealed greater activity in bilateral anterior premotor cortex (BA 6/8) and in the right orbitofrontal cortex (BA11). The bilateral temporal cortex was more activated in controls than in ASD during visual change perception. Conversely, adults with ASD showed stronger BOLD signal in bilateral visual areas (BA 18/19) and the ACC (BA 32/24).

3.2.3. PPI analysis

Using PPI analyses, we found significant between group differences in the connectivity maps of the seed region (Table 3, Fig. 4). While the ACC displayed functional connectivity during deviancy detection with the orbitofrontal cortex (BA 11), the anterior premotor cortex (BA 6), the posterior parietal cortex (BA 7) and the inferior temporal cortex (BA 7) in the control group, this seed region only showed functional connectivity with occipital regions (BA 18/19) and posterior parietal cortex (BA 7) in ASD.

4. Discussion

The present study is the first to demonstrate brain activations associated with automatic visual change detection in adults with ASD. An oddball paradigm with standard, deviant and novel stimuli was used to localize brain correlates of passive visual change processing, according to the salience of the change.

Combined results across participants highlight the involvement of both occipital (Kimura et al., 2010; Urakawa et al., 2010; Yucel et al., 2007) and frontal (Czigler et al., 2004; Kimura et al., 2011) regions in visual change detection. Both deviant and novel stimuli elicited activations in occipital (BA 19), posterior parietal (BA 7), anterior

Table 1
Main results from the ROI analysis of brain activations elicited in both groups by deviant stimuli compared to standard stimuli (N=29; control+autism; P<0.05, small volume correction). R=right; L=left.

| Functional comparison | Region | BA | Structures | Talairach coordinates | Voxels | t | P |
|-----------------------|--------|----|------------|-----------------------|--------|---|---|
| Dev>Sta               | Anterior premotor cortex | 8  | L middle frontal gyrus | −44 10 21 | 159 | 3.29 | 0.001 |
|                       | Orbitofrontal cortex | 11 | L medial frontal gyrus | −6 42 33 | 119 | 2.75 | 0.005 |
|                       | Occipital cortex | 19 | R middle occipital gyrus | 38 −84 21 | 73 | 2.66 | 0.006 |
|                       |         | 19 | L middle occipital gyrus | −40 −74 42 | 47 | 2.45 | 0.010 |
| Nov>Sta               | Posterior parietal cortex | 7 | L precuneus | −38 −72 46 | 267 | 3.49 | 0.001 |
|                       | Occipital cortex | 19 | R middle occipital gyrus | 38 −85 21 | 287 | 3.49 | 0.001 |
|                       |         | 19 | L middle occipital gyrus | −30 −83 19 | 270 | 2.92 | 0.003 |
|                       | Anterior premotor cortex | 8 | L middle frontal gyrus | −50 14 42 | 151 | 3.15 | 0.002 |
|                       | Orbitofrontal cortex | 11 | L orbital gyrus | −2 42 −19 | 93 | 2.98 | 0.003 |
|                       |         | 11 | R orbital gyrus | 2 42 −19 | 65 | 2.85 | 0.004 |
|                       | Posterior parietal cortex | 7 | L superior parietal lobe | −18 −30 38 | 9 | 2.30 | 0.014 |
premotor (BA 6/8) and orbitofrontal (BA 11) cortices. A salience effect was observed, as novel stimuli elicited greater activity in the sensory occipital regions (BA 19) than deviant stimuli, suggesting that novelty detection involves an additional activation of sensory areas to process unexpected change in shape and in motion.

The main result of the group comparison during visual change detection was that adults with ASD showed stronger activity in the bilateral occipital cortices (BA 18/19) than controls. Several neuroimaging studies have revealed stronger task-related activity in visual cortex in autism, shown as higher levels of activity associated with visual information processing (Belmonte and Yurgelun-Todd, 2003; Brown et al., 2005). Atypical perceptual processing, often manifested as enhanced perceptual performance (Dakin and Frith, 2005), is now included as an associated feature of the autistic phenotype (Belmonte et al., 2004). Autistic visual strengths are consistently reported for the Block Design subtest of the Wechsler Intelligence Scales (Caron et al., 2006; Shah and Frith, 1993), the Embedded Figures Task (Joliffe and Baron-Cohen, 1997), visual search tasks (Joseph et al., 2009; Kemner et al., 2008; O’Riordan, 2004; O’Riordan et al., 2001), and visual discrimination tasks (Bertone et al., 2005; Plaisted et al., 1998). In addition, an increasing number of studies have demonstrated early sensory processing advantages or atypicalities in stimulus dimension extraction in ASD, with examples including crowding (Baldassi et al., 2009; Keita et al., 2010), contour and texture processing (Pei et al., 2009; Vandenbroucke et al., 2008) and spatial frequency processing (Jemel et al., 2010; Milne et al., 2009). Higher activity in the occipital cortex in ASD was also reported in an fMRI study in relation to increased search efficiency during a visual search task (Keehn and Joseph, 2008). These results suggest that ASD behavioral advantages might arise from stronger and more pervasive engagement of sensory processing mechanisms. These behavioral

Table 2

Group comparisons of the main findings from the ROI analysis of brain activations elicited by deviant stimuli compared to standard stimuli and by novel stimuli compared to standard stimuli (P<0.05, small volume correction). R = right; L = left.

| Functional comparison | Region | BA | Structures | Talairach coordinates | Voxels | t  | p   |
|-----------------------|--------|----|------------|-----------------------|--------|----|-----|
| Controls>ASD Dev>Sta | Anterior premotor cortex | 6  | R medial frontal gyrus | 6−22 56 | 751 | 4.03 | <0.001 |
|                       |        | 6  | L medial frontal gyrus  | −2−23 55 | 222 | 2.48 | 0.010 |
|                       |        | 8  | L middle frontal gyrus  | −38 12 47 | 152 | 2.83 | 0.004 |
|                       | Orbitofrontal cortex | 11 | R middle frontal gyrus  | 39 37 55 | 35  | 3.50 | 0.001 |
|                       | Inferior temporal cortex | 20 | R inferior temporal gyrus | −58−19 70 | 30  | 2.89 | 0.004 |
| Nov>Sta              | Anterior premotor cortex | 6  | L medial frontal gyrus  | −2−23 55 | 560 | 3.85 | <0.001 |
|                       |        | 6  | L middle frontal gyrus  | 4−26 60 | 101 | 2.97 | 0.003 |
|                       | Orbitofrontal cortex | 11 | R middle frontal gyrus  | 38 38 −6 | 281 | 3.43 | 0.001 |
|                       | Inferior temporal cortex | 20 | L inferior temporal gyrus | −61−18 43 | 3.70 | <0.001 |
|                       |        | 20 | L inferior temporal gyrus | −53−19 33 | 2.89 | 0.004 |
| ASD>controls Dev>Sta | Occipital cortex | 18 | R cuneus | 20−68 7 492 | 3.82 | <0.001 |
|                       |        | 18 | L cuneus | −10−70 7 369 | 2.95 | 0.003 |
|                       |        | 19 | L superior occipital gyrus | −40−84 24 | 86  | 3.14 | 0.002 |
|                       | Posterior parietal cortex | 7  | L superior parietal lobule | −14−39 62 | 75  | 2.16 | 0.020 |
|                       | Anterior Cingulate cortex | 32 | R anterior cingulate gyrus | 4−18 18 1024 | 3.85 | <0.001 |
|                       | Occipital cortex | 18 | R cuneus | 20−68 7 1024 | 3.85 | <0.001 |
|                       |        | 18 | L cuneus | −12−68 7 609 | 3.41 | 0.001 |
|                       |        | 19 | L superior occipital gyrus | −32−90 23 | 86  | 3.14 | 0.002 |
| Nov>Sta              | Posterior parietal cortex | 7  | L superior parietal lobule | −16−59 62 | 206 | 3.68 | 0.001 |
|                       |        | 7  | R superior parietal lobule | 12−56 64 178 | 3.23 | 0.002 |
characteristics, along with other aspects of the autistic perceptual phenotype, have been summarized in the Enhanced Perceptual Functioning Model (EPF) (Mottron et al., 2006). Assuming generally stronger physiological engagement of the visual system in autism, this model predicts superior perceptual performance and a wider role for perceptual processes in autistic cognition.

Associated with this greater occipital activation, adults with ASD showed less activity than controls in anterior premotor (BA 6) and orbitofrontal cortices (BA 11). It is well established that damage to orbitofrontal cortex (OPC) and adjacent medial prefrontal cortex can result in impairments to flexibly modulate action selection in the face of changing contingencies (Fellows and Farah, 2005; Hornak et al., 2004). The FEF (BA 6/8) regions have been shown to play a major role in the voluntary shift of visual attention and to be particularly important for top-down regulated attentional processes (Donner et al., 2000; Goebel et al., 1998; Schall, 2002; Wojciulik and Kanwisher, 1999). This literature suggests that the brain activations observed in orbitofrontal regions and anterior premotor cortex are related to the inhibition of motor responses to task-irrelevant stimulus deviations. Reduced frontal activity in association with larger occipital activity in ASD has also been reported for tasks incorporating a broad range of cognitive and perceptual components, including embedded figure detection (Ring et al., 1999), attention shifting (Belmonte and Yurgelun-Todd, 2003), saccades to visual targets (Luna et al., 2002), working memory (Koshino, 1999), and anticipation of cognitively demanding tasks (Carter et al., 1999; Posner and Petersen, 1990; Reischies et al., 2005; Taylor et al., 2007).

The third main group differences in brain structures involved in visual change perception were the greater activity observed in the ACC in ASD than in controls. The ACC is a complex structure which has been functionally and anatomically dissociated into 3 subdivisions: affective, cognitive and motor. The abnormal activity we found in ASD was located in the cognitive part of the ACC. This cognitive subdivision is part of a distributed attentional network and has been assigned with various functions, including modulation of attention or executive functions by influencing sensory or response selection (or both); monitoring competition, complex motor control, novelty and error detection; and anticipation of cognitively demanding tasks (Carter et al., 1999; Posner and Rothbart, 1998) (Cabeza et al., 1997; Devinsky et al., 1995; Elliott and Dolan, 1998; Garavan et al., 2002; Menon et al., 2001; Posner and Petersen, 1990; Reischofs et al., 2005; Taylor et al., 2007).

In view of the processes engaged during the paradigm we used, has been proposed in ASD (Just et al., 2004; Thai et al., 2009; Wicker et al., 2008). This theory suggests that the behavioral markers of autism are directly or indirectly caused by limitations in communication between frontal and posterior brain regions, and predicts that these limitations will impact those tasks that require extensive coordinated functioning of frontal and posterior processing centers. The theory accounts for restricted repetitive and stereotyped patterns of behavior in terms of the inability of the frontal executive system to exert control over posterior processing centers. Thus the theory posits a biological mechanism, frontal–posterior connectivity disruption, which may be able to explain diverse impairments that characterize ASD (Schipul et al., 2011).

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The third main group differences in brain structures involved in visual change perception were the greater activity observed in the ACC in ASD than in controls. The ACC is a complex structure which has been functionally and anatomically dissociated into 3 subdivisions: affective, cognitive and motor. The abnormal activity we found in ASD was located in the cognitive part of the ACC. This cognitive subdivision is part of a distributed attentional network and has been assigned with various functions, including modulation of attention or executive functions by influencing sensory or response selection (or both); monitoring competition, complex motor control, novelty and error detection; and anticipation of cognitively demanding tasks (Carter et al., 1999; Posner and Rothbart, 1998) (Cabeza et al., 1997; Devinsky et al., 1995; Elliott and Dolan, 1998; Garavan et al., 2002; Menon et al., 2001; Posner and Petersen, 1990; Reischofs et al., 2005; Taylor et al., 2007).

In view of the processes engaged during the paradigm we used, has been proposed in ASD (Just et al., 2004; Thai et al., 2009; Wicker et al., 2008). This theory suggests that the behavioral markers of autism are directly or indirectly caused by limitations in communication between frontal and posterior brain regions, and predicts that these limitations will impact those tasks that require extensive coordinated functioning of frontal and posterior processing centers. The theory accounts for restricted repetitive and stereotyped patterns of behavior in terms of the inability of the frontal executive system to exert control over posterior processing centers. Thus the theory posits a biological mechanism, frontal–posterior connectivity disruption, which may be able to explain diverse impairments that characterize ASD (Schipul et al., 2011).

**Table 3**

| Functional comparison | Region | BA | Structures | Talairach coordinates | Voxels | t | p |
|-----------------------|--------|----|------------|-----------------------|--------|---|---|
| Controls > ASD | Orbitofrontal cortex | 11 | R medial frontal gyrus | 8 40 −15 | 310 | 4.15 | <0.001 |
| Dev> Sta | Anterior premotor cortex | 6 | L middle frontal gyrus | −42 9 55 | 113 | 3.79 | 0.001 |
| ASD > controls | Posterior parietal cortex | 7 | L superior parietal lobule | −34 −73 46 | 79 | 3.42 | 0.002 |
| Dev> Sta | Inferior temporal cortex | 20 | R inferior temporal gyrus | 63 −18 −18 | 54 | 3.09 | 0.003 |
| | | 20 | L inferior temporal gyrus | −64 −18 −22 | 51 | 3.02 | 0.004 |
| | Occipital cortex | 18 | L middle occipital gyrus | −32 −80 11 | 381 | 3.22 | 0.002 |
| | | 19 | R superior occipital gyrus | 32 −78 26 | 296 | 3.40 | 0.002 |
| | | 19 | R fusiform gyrus | 32 −76 −9 | 222 | 4.37 | <0.001 |
| | | 18 | L cuneus | −6 −94 26 | 34 | 2.05 | 0.008 |
| | | 7 | L superior parietal lobule | −32 −48 59 | 28 | 3.00 | 0.004 |

Fig. 3. Group comparisons of the main findings from the ROI analysis of brain activation elicited by deviant stimuli compared to standard stimuli. Regions more activated in the control group than in ASD are shown in yellow and conversely, regions more activated in ASD than in controls are shown in blue. Voxels with activation significant at P < 0.05 after small volume correction.
in the strength of long-distance pathways in ASD may thus be
long-distance pathways (Zikopoulos and Barbas, 2010). Reduction
occupation of sites normally available to the considerably sparser
prefrontal areas revealed an exuberance of thin axons that course over
tomically, recent studies of axonal connectivity of area 32 of ACC and
ASD, the ACC was more functionally connected to sensory regions
PPI analyses, with the ACC as the seed region. Results showed that in
of this structure with other brain areas in our paradigm, we conducted
increased functional connectivity with other brain regions (Kana et al.,
2004). Aberrant connectivity is also suggested by
tions between this region and other brain structures (Barnea-Goraly
2000) and of reduced fractional anisotropy in the white matter adjacent
to the anterior cingulate gyri, suggesting a disruption of neural connec-
tions between this region and other brain structures (Barnea-Goraly
et al., 2004). Aberrant connectivity is also suggested by findings of de-
creased functional connectivity with other brain regions (Kana et al.,
2007). In order to investigate the role and the functional connectivity of
this structure with other brain areas in our paradigm, we conducted PPI analyses, with the ACC as the seed region. Results showed that in
ASD, the ACC was more functionally connected to sensory regions
than to prefrontal and orbitofrontal cortices as seen in controls. Ana-
atomically, recent studies of axonal connectivity of area 32 of ACC and
prefrontal areas revealed an exuberance of thin axons that course over
short or medium distances in the ASD brain, which may lead to
occupation of sites normally available to the considerably sparser
long-distance pathways (Zikopoulos and Barbas, 2010). Reduction
in the strength of long-distance pathways in ASD may thus be
secondary to the excessive short-range connections of ACC. Again,
this connectivity bias may help in explaining why individuals with
ASD do not adequately shift attention when necessary, and engage in
repetitive and inflexible behavior (Gomot and Wicker, 2012). The
atypical involvement of the ACC in visual change detection can
be related to previous results of Gomot et al. (2006) investigating the
change detection in ASD in the auditory modality. However, the
authors reported atypical inhibitory mechanisms in this region that
could prevent appropriate allocation of pre-attentional processes to
changing events. Our results thus cannot be interpreted as highlight-
ing the same atypical involvement of the ACC in automatic change
detection, regardless of the sensory modality. However, it could be
hypothesized that inappropriate allocation of pre-attentional
resources interfere with change detection and may contribute to
intolerance of change observed in ASD.

In the same vein, several reports suggested that individuals with
ASD focus their attention on less contextually relevant aspects of a
visual scene and notice details which are often ignored by typical
observers. The ability to detect changes in a visual scene has therefore
been investigated in ASD using the change blindness paradigm that
makes it possible to assess unnoticed change effects (Beck et al.,
2001; Rensink et al., 1997). However, analysis of the few studies in
this domain reveals inconsistent findings showing either superior
levels of task performance (Smith and Milne, 2009), similar error
detection rate (Fletcher-Watson et al., 2008) or decreased levels of
performance in ASD (Kikuchi et al., 2009) the latter being mainly re-
lated to a default in context facilitation effect (Fletcher-Watson et al.,
2006; Loth et al., 2008). These findings suggest a weaker influence of
schematic expectations on spontaneous attention to change in indi-
viduals with ASD, but highlight the fact that the brain processes
engaged during both noticed and unnoticed changes need further
study in this population.

In conclusion we found atypical brain correlates of automatic visual
change detection in adults with ASD. Stronger sensory activation has
been highlighted in association with reduced frontal activity in ASD,
congruent with the idea of atypical connectivity between these regions
described in the literature.

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