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A failure to grasp the affective meaning of actions in autism spectrum disorder subjects

J. Grèzes[a,*], B. Wicker[b], S. Berthoz[c], B. de Gelder[d]

[a] Laboratoire de Neurosciences Cognitives, INSERM U960 & DEC, Ecole Normale Supérieure, 29 Rue d'Ulm, 75005 Paris, France
[b] Institut de Neurosciences Cognitives de la Méditerranée, CNRS, Université de Provence, Marseille, France
[c] INSERM U669 & Institut Mutualiste Montsouris, Universités Paris Sud & Paris René Descartes, Paris, France
[d] Donders Laboratory for Cognitive and Affective Neurosciences, Tilburg, The Netherlands

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ABSTRACT

The ability to grasp emotional messages in everyday gestures and respond to them is at the core of successful social communication. The hypothesis that abnormalities in socio-emotional behavior in people with autism are linked to a failure to grasp emotional significance conveyed by gestures was explored. We measured brain activity using fMRI during perception of fearful or neutral actions and showed that whereas similar activation of brain regions known to play a role in action perception was revealed in both autistics and controls, autistics failed to activate amygdala, inferior frontal gyrus and premotor cortex when viewing gestures expressing fear. Our results support the notion that dysfunctions in this network may contribute significantly to the characteristic communicative impairments documented in autism.

1. Introduction

Watching someone running with the hands protectively in front of his/her face triggers in the observer a representation of the action of running away, but also prompts the recognition of the emotional context: that the person runs for cover because he/she is frightened. Grasping the emotional component of the various actions we observe around us is a crucial prerequisite for social communication. As the example shows, the skills needed to decode the emotional components of actions reach beyond the visuo-motor representation of the observed movements. Additional perceptual and cognitive abilities are required to represent the emotional significance of the observed movements. The observer needs to appreciate that running and hiding are significant components of a fear response. Grasping the fear dimension in the actions we observe directs our attention to potential social or environmental threat, which is important for preparing an appropriate adaptive reaction. While facial expressions provide information about feelings and mental states, emotionally elicited behavior is, as stressed by Darwin, at the core of the adaptative significance of experiencing emotions. Therefore, a focus on the perception of gestures and their emotional content provides a unique opportunity to investigate nonverbal aspects of inter-personal communication (de Gelder, 2006). Because fear is phylogenetically primitive and is processed relatively automatically and relatively independently of higher cognitive processes we deemed it is important to investigate how a population with social communicative deficits processes fear expressions communicated by social gestures.

Autism is a neurodevelopmental disorder characterized by a unique profile of impaired social communication and interaction (e.g. Lord et al., 1989) with a major impact on adaptive social behavior (American Psychiatric Association, 1996). Subjects with autism spectrum disorder (ASD) typically lack the ability to grasp the emotional dimension of human actions. Several biological hypotheses have been advanced to account for this problem including amygdala, fusiform and superior temporal gyrus dysfunction (Ashwin, Baron-Cohen, Wheelwright, O'Riordan, & Bullmore, 2007; Baron-Cohen et al., 1999; Pierce, Haist, Sedaghat, & Courchesne, 2004; Schultz, 2005; Zilbovicius et al., 2006), impaired functioning of mirror neuron system (Dapretto et al., 2006; Hadjikhani, Joseph, Snyder, & Tager-Flusberg, 2006; Theoret et al., 2005; Williams, Whiten, Suddendorf, & Perrett, 2001) or abnormal cerebral connectivity (Bachevalier & Loveland, 2006; Belmonte et al., 2004; Geschwind & Levitt, 2007; Frith, 2004; Horwitz, Rumsey, Grady, & Rapoport, 1988; Just, Cherkassky, Keller, & Minshew, 2004; Wickelgren, 2005). So far, these hypotheses have been pursued by

Abbreviations: BOLD, blood oxygenation level-dependent; fMRI, functional MRI; DCM, Dynamic Causal Modelling; AMG, amygdala; PM, premotor; IFG, inferior frontal gyrus; STS, superior temporal sulcus.

* Corresponding author. Tel.: +33 1 44 32 26 76; fax: +33 1 44 32 26 86.
E-mail address: julie.grezes@ens.fr (J. Grèzes).

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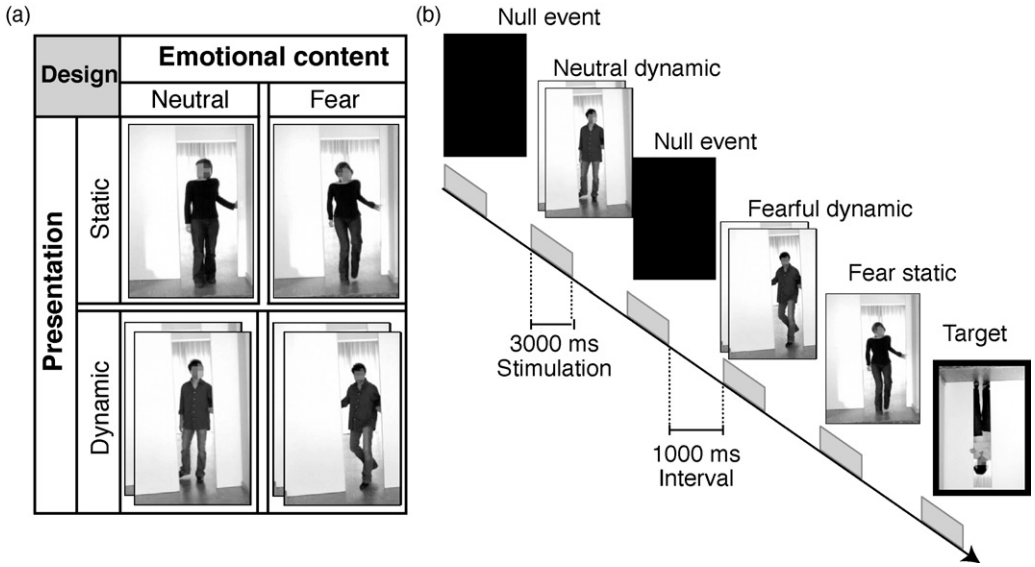

Fig. 1. Design and examples of stimuli. (a) 2 × 2 factorial design. Images were either static or dynamic and consisted of whole-body images of actors opening a door in a neutral or fearful mode. (b) Example of an experimental run and timing. Participants were given an explicit task being instructed to press a button when they saw an upside-down video-clip interspersed among normal videos of body expressions (50%), scrambled ones (25%) and null stimuli (25%). The targets represented 10% of all videos shown. Video stimuli were shown for 3000 ms each with a 1000 ms duration black screen between them.

investigation of deficits in visuo-motor abilities (Williams et al., 2001) and/or face perception (Schultz, 2005).

This study aimed at investigating the cerebral correlates of viewing actions with and without an emotional meaning in a group of normal subjects and a group of subjects with ASD. Additionally, we sought to address directly the hypothesis that autism-associated dysfunction may result from abnormal inter-regional 'effective' cerebral connectivity. Normal and ASD adults underwent fMRI scanning during passive observation of still images (static condition) and short movies (dynamic condition) of fearful or neutral actions (see Fig. 1). To ensure sustained attention during stimulus presentation, participants were instructed to detect occasional upside-down images occurring randomly during a block. This simple task performed equally well by both groups provided a control for visual attention. By contrasting movies to still images we identified brain regions activated by action perception, irrespective of their emotional content. Conversely, by comparing fearful (dynamic and static) to neutral (dynamic and static) stimuli, we revealed activations in the amygdala and other 'social' brain areas, irrespective of the presence of dynamic information. These comparisons allowed us to address directly whether brain areas associated with action perception and recognition of emotional messages were differentially engaged in the two groups.

2. Materials and methods

2.1. Participants

Twelve adults with a diagnosis of ASD (10 male and 2 female; 10 Asperger Syndrome and 2 High-functioning Autistic; age range: 18–56) participated in the experiment. All participants in the ASD group had been diagnosed according to conventional criteria and a review of available medical records confirmed that all met DSM-IV (American Psychiatric Association, 1996) criteria for ASD. Brief interviews ensured that none of them suffered from any mental or neurological disorder other than ASD and that they were free of medication.

The participants of the control group were recruited from a large sample of healthy individuals (see Berthoz, Wessa, Kedia, Wicker, & Grezes, 2008). Twelve controls (all adult males), free of current or past psychiatric or neurological disorders, with low levels of current depressive mood (mean depression score ± SD for the French version of the 13-item Beck Depression Inventory (Collet & Cotraux, 1986) = 2 ± 1.7) and state anxiety (mean anxiety score ± SD for the state portion of the French State-Trait Anxiety Inventory (Bruchon-Schweitzer & Paulhan, 1993) = 35 ± 11) on the day of the scanning session were included. Written consent was obtained after the procedure has been fully explained. The study was approved by the local Ethics Committee and was conducted in accordance with the Declaration of Helsinki. The participants were not specifically informed about the aim of the study. Control subjects were paid for their participation. The participants' descriptive statistics are presented in Table 1. The 2 groups did not differ on age or full-scale IQ (as measured by the Wechsler Abbreviated Scale of Intelligence, Wechsler, 1999).

2.2. Stimuli and experimental design

2.2.1. Materials

48 full-light videos (24 fear and 24 neutral) of 3 s were used for the present experiment. Videos were chosen from a wider set of stimuli on the basis of the reliability of responses from subjects in a pilot study. Details about this validation and the edition of stimuli can be found elsewhere (Grèzes, Pichon, & de Gelder, 2007; Pichon, de Gelder, & Grèzes, 2008). The recordings of stimuli involved 12 professional actors (6 females, 6 males) performing the simple action of opening a door and facing a threat for the "fear" script", opening the same door in a relaxed natural manner and looked ahead for the "neutral script". Actors were filmed in frontal view. Importantly, faces were blurred afterwards such that only information from the body was available. 48 static stimuli (24 fear and 24 neutral) were obtained by selecting a frame at the perceived height of emotional expression.

2.2.2. fMRI experimental design (cf. Fig. 1)

A factorial design with one between-group factor (ASD and controls) and two within group factors ('stimuli': dynamic and static stimuli; 'emotion': fearful and neutral actions) was tested. The experiment consisted of two scanning sessions. During each, a total of 136 stimuli were presented corresponding to 24 stimuli from each category (dynamic fear, static fear, dynamic neutral, static neutral), 10 oddball stimuli (upside-down video-clips) and 30 null events (black screen). A stimulus lasted 3 s and was followed by a black screen of 600 ms. Order of stimuli was fully randomized. Subjects were asked to press a button each time the image was upside-down so that trials of interest were uncontaminated by motor response. A between groups comparison for accuracy and reaction times in the oddball task was performed. For technical reasons, the motor responses were only recorded for 8 subjects per group. There was no difference between groups either in terms of number of responses (Mean Controls = 98%, Mean Autistics = 85%; Two-sample *T*-test, $p > 0.05$) or in terms of reaction times (Mean Controls = 1029.53; Mean Autistics = 1288.57; Two-sample *T*-test, $p > 0.05$). The same results were obtained with the non-parametric Mann–Whitney test (Performance: $p = 0.279$; Reaction Times: $p = 0.161$). Although it is possible that the small sample size may mask a behavioral

Table 1
Summary of age and IQ characteristics of the ASD and control groups.

Measure	ASD ($n = 12$)		Control ($n = 12$)		Mann–Whitney test
	M	S.D.	*M*	S.D.	
Age (years)	26.6	10.4	21	1.6	$p = 0.410$
IQ	102	20.6	119	6.6	$p = 0.195$

Table 2
Conjunction analysis and between-group comparisons for the contrasts revealing the brain regions activated during the perception of Dynamic vs. Static body expressions, irrespective of the emotional content [(Fd + Nd) – (Fs + Ns)].

Brain regions	MNI coordinates			*Z* score	No. voxels
	x	*y*	*z*		
Controls and ASD					
L Inferior occipital–temporal gyrus	−50	−76	0	5.26	1699
L Middle occipital gyrus (Ba 18)	−28	−88	24	4.68	1699
L Middle temporal gyrus	−52	−56	2	4.00	1699
L Middle occipital gyrus	−24	−94	8	4.40	1699
L Superior occipital gyrus	−24	−94	30	3.59	1699
R Inferior temporal cortex (MT/V5)	50	−76	6	3.79	2312
R Middle temporal gyrus	48	−58	0	4.56	2312
R Superior temporal gyrus	56	−40	16	4.18	2312
R Superior temporal sulcus (STS)	56	−46	10	3.75	2312
R Inferior occipital gyrus	44	−68	−16	3.53	2312
R Inferior occipital gyrus (Ba 18/17)	28	−96	4	4.43	202
R Intraparietal sulcus	32	−50	50	3.83	44
R Superior occipital gyrus	36	−78	24	3.61	82
R Precentral gyrus (Ba 6)	44	4	54	3.30	39
R Inferior frontal gyrus (Ba 44/45)	44	18	24	3.08	12
L Temporo-parietal junction, STG	−68	−46	16	3.06	15
Controls > ASD					
R Temporo-parietal junction, STG	54	−36	18	4.32	54
R Inferior temporal gyrus (MT/V5)	46	−74	−6	3.72	204
L Inferior temporal gyrus	−52	−54	0	3.52	71
R Medial superior frontal gyrus	14	48	54	3.63	40
R Superior temporal sulcus, middle part	48	−32	0	3.63	126
R Precentral gyrus (Ba 6)	44	−4	50	3.47	14
L Inferior frontal gyrus (Ba 44/45)	−64	16	12	3.39	13
R Precuneus	10	−68	56	3.37	13
R Middle frontal gyrus	54	14	50	3.33	36
R Inferior temporal gyrus (MT/V5)	−54	−72	6	3.15	18
R Fusiform gyrus/cerebellum	42	−42	−26	3.10	16

$p \leq 0.001$ non-corrected. The direct comparisons were masked inclusively by the contrast of each group at $p < 0.001$.

difference between the two groups, we would like to emphasize that none of our fMRI results and their interpretation presented below are related to the behavioral performance. The oddball task was designed as to ensure that subjects would pay attention to the stimuli. In this respect, the level of performance in both groups indicates that the subjects were indeed attending to the stimuli and detected with accuracy far above the chance level if a stimulus was played upside down.

2.3. fMRI data acquisition

Images were acquired using a 3-T whole-body imager equipped with a circular polarized head coil. For each participant, we first acquired a high-resolution structural T1-weighted anatomical image (inversion-recovery sequence, 1 mm × 0.75 mm × 1.22 mm) parallel to the AC–PC plane, covering the whole brain. For functional imaging, we used a $T2^*$-weighted echo-planar sequence at 36 interleaved 3.5-mm-thick axial slices with 1 mm gap (TR = 2995 ms, TE = 35 ms, flip angle = 80°, FOV = 19.2 cm × 19.2 cm, 64 × 64 matrix of 3 mm × 3 mm voxels). For each session, 173 volumes were acquired.

2.4. fMRI data: statistical analyses

Image analysis was performed with SPM2 (Statistical Parametric Mapping, www.fil.ion.ucl.ac.uk/spm). The first 4 volumes of each functional session were discarded to allow for T1 equilibration effects. The remaining 169 functional images were reoriented, slice-time corrected to the middle slice and spatially realigned to the first volume. These images were normalized to the standard MNI template and sub-sampled at an isotropic voxel size of 2 mm. The normalized images were smoothed with an isotropic 6-mm full-width-half-maximum (FWHM) Gaussian kernel.

A two-stage general linear model was used to examine the effect sizes of each key condition and compare them to the group level. Statistical analysis was also carried out using Statistical Parametric Mapping (SPM2). At the first level, the five following conditions were modelled for each session for each subject: two where subjects saw fearful body expressions, presented in dynamic (Fd) or static format (Fs), two where subjects saw neutral body expressions presented in dynamic (Ns) or static formats (Nd), one where subjects saw oddball-inverted stimuli (Odd). Null events were implicitly modelled. The BOLD response to the stimulus onset for each event-type was convolved with a canonical haemodynamic response function of 3 s. Also included for each subject session were six covariates, corresponding to the temporal derivatives of the realignment parameters (the 3 rigid-body translations and 3 rotations determined from initial image co-registration) in order to capture residual movement-related artefacts, plus a single covariate representing the mean (constant) BOLD signal over scans. The data were high-pass filtered with a frequency cut-off at 128 s.

To compare the groups, a random effects analysis was performed consisting of ANOVAs implemented in SPM2. To do this, we first created images of parameter estimates for the following contrasts for each subject at the first level:

1. Main effects of Dynamic vs. Static actions [(Fd + Nd) – (Fs + Ns)] (see Table 2).
2. Main effects of Fearful vs. Neutral actions [(Fs + Fd) – (Ns + Nd)] (see Table 3).
3. Interaction between Fearful and Dynamic actions [(Fd – Fs) – (Nd – Ns)] (see Table 4).

These contrast images were smoothed with an isotropic 6-mm full-width-half-maximum (FWHM) Gaussian kernel. The effect of Group (Controls vs. ASD) was then computed for each of the 3 contrasts. A non-sphericity correction was applied for variance differences between groups. For each ANOVA, we performed a conjunction analysis to investigate regions of activation that were common to both ASD and control groups. This analysis allows rejection of the null hypothesis only if all the comparisons in the conjunction are individually significant (Friston, Penny, & Glaser, 2005). We also calculated the contrasts between groups to reveal brain areas that were significantly more activated in one group compared to the other.

The statistical parametric maps for the conjunction analyses and the between-group comparisons were thresholded at $Z = 3.09$, $p \leq 0.001$ (uncorrected). These maps were overlaid on the MNI template and labeled using the atlas of Duvernoy (1999) and the anatomy toolbox (www.fzjuelich.de/ime/spm_anatomy_toolbox and for a description, Eickhoff et al., 2005).

2.5. fMRI data: connectivity analyses

Connectivity analyses were carried out with the DCM toolbox in SPM2. Functional imaging data were remodelled at the first level for each subject and for each session, with a design matrix comprising the five following regressors, encoding (a) dynamic trials, (b) static trials, (c) fearful trials, and (d) neutral trials and (e) oddball-inverted trials. Null events were implicitly modelled. The BOLD response to the stimulus onset for each event-type was convolved with a canonical haemodynamic response function of 3 s. Also included for each subject session were six covariates, corresponding to the temporal derivatives of the realignment parameters (the 3 rigid-body translations and 3 rotations determined from initial image co-registration) in order to capture residual movement-related artefacts, plus a sin-

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Table 3
Conjunction analysis and between-group comparisons for the contrasts revealing the brain regions activated during the perception of Fearful vs. Neutral actions, irrespective of Static or Dynamic information [(Fs + Fd) – (Ns + Nd)].

Brain regions	MNI coordinates			*Z* score	No. voxels
	x	*y*	*z*		
Controls and ASD					
L Inferior temporal gyrus (MT/V5)	−48	−76	4	3.86	87
R Superior temporal sulcus (STS)	54	−44	10	3.07	86
R Inferior temporal gyrus (MT/V5)	48	−64	6	3.14	71
L Linual gyrus (Ba 18)	−24	−100	−10	3.23	22
L Superior temporal sulcus (STS)	−46	−52	10	3.23	55
Controls > ASD					
R Inferior frontal gyrus (Ba 45)	52	22	0	3.71	46
R Precentral gyrus (Ba 6)	44	−6	56	3.53	76
R Inferior temporal gyrus	46	−16	−24	3.33	21
R Precentral gyrus (Ba 6)	22	−16	74	3.12	11
R AMG	36	−4	−20	3.03	6
R Middle/inferior temporal gyrus	58	−44	−6	3.01	10
ASD > Controls					
L Medial anterior superior frontal gyrus	-6	62	10	3.62	10

$p \leq 0.001$ uncorrected; the direct comparisons were masked inclusively by the contrast of each group at $p < 0.001$.

Table 4
Conjunction analysis and between-group comparisons for the contrasts revealing the brain regions activated for the interaction between Fearful body expression and Dynamic information [(Fd – Fs) – (Nd – Ns)].

Brain regions	MNI coordinates			*Z* score	No. voxels
	x	*y*	*z*		
ASD and Controls					
R Superior temporal sulcus (STS)	60	−48	10	3.17	11
Controls > ASD					
R Precuneus	18	−54	48	4.29	32
R Superior temporal sulcus (STS)	44	−60	20	4.19	19
R Inferior frontal gyrus, *pars triangularis*	62	28	20	3.52	21
R Middle cingulate cortex	12	−42	44	3.50	13
R Linual gyrus (Ba 17/18)	16	−60	8	3.21	17
ASD > Controls					
R Temporal gyrus, anterior part	44	0	−20	5.08	65
L Temporal pole/insula	−34	10	−16	3.94	19
L Temporo-parietal junction	−36	−38	20	4.90	27

$p \leq 0.001$ uncorrected; the direct comparisons were masked inclusively by the contrast of each group at $p < 0.001$.

gle covariate representing the mean (constant) BOLD signal over scans. The data were high-pass filtered with a frequency cut-off at 128 s.

For each subject, two dynamic causal models were then constructed which involved 6 right-lateralized regions of interest. These included the right occipital gyrus (OCC) [mean coordinates Controls (*x*, *y*, *z*): 30, −98 4; mean coordinates ASD (*x*, *y*, *z*): 28 −96 2], the right superior temporal sulcus (STS) [mean coordinates Controls (*x*, *y*, *z*): 58 −40 10; mean coordinates ASD (*x*, *y*, *z*): 56 −40 10], the right fusiform gyrus (FG) [mean coordinates Controls (*x*, *y*, *z*): 44 −58 −20; mean coordinates ASD (*x*, *y*, *z*): 44 −58 −18], the right amygdala (AMG) [mean coordinates Controls (*x*, *y*, *z*): 24 −4 −20; mean coordinates ASD (*x*, *y*, *z*): 24 0 −22], the right premotor cortex (PM) [mean coordinates Controls (*x*, *y*, *z*): 44 0 54; mean coordinates ASD (*x*, *y*, *z*): 42 0 52] and the right inferior frontal gyrus (IFG) [mean coordinates Controls (*x*, *y*, *z*): 52 26 0; mean coordinates ASD (*x*, *y*, *z*): 56 28 0]. The coordinates (in terms of *x*, *y* and *z*) did not differ between the 2 groups ($p > 0.05$). The above mentioned 6 ROIs, defined as 5 mm-radius spheres, were extracted on peak effects in each subject-specific statistical parametric map at $p = 0.05$ and adjusted for effect of interests. To do so, we used the coordinates found in the control group only as a start, to then look, in each subject-specific statistical parametric, for the closest maxima which corresponded to the individual peak effect.

The ROIs were then fed into separate DCMs for each subject/session. In the first model, a stimulus function that encoded the visual input (Dynamic and Static stimuli) was connected to the right STS (see Fig. 4, schema), whereas in the second model, it was connected to the OCC. In the first model (STS, AMG, PM, IFG), "bilinear terms" which refer to changes in effective connectivity were specified to examine the influence of context type on all backward and forward connections between the STS, the AMG, the PM and the IFG (see Fig. 4, schema). This influence was encoded as a canonical haemodynamic response function of 3 s, indicating the context type (neutral or fearful). The second DCM model also comprised backward and forward connections between OCC and FG, OCC and STS, STS and AMG, as well as FG and AMG. This later model aimed at testing whether there was a failure of feed-forward visual signals to reach STS and/or AMG from fusiform and extra-striate regions as previously suggested in the literature (Castelli, Frith, Happe, & Frith, 2002; Pierce et al., 2004; Schultz, 2005). The connections between our regions of interest within the two estimated DCM models were motivated by our current knowledge of anatomical connections in macaque monkeys (Amaral, Behniea, & Kelly, 2003; Amaral & Price, 1984; Avendano, Price, & Amaral, 1983; Barbas, 2000; Carmichael & Price, 1995; Luppino, Calzavara, Rozzi, & Matelli, 2001).

After DCMs had been estimated, we extracted and averaged the coefficients across sessions for each subject and then take the ensuing subject-specific parameters to a second level for population inference (Holmes & Friston, 1998) using SPSS software. The modulatory effects for the comparison between Fearful and Neutral contexts on the connectivity strength are presented for the ASD and control groups in Tables 5 and 6 and are shown in Fig. 4. Two-sample *T*-tests were used to assess statistical significance. A threshold of $p < 0.05$ was used for all connectivity analyses.

3. Results and discussion

First, we assessed the commonalities between the two groups while subjects perceived dynamic as compared to static whole-body actions. To do so we performed a conjunction analysis for the contrasts between dynamic and static stimuli in each group thus revealing a common distributed network of brain regions. This network includes the posterior part of the superior temporal sulcus (STSp), the intraparietal sulcus (IPS), the precentral gyrus and the dorsal part of inferior frontal gyrus (BA 6 and BA 44) (cf. Fig. 2a–d and Table 2). The identified set of brain areas corresponds to the areas frequently observed in previous human and non-human primate studies of action perception and motor execution and it is

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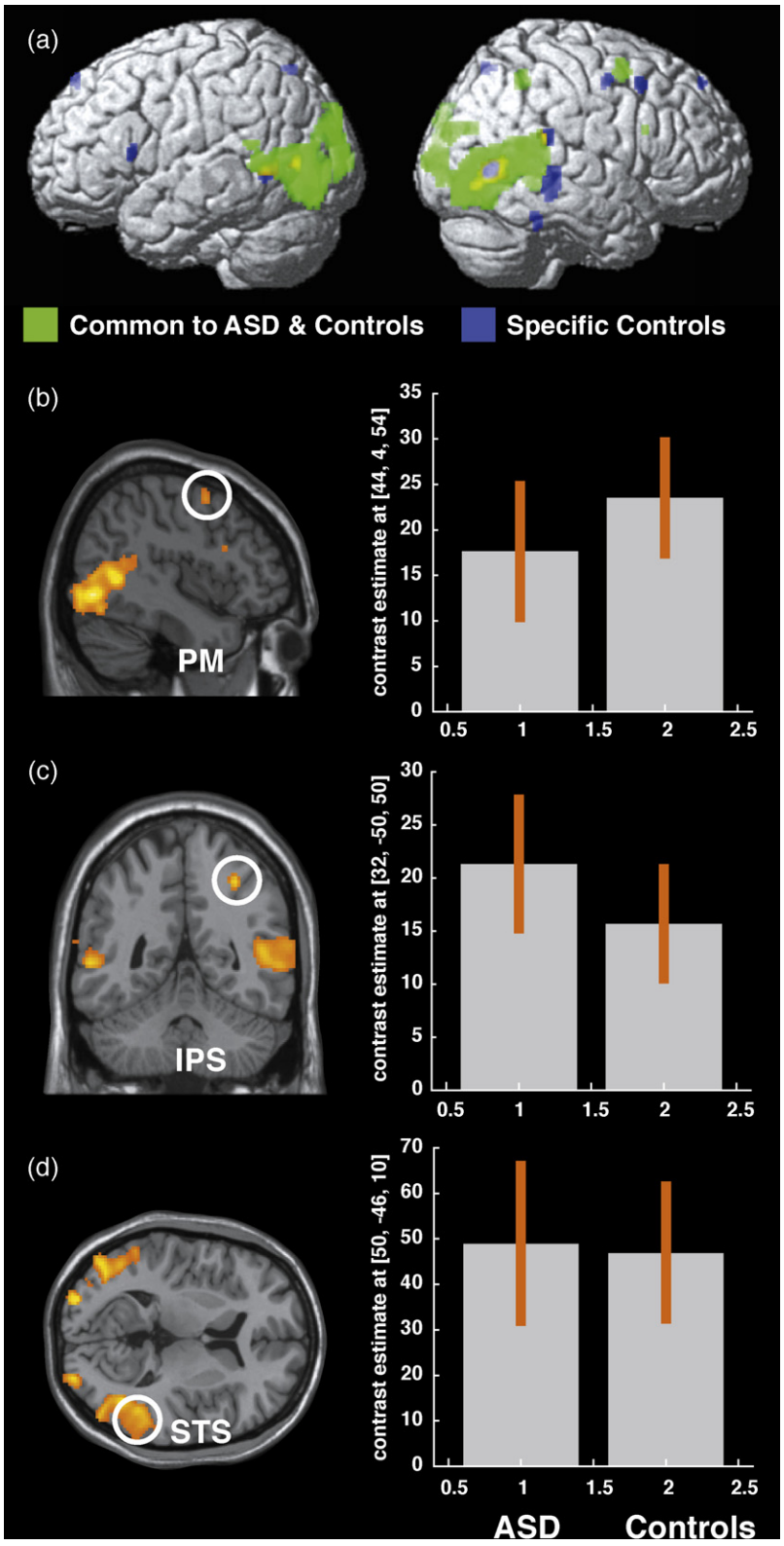

Fig. 2. (a) Brain regions common to ASD and controls as revealed by a conjunction analysis (Green) or specific to controls (Blue) showing amplitude differences when subjects saw Dynamic vs. Static body expressions, irrespective of emotional content and rendered on the MNI brain. (b) Common activation of the right premotor cortex (PM) superimposed on a saggital section of the MNI brain and mean value of the parameter estimates (arbitrary units, mean centered) for the maxima of the right PM (x, y, z = 44 4 54) for both groups. (c) Common activation of the right intraparietal sulcus (IPS) superimposed on a coronal section of the MNI brain and mean value of the parameter estimates (arbitrary units, mean centered) for the maxima of the right IPS (x, y, z = 32 −50 50) for both groups. (d) Common activation of the right superior temporal sulcus (STS) superimposed on a coronal section of the MNI brain and mean value of the parameter estimates (arbitrary units, mean centered) for the maxima of the right STS (x, y, z = 50 −46 10) for both groups.

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Table 5
Model testing for changes in connectivity strength during Fearful context as compared to Neutral context in ASD and control groups. STS: superior temporal sulcus, AMG: amygdala, PM: premotor, IFG: Inferior frontal gyrus.

Connections	Changes in connectivity strength for Fear vs. Neutral context	
	ASD Fear vs. Neutral	Controls Fear vs. Neutral
STS–AMG	0.032	0.040
STS–PM	0.023	0.067
STS–IFG	0.037	0.085
AMG–STS	0.007	0.019*
AMG–PM	0.001	0.015*
AMG–IFG	0.004	0.012*
PM–STS	0.012	0.028*
PM–AMG	0.012	0.004
PM–IFG	0.011	0.022
IFG–STS	0.009	0.017
IFG–AMG	0.008	0.003
IFG–PM	0.003	0.013*

* $p < 0.05$.

Table 6
Model testing for changes in connectivity strength during Fearful context as compared to Neutral context between the occipital region (OCC), the fusiform gyrus (FG), the superior temporal sulcus (STS) and the amygdala (AMG) in ASD and control groups.

Connections	Changes in connectivity strength for Fear vs. Neutral context	
	ASD Fear vs. Neutral	Controls Fear vs. Neutral
OCC–FG	0.073*	−0.453
OCC–AMG	0.043	0.062
OCC–STS	0.063	0.067
FG–OCC	0.007	0.001
FG–AMG	0.013	0.020
FG–STS	0.016	0.019
AMG–OCC	−0.000	0.010
AMG–FG	0.005	−0.003
AMG–STS	0.005	0.011
STS–OCC	0.003	0.005
STS–FG	0.022*	−0.016
STS–AMG	0.021	0.021

* $p < 0.05$.

considered to reflect automatic activation of motor representations during action perception (Decety & Grèzes, 1999; Gallese, Fadiga, Fogassi, & Rizzolatti, 1996; Gallese, Keysers, & Rizzolatti, 2004; Jeannerod, 2001; Rizzolatti, Fadiga, Gallese, & Fogassi, 1996; Rizzolatti, Fogassi, & Gallese, 2001).

The group-by-dynamic interaction, independent of emotional content, revealed that the activations in control subjects are more spread than in ASD; therefore significant differences were found in the right temporo-parietal junction (TPJ), the inferior temporal gyrus and the middle parts of the STS, the precentral gyrus and the inferior and middle frontal gyri (see Fig. 2a and Table 2). This is consistent with previous findings using fMRI (Dapretto et al., 2006; Hadjikhani et al., 2006). However, as shown in Fig. 2a, these activations (in blue) surround the areas that are commonly activated in both groups (in green) by dynamic stimuli, and involve the same anatomical regions. While neuroimaging papers on mirror neurons and ASD have looked for differences rather than commonalities between groups (Dapretto et al., 2006; Hadjikhani et al., 2006; Theoret et al., 2005; Williams et al., 2001), the present results suggest that, even if there are some differences between the two groups, it seems that controls and ASD share more in common than differ when they perceive actions. Thus, the common activations of parietal and premotor areas in both subject groups imply that the system matching perceived actions onto representations of one's own action can be functional in this cohort of ASD subjects, consistent with behavioral (Hamilton, Brindley, & Frith, 2007; Nadel, 2008; Sebanz, Knoblich, Stumpf, & Prinz, 2005), and MEG data (Avikainen, Kulomaki, & Hari, 1999).

The critical question is whether ASD subjects also activate emotion-associated brain regions when perceiving gestures with an emotional content. A conjunction analysis of the contrast between fearful and neutral actions, irrespective of whether stimuli were static or dynamic, shows that the perception of emotional stimuli elicits similar bilateral activations of the posterior part of STS in both groups (see Table 3). Moreover, STSp is the site of an interaction between emotional content and movement, irrespective of group (Table 4). These results are consistent with the involvement of STSp in the processing of social and emotional information (Allison, Puce, & McCarthy, 2000; Puce & Perrett, 2003) and thus suggest that STS in its posterior part could be – at least partially – functional in ASD. In contrast, there is a group-by-emotion interaction, irrespective of whether stimuli were static or dynamic, showing that only control subjects activate the AMG, the lateral IFG (Ba 45), and the dorsal PM (see Fig. 3b–d) while observing emotional gestures. The observed brain network is consistent with previous fMRI studies on the perception of emotions in dynamic body expressions (Grèzes et al., 2007; Pichon et al., 2008) and with a recent meta-analysis on emotions (Kober et al., 2008). Our fMRI findings suggest that while both the action representation system and the STSp may be functional in ASD subjects, the brain regions more specific to emotional processing such as amygdala, inferior frontal gyrus and dorsal premotor cortex are not. These brain results could account for the behavioral body of evidence showing that children and adolescents with autism are atypical in the ways they perceive and express emotions (see Hobson, 2005 for a review).

The fact that the ASD group fails to engage emotion-associated cerebral regions raises questions about the connectivity between them (Bachevalier & Loveland, 2006; Belmonte et al., 2004; Horwitz et al., 1988; Just et al., 2004; Wickelgren, 2005). An adequate understanding of the neuronal basis of behavior needs to take into account the connectivity characteristics of functional networks (Passingham, Stephan, & Kotter, 2002). Abnormal correlated activity between visual regions and STS or IFG, and between the fusiform gyrus and amygdala, has already been described (Castelli et al., 2002; Villalobos, Mizuno, Dahl, Kemmotsu, & Muller, 2005). The interpretation of these reports is limited by the fact that simple correlations only reflect associations between neurophysiological events without providing direct insight into how such correlations are mediated. Conversely, Dynamic Causal Modelling (DCM) is considered to assess 'effective' connectivity between brain areas where 'effective' means causal connectivity in the sense of the effect of one area on another. Therefore, effective connectivity analysis provides estimates of the coupling among brain areas and of experimental condition-specific influences on these couplings (Friston, Harrison, & Penny, 2003). Treating the brain as an input-state-output system, DCM estimates how (output) haemodynamic activity from a given brain region depends on (input) variables manipulated in an experiment (e.g. still or dynamic stimuli) and on its inter-connectivity with other regions in which activity correlates with experimental context (i.e., neutral and fearful). Accordingly, we created a simple dynamic causal model (Fig. 4) of the interactions between four fear-related brain areas (STS, AMG, dPM, IFG) based on known direct and long-range anatomical connections in macaque monkeys (e.g. Barbas, 2000).

In the control group, emotional gestures significantly enhance all reciprocal connections between modelled areas (cf. Table 5) providing evidence that processing the emotional meaning of the observed actions is mediated by transient modulation of connectivity within a specific network of brain regions. The same analysis carried out on data from the ASD group reveals significantly weaker connectivity in the emotional context ($p < 0.05$, Table 5). In fact,

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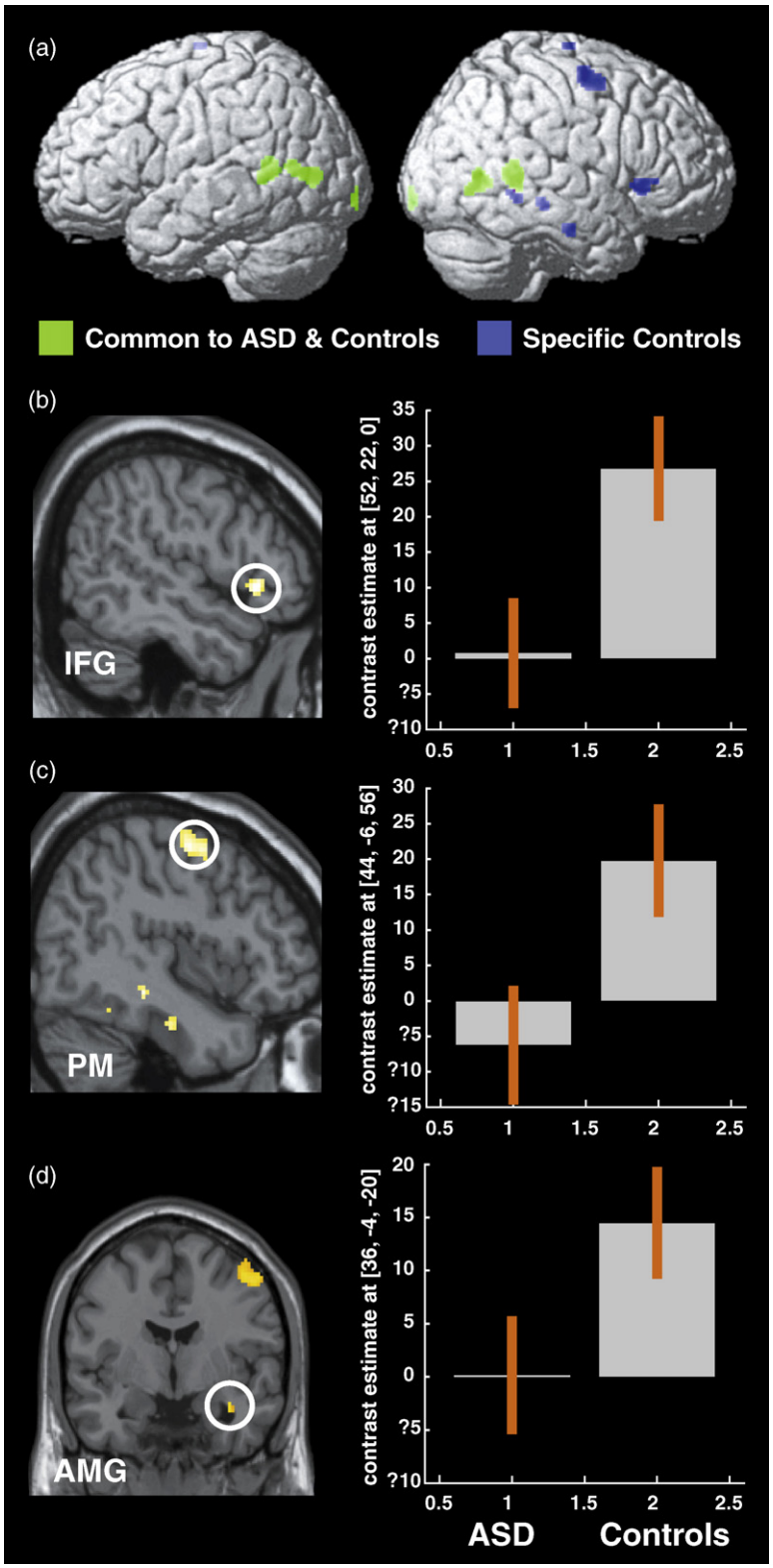

Fig. 3. (a) Brain regions common to ASD and controls as revealed by the conjunction analysis (Green) or specific to controls (Blue) showing amplitude difference when subjects perceive Fearful vs. Neutral expressions, irrespective of whether the stimuli were static or dynamic and rendered on the MNI brain. (b) Specific activation to the controls in the right inferior frontal gyrus (IFG) superimposed on a saggital section of the MNI brain and mean value of the parameter estimates (arbitrary units, mean centered) for the maxima of the right IFG (x, y, $z = 52\ 22\ 0$) for both groups. (c) Specific activation to the controls in the right precentral gyrus (PM) superimposed on a saggital section of the MNI brain and mean value of the parameter estimates (arbitrary units, mean centered) for the maxima of the right PM (x, y, $z = 44\ -6\ 56$) for both groups. (d) Specific activation to the controls in the right amygdala (AMG) superimposed on a coronal section of the MNI brain and mean value of the parameter estimates (arbitrary units, mean centered) for the maxima of the right AMG (x, y, $z = 36\ -4\ -20$) for both groups.

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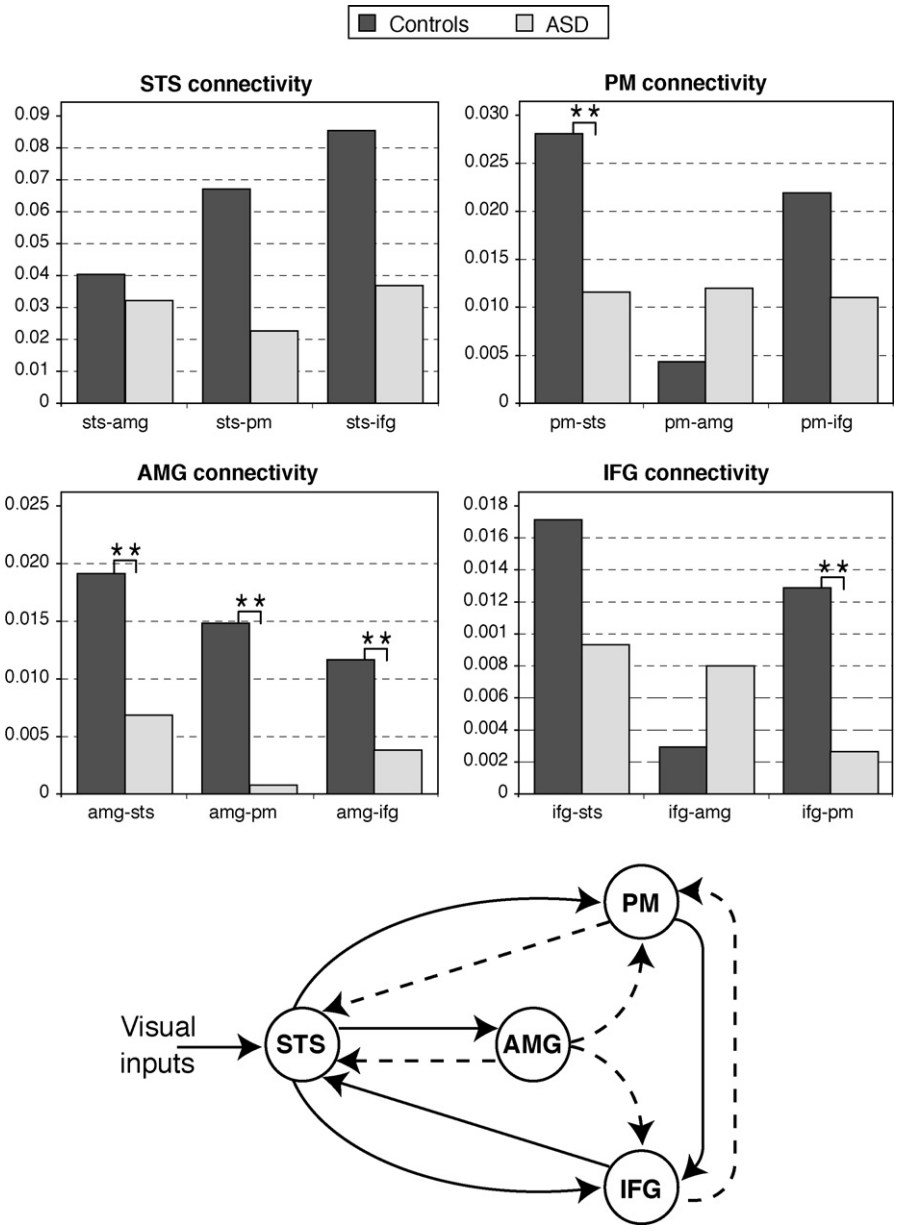

Fig. 4. Connectivity analysis. Plots: Enhancement of connectivity strength during fearful context as compared to neutral context within this network for ASD and control groups. Schema: A simple dynamic causal model with bidirectional connections between STS, AMG, PM, and IFG. We modelled static and dynamic stimuli as inputs to STS. ** and dashed lines correspond to significant differences in effective connectivity between ASD and control groups at $p < 0.05$.

there is no enhancement of connectivity between AMG and STS in ASD subjects. This result cannot be explained by failure of feed-forward visual signals to reach STS and/or AMG from fusiform and extra-striate regions (Castelli et al., 2002; Pierce et al., 2004; Schultz, 2005). We used a second DCM model to measure coupling between occipital (OCC) and fusiform areas (FG), OCC and STS, STS and AMG, and FG and AMG regions in fearful compared to neutral contexts. There is no difference in effective connectivity between the two groups on the forward connections between OCC and AMG, STS and AMG, and FG and AMG (see Table 5). These results confirm normal bottom-up connections and hence a lack of feedback influence from the AMG on STS during the processing of fearful actions in ASD subjects. Anatomical tracing studies in monkeys provide compelling evidence that AMG can modulate the processing of emotional expressions in visual cortex with demonstration of massive projections from it to all levels of the ventral visual pathway (Amaral et al., 2003). There are also functional imaging data from normal subjects to confirm this supposition (Morris et al., 1998).

A weaker connectivity is also revealed between AMG and lateral IFG in ASD subjects. It has been shown that the densest projections from AMG to prefrontal cortex terminate in medial and lateral orbital cortex including lateral area 12 in monkey, which may correspond to the lateral inferior frontal gyrus in humans (BA 45/47, IFG in this study) (Amaral & Price, 1984). Also, the lateral IFG receives direct visual information from temporal cortex, including the STS. This three-sided network linking AMG, IFG and STS was therefore proposed to play a crucial role in assigning emotional significance to perceived events (Barbas, 2000). Our results support the hypothesis that reduced activity within those brain areas or reduced connectivity between AMG and prefrontal limbic cortex may impair decoding of the emotional colouring of events and explain the flattening of emotions in ASD (Barbas, 2000). Consistent with this are observations in normal subjects showing that activity in AMG and

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IFG normally decrease when stimuli lose their motivational value (Schoenbaum, Chiba, & Gallagher, 2000).

Finally, we observe significantly less activity within the AMG and dPM in ASD subjects, as well as an abnormal influence of AMG on PM. This result may provide a possible explanation for the clinical observation that emotional content of observed events fails to trigger adaptive behavior in this group (American Psychiatric Association, 1996). A number of studies showed that lesions of the AMG not only disrupt the ability to process fear signals (LeDoux, 2000) but can also abolish characteristic fear behavior in primates (Bauman, Lavenex, Mason, Capitanio, & Amaral, 2004). The AMG plays a critical role in initiating adaptive behavior to perceived social signals *via* its connections with sub-cortical areas and *via* the dPM cortex (Amaral & Price, 1984; Avendano et al., 1983). The lack of modulation we find from AMG to dPM is associated with abnormal connectivity between PM and IFG. Lateral area 12 in monkey, corresponding to IFG, is also connected to dPM (Carmichael & Price, 1995). By receiving direct and indirect sensory inputs through AMG, the IFG processes sensory inputs into an appropriate context for action (Barbas, 2000). As a consequence, reduced connectivity from AMG to dPM and from IFG to dPM in ASD subjects may account for their inability to react appropriately to social situations.

To conclude, we show that ASD subjects fail to engage cerebral regions involved in grasping the emotional meaning of the actions they observe. We suggest that this deficit may reflect a crucial failure of the mechanism controlling normal behavioral responses to emotional signals provided by the behavior of others. The ensuing deficiency in the appraisal of emotional cues may lead to the inappropriate behavioral responses and the social difficulties that are characteristic of this population. Our data suggest that while the brain resources involved in motor representation of perceived action could be functional in the present cohort of ASD subjects, their failure to grasp action-related emotional content could find its origin in abnormal activation and reduced effective connectivity of the amygdala with other areas comprising the emotional brain.

Yet, knowing that autism is a complex disorder that is highly heterogeneous due to a considerable variability between individuals (Frith, 2001), further studies are needed to assess action and emotion processing in other cohorts of patients. Also, the present cohort of ASD being constituted of only high-functioning subjects, it would be interesting to test low functioning subjects to assess whether our results can be generalized to the other end of the Autistic Spectrum. Finally, correlation analyses between structure, function, and behavior should provide useful information for a better definition of neuro-cognitive phenotypes associated with inadequacy in everyday social relations that are the core deficits in ASD.

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