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Direct Gaze Elicits Atypical Activation of the Theory-of-Mind Network in Autism Spectrum Conditions

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Eye contact plays a key role in social interaction and is frequently reported to be atypical in individuals with autism spectrum conditions (ASCs). Despite the importance of direct gaze, previous functional magnetic resonance imaging in ASC has generally focused on paradigms using averted gaze. The current study sought to determine the neural processing of faces displaying direct and averted gaze in 18 males with ASC and 23 matched controls. Controls showed an increased response to direct gaze in brain areas implicated in theory-of-mind and gaze perception, including medial prefrontal cortex, temporoparietal junction, posterior superior temporal sulcus region, and amygdala. In contrast, the same regions showed an increased response to averted gaze in individuals with an ASC. This difference was confirmed by a significant gaze direction × group interaction. Relative to controls, participants with ASC also showed reduced functional connectivity between these regions. We suggest that, in the typical brain, perceiving another person gazing directly at you triggers spontaneous attributions of mental states (e.g. he is "interested" in me), and that such mental state attributions to direct gaze may be reduced or absent in the autistic brain.

Keywords: autism, connectivity, eye gaze, theory-of-mind

Introduction

Eye gaze is a salient social cue that plays an important role in social interaction and communication. Gaze perception activates a network of brain regions, including both the posterior superior temporal sulcus (pSTS) and amygdala, which are central to the perception of biological motion and social cognition (Baron-Cohen 1994, 1995; Nummenmaa and Calder 2009). In keeping with the idea that the eyes provide a "window on the mind," gaze perception also activates regions implicated in inferring the mental states of others (or "theory-of-mind", ToM), including the medial prefrontal cortex and temporoparietal junction (TPJ; Calder et al. 2002; Kampe et al. 2003; Wicker et al. 2003; Williams et al. 2005).

The direction of gaze is particularly relevant in social interactions, with mutual or direct gaze forming a key component, signaling interest in the recipient, the intent to communicate, and potential approach, whereas averted gaze generally signals a lack of interest and avoidance. The relative importance of direct over averted gaze is apparent from a very early age with newborns spending longer looking at a face with direct gaze than one with averted gaze (Farroni et al. 2002). By 6 months, infants only follow an adult's gaze toward an object when it is preceded either by direct gaze or by infant directed speech. Direct gaze also captures and holds attention more readily than averted gaze (von Grunau and Anston 1995; Senju et al. 2005; Fox et al. 2007), and facilitates recognition memory for faces, and categorization of facial gender and selected facial expressions (Macrae et al. 2002; Adams and Kleck 2003, 2005; Vuilleumier et al. 2005). Toddlers also use gaze direction in language learning (Baron-Cohen et al. 1997).

In autism spectrum conditions (ASCs), a group of neurodevelopmental conditions characterized by difficulties in social interactions and communication alongside unusually narrow interests and resistance to change, direct gaze does not confer these same perceptual benefits. For example, individuals with an ASC do not show faster detection of direct relative to averted gaze (Senju et al. 2003, 2008), and their categorization of faces' sex and emotional expression are not modulated by gaze direction (Akechi et al. 2009; Pellicano and Macrae 2009). Atypical processing of direct gaze in ASC is further underlined by electrophysiological studies showing abnormal event-related potentials to direct gaze in children with autism (Grice et al. 2005; Senju et al. 2005) and infant siblings of children with autism (Elsabbagh et al. 2009, 2012).

Although atypical processing of gaze in ASC is thought to reflect an impairment in understanding the intentional nature of gaze cues, little evidence has emerged in the form of atypical engagement of brain regions implicated in ToM or mentalizing (e.g. medial prefrontal cortex and TPJ) during gaze perception. Recent neuroimaging studies have shown that individuals with an ASC show an atypical neural response in the pSTS and areas of the attention networks when viewing faces orienting their gaze toward or away from target objects (Pelphrey et al. 2005; Greene et al. 2011). This has been interpreted as atypical social orienting (Greene et al. 2011) or problems in differentiating between expected and unexpected gaze shifts (Pelphrey et al. 2005) in individuals with ASC. However, given the central nature of atypical eye contact in ASC, and the prominent role of direct gaze in social interaction and communication (Csibra and Gergely 2006), the current study focused on identifying brain areas showing differential processing of direct gaze in adults with ASC relative to typical individuals. In particular, we focused on the medial prefrontal cortex, TPJ, pSTS, and amygdala, in light of previous evidence showing their involvement in inferring the mental states of others and gaze perception (Baron-Cohen et al. 1999; Amaral et al. 2008; Nummenmaa and Calder 2009; Lombardo et al. 2010).

Since direct gaze often conveys communicative intent directed toward the observer, we were particularly interested

in Amodio and Frith's (2006) proposal that the anterior section of rostral medial frontal cortex (arMFC) is activated when there is a perceived attempt to communicate with the observer (Kampe et al. 2003; Amodio and Frith 2006; Frith and Frith 2006). Of particular relevance for the current study, increased activation in this region has been reported in response to viewing direct gaze relative to averted gaze (Kampe et al. 2003; Schilbach et al. 2006), as well as in response to the longer duration of direct gaze (Kuzmanovic et al. 2009). Similarly, the same area of arMFC responds to hearing one's own name relative to hearing another person's name, another ostensive cue conveying communicative intent directed toward the observer (Kampe et al. 2003). Additional evidence comes from work using very different paradigms. Walter et al. (2004) showed increased activation in the arMFC in response to communicative intent conveyed by gestures, such as presenting a map as if to ask for directions. In contrast, viewing a scene conveying the private intentions of an agent (e.g. changing a lightbulb to read) showed no significant activation in this region. Grézes et al. (2004) found greater arMFC activation when participants detected that an actor was attempting to deceive them about the weight of a box they were lifting, relative to when the lifting action was perceived as genuine. Thus, we were interested in whether direct gaze would elicit reduced arMFC activation in individuals with ASC, suggesting atypical response to ostensive, self-oriented cues.

A well-established clinical observation is the tendency of some individuals with ASC to avoid direct gaze or eye contact. This observation has been confirmed by several eye-tracking studies, which show that individuals with ASC spend more time looking at both the mouth and nose regions of a face than at the eyes, the opposite pattern to neurotypical controls (Klin et al. 2002; Pelphrey et al. 2002; Dalton et al. 2005). To ensure that any differences we observed could not be attributed to avoidance of the eye region, we instructed participants to look at the eyes and monitored their eye movements throughout.

Materials and Methods

Participants

Twenty-five "typical" male participants and 21 males with ASC (2 with high-functioning autism and 19 with Asperger's syndrome) participated in the study for payment. All ASC subjects had a confirmed diagnosis of an ASC: 5 using the Autism Diagnostic Interview-Revised (ADI-R; Lord et al. 1994) as part of a previous study at the Autism Research Centre, University of Cambridge, 2 by using the Autism Diagnostic Observation Schedule (ADOS; Lord et al. 2000), and the remainder had written confirmation of independent diagnosis by a qualified clinician using DSM-IV (1994) criteria. None of the control group had a diagnosis of ASC or a history of any other psychiatric or neurological disorder.

All participants had normal or corrected-to-normal vision and completed the Wechsler Abbreviated Scale of Intelligence (WASI, The Psychological Corporation, 1999) and the Autism Spectrum Quotient (AQ; Baron-Cohen et al. 2001). Details of all participants, following the removal of 2 controls and 3 ASCs due to excessive movement in the scanner (see fMRI preprocessing section below), are shown in Table 1. The study was approved by the National Research Ethics Service Committee East of England, and all participants provided written informed consent.

Table 1
Participant details

	Age	AQ	WASI-full	WASI-Perf	WASI-Verb
ASC ($n = 18$)	29 ± 7	34 ± 8	112 ± 16	112 ± 14	109 ± 15
Controls ($n = 23$)	26 ± 6	15 ± 6	117 ± 14	117 ± 14	114 ± 13
P-value	0.18	<0.001	0.30	0.29	0.38

Data are listed as mean ± standard deviation.
P-values are significance levels based on Student's *t*-test.
WASI, Wechsler Abbreviated Scale of Intelligence; Perf, performance subscale of WASI; Verb, verbal subscale of WASI.

Experimental Design

Full-face, computer-generated images of 5 male and 5 female identities with neutral facial expressions were generated with the DAZ Studio software (DAZ Productions, Draper, UT, USA). Participants viewed alternating epochs of dynamic averted gaze and dynamic direct gaze events. Epochs were 21 s long and consisted of 6 presentations of averted gaze or direct gaze intermixed with 6 null events. A single trial comprised a 1000-ms presentation of a face displaying direct or averted gaze followed by a low-contrast central cross (750 ms). Averted gaze shift events comprised 2 consecutive 500-ms frames showing leftward gaze followed by rightward gaze or vice versa; this produced a strong illusion of a dynamic gaze shift (Fig. 1*A*). Similarly, direct gaze events consisted of consecutive 500-ms presentations of closed eyes followed by open eyes with direct gaze or vice versa, again this produced an illusion of movement (Fig. 1*B*). Null events comprised a 1750-ms presentation of the low-contrast cross (Fig. 1*C*). The faces' gender and identity were fully counterbalanced across averted and direct gaze epochs, which contained an equal number of the 2 averted and 2 direct gaze event types, respectively. Participants were instructed to decide whether the face was male or female and to respond by button press. They were also instructed to keep their eyes on the eye region of the face and were told that their eye movements were being monitored through the use of an eyetracker. Participants practiced the task outside the scanner prior to the functional magnetic resonance imaging (fMRI) experiment.

Four control subjects and 3 ASC participants viewed 10 epochs of each stimulus condition, for a total of 120 face trials (60 averted gaze shifts and 60 direct gaze blinks). The remaining participants viewed 14 epochs of each stimulus condition for a total of 168 face trials (84 averted gaze shifts and 84 direct gaze blinks). The order of the stimuli during each epoch was pseudorandomized with respect to the trial type (face or null), such that no more than 3 consecutive trials were of the same type. This pseudorandomization enhanced design efficiency while preserving the unpredictability of stimulus onsets in naive participants. The total task duration was 7 min for 10 epochs of the experiment, and 9 min 48 s for 14 epochs.

Eye tracking

A 50-Hz monocular MRI-compatible infrared eyetracker (SensoMotoric Instruments [SMI], Teltow, Germany) was used to monitor and record participants' eye movements while in the scanner. Eye tracking data were analyzed with the SMI BeGaze3.0 software. Due to difficulties in tracking some participants' pupils (e.g. drooping eyelids, corrective lenses), reliable eye tracking data were collected in 15 of the 23 control participants, and in 13 of the 18 ASC participants. A rectangular area-of-interest (AOI) was created around the eye region of the stimuli (same size and location for all face stimuli), and the average dwell time in that AOI was determined as a percentage of total time the face was present (excluding artifacts like blinks) to ascertain whether typical and ASC participants looked at the eye region of the faces for similar amounts of time.

fMRI Data Acquisition

Data were acquired using a 3-T Tim Trio (Siemens, Erlangen, Germany) scanner. Whole-brain T_2*-weighted echo planar images

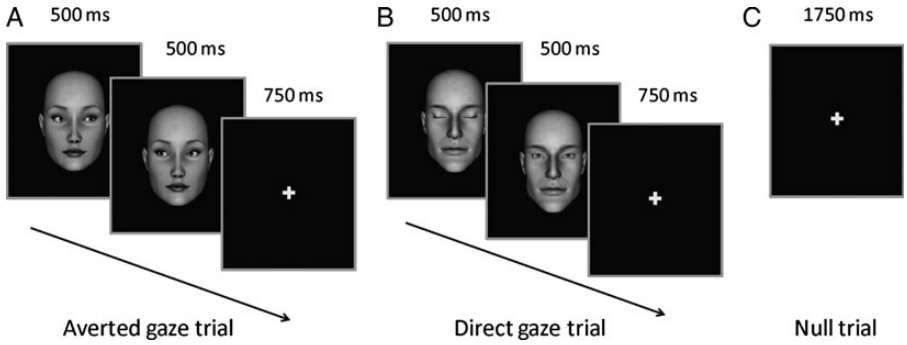

Figure 1. Trial structure for a sample averted gaze trial (*A*), direct gaze trial (*B*), and null trial (*C*).

(EPIs) were acquired with a repetition time (TR) = 2190 ms, echo time (TE) = 30 ms, flip angle = 78°, 36 oblique slices, 3 × 3 mm inplane resolution, and 3-mm slice thickness with a 0.75-mm slice gap. A total of 204 image volumes (for 10 epochs) or 282 image volumes (for 14 epochs) were acquired. In each case, the first 3 volumes were discarded to allow for equilibration effects. A high-resolution structural magnetization-prepared rapid-acquisition gradient echo scan was also acquired for normalization purposes (voxel size 1 × 1 × 1 mm, TR = 2250 ms, TE = 2.99 ms, inversion time = 900 ms, flip angle = 9°, total scan time 4 min 16 s).

fMRI Preprocessing

fMRI data preprocessing and analysis were carried out in SPM5 (Wellcome Trust Centre for Neuroimaging, www.fil.ion.ucl.ac.uk/spm). The EPI images were sinc interpolated in time to correct for slice time differences and realigned to the first scan by rigid body transformations to correct for head movements. EPI and structural scans were coregistered and normalized to the T_1 standard template in Montreal Neurological Institute space (Montreal Neurological Institute—International Consortium for Brain Mapping) using linear and nonlinear transformations and smoothed with a Gaussian kernel of 8-mm full-width at half-maximum. Three subjects with ASC and 2 control subjects had to be removed from the analysis due to excessive head movements (>3 mm).

fMRI Statistics

Data were analyzed by 2-stage implementation of a random effects model. At the first level, the general linear model (GLM) included regressors for 3 conditions: Averted gaze, direct gaze, and null events. Spatial realignment parameters were included as regressors of no interest in the model to account for residual movement-related variance. Data were high-pass filtered at 128 s to remove low-frequency signal drifts. Individual subjects' contrast images were created by contrasting each of the averted gaze and direct gaze conditions with null trials. The second-level GLM consisted of a 2 × 2 factorial design with both group (controls and ASCs) and gaze direction (averted gaze vs. null and direct gaze vs. null) as the main factors.

As we were expecting group differences in the processing of the social aspects of eye gaze, we had a priori regions-of-interest (ROIs) based on the ToM network: Bilateral TPJ and pSTS, arMFC, and bilateral amygdala. We used these ROIs to correct for multiple comparisons at the family-wise error (FWE) level using small-volume corrections. As the amygdala is a discrete anatomical region, we used the Automated Anatomical Labeling to define both the left and right amygdala ROIs. For bilateral TPJ, pSTS, and arMFC, we used 20-mm radius spheres centered on the average activation coordinates of 10 ToM studies listed in Frith and Frith (2003) (combined pSTS and TPJ ROIs: Left $x = -53$, $y = -56$, $z = 11$ and right $x = 57$, $y = -52$, $z = 10$; arMFC: $x = -1$, $y = 47$, $z = 4$).

fMRI Connectivity

To determine the strength of correlation or connectivity between the activated regions, time series data across all conditions (direct gaze, averted gaze, and null) were extracted for each subject from spherical 5-mm radius ROIs centered on the peak coordinates of significant gaze direction by group interactions in the arMFC ($x = 14$, $y = 60$, $z = 2$), left TPJ ($x = -52$, $y = -64$, $z = 24$), right TPJ ($x = 54$, $y = -56$, $z = 18$), right middle temporal gyrus (MTG) including pSTS ($x = 62$, $y = -46$, $z = -6$) and left amygdala ($x = -26$, $y = -2$, $z = -24$). Extracted time series were adjusted for effects of interest in each subject. The first eigenvariate was determined from the extracted time series, and Pearson's correlations between each pair of regions were determined. Correlation values were Z-transformed (Fisher's Z) to normalize the distribution, and group differences determined by analysis of variance (ANOVA) with group (control and ASC; between subjects) and connection (all combinations of ROIs above for a total of 10 connections; repeated measures) as factors. When appropriate, *P*-values were corrected for nonsphericity using the Huynh–Feldt correction.

In order to determine whether connectivity differences were specific to the ToM network or reflected widespread reduction in connectivity in ASC, we performed correlation analyses on 2 additional "control" networks: A motor network and a visual network based on the contrast of faces versus null. Using the same methods as described above, time series data were extracted from 4 ROIs comprising a motor network, and 3 ROIs comprising a visual network. Each ROI had a radius of 5 mm and was centered on the peak coordinate in that region for the contrast of all gaze trials (direct and averted) compared with all null trials (FWE corrected for multiple comparisons at the whole-brain level). The motor network comprised of left primary motor cortex ($x = -40$, $y = -22$, $z = 58$), left supplemental motor area ($x = -4$, $y = -2$, $z = 54$), and left ($x = -56$, $y = 4$, $z = 38$) and right ($x = 54$, $y = 4$, $z = 44$) premotor cortex. The visual network comprised of left ($x = -34$, $y = -78$, $z = -16$) and right ($x = 30$, $y = -78$, $z = -12$) inferior occipital gyrus, and right fusiform gyrus ($x = 38$, $y = -46$, $z = -22$).

Although we incorporated movement parameters into both our first-level GLM and our connectivity analysis, we also calculated root mean square movement in each of the 3 translation and rotation directions for each subject and entered these data into a repeated-measures ANOVA. There were no significant group differences in movement ($F < 1$, $P = 0.7$). Hence, any group differences in the results are unlikely to be driven by differences in simple movement.

Results

Behavioral Results

There was no difference between groups in accuracy on the gender discrimination task with both groups showing high levels of performance (mean ± standard deviation: Controls

98 ± 3% and ASC 97 ± 4%). An analysis of correct reaction times showed no significant main effect of group ($F_{1,39} = 0.005$, $P = 0.94$) or gaze direction ($F_{1,39} = 0.42$, $P = 0.52$), neither was there a significant group × gaze direction interaction ($F_{1,39} = 0.39$, $P = 0.54$).

Eye tracking

An analysis of the average dwell time within the AOI encompassing the eye region showed no significant main effect of group ($F_{1,26} = 0.06$, $P = 0.80$) or gaze direction ($F_{1,26} = 0.84$, $P = 0.37$), neither was there a significant group × gaze direction interaction ($F_{1,26} = 0.33$, $P = 0.57$; Fig. 2).

fMRI: Gaze Direction

We compared the responses to both averted and direct gaze between the groups in a 2 × 2 factorial design with group (controls and ASCs) and gaze direction (averted gaze vs. null and direct gaze vs. null) as the main factors. Consistent with our hypothesis, we found a significant gaze direction by group interaction in the arMFC. A breakdown of this interaction revealed that controls showed an increased response to direct gaze relative to averted gaze, consistent with previous research (Kampe et al. 2003; Schilbach et al. 2006). In contrast, individuals with ASC showed the reverse, with an increased response to averted gaze. This pattern was mirrored across other regions of the ToM network, including bilateral TPJ, left amygdala, and right MTG extending into the pSTS; borderline significant effects were found in both the left pSTS and right amygdala (Fig. 3 and Table 2). While the significant interactions in each of the a priori ROIs highlight statistically distinct patterns in the 2 groups, separate analyses for each group showed that this was most robust in the arMFC, TPJ, and amygdala (Table 2). No ROIs displayed a greater response to averted gaze than to direct gaze in the control group. Similarly, none showed a greater activation in the ASC group when direct gaze was compared with averted gaze.

There was no main effect of gaze direction irrespective of group in any of our ROIs. There was also no main effect of group in our ROIs, indicating that the 2 groups did not differ in the overall response of these regions to gaze cues.

In order to rule out the possibility that individuals for whom we did not have eye tracking data were driving the group differences we observed, we repeated the group analysis using only those subjects with eye tracking data (15 controls and 13 ASCs). We again found a significant group by gaze direction interaction effect in right TPJ, arMFC, and left amygdala (Supplementary Table 1). Including the fraction of time spent in the eye region of the face as a covariate of no interest in the model also did not change these results (Supplementary Table 2).

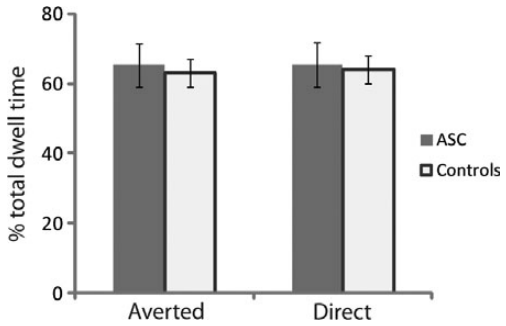

Figure 2. Average percent total dwell time on the eye region for each gaze direction condition and each group. Error bars represent the standard error of the mean.

fMRI Connectivity

In order to examine whether connectivity between pairs of areas involved in gaze processing differed between the control and ASC groups, we performed a correlation analysis of the time series data for all regions that showed a significant group by gaze direction interaction (arMFC, left and right TPJ, right MTG/pSTS, and left amygdala). The correlations between these regions were significantly different between groups (Fig. 4; $F_{1,39} = 5.05$, $P = 0.03$) with the ASC group showing an overall reduction in connectivity. There was also a main effect of connection ($F_{5.6,216.9} = 28.8$, $P < 0.001$), but no significant group by connection interaction ($F_{5.6,216.9} = 1.1$, $P = 0.37$). Thus, while areas of the ToM and gaze perception networks in the control and ASC groups did not differ in their overall response to direct and averted gazes (no main effect of group in the above analysis of voxel wise effects), the connectivity between the components of this network is significantly reduced in ASC during a sequence of direct and averted gaze trials. Note that this connectivity analysis refers to the correlation between regions across the whole time series, not differential connectivity between trial types: It is independent of whether particular trials display direct gaze, averted gaze, or null events.

Connectivity within 2 further networks, a motor network and an early visual network, was also examined in order to determine whether differences in connectivity were specific to the ToM network or simply reflected generally reduced connectivity in the ASC group. As with the ToM network regions, none of the motor or visual regions identified in the faces versus null contrast showed a main effect of group. A correlation analysis of the motor and visual networks showed no differences in connectivity between the 2 groups (Fs < 1, Ps > 0.8), despite showing a main effect of connection (motor $F_{4.5,174.9} = 36.5$, visual $F_{1.8,69.1} = 61.8$, Ps < 0.001). There were no group by connection interactions (Fs < 2, Ps > 0.3). Since these 2 networks are local in their extent and do not include longer range connections, similar to those seen in the ToM network, we also ran a correlation analysis of the visual and motor network combined (Supplementary Figure 1). Again, we found no significant differences between groups ($F_{1,39} < 1$, $P = 0.98$), no connection by group interaction ($F_{11,431} < 1$, $P = 0.87$), but a main effect of connection as expected ($F_{11,431} = 54$, $P < 0.001$).

Discussion

Research with typical individuals has shown that the arMFC is involved in reading another's intent to communicate with the observer (Amodio and Frith 2006). We provide the first evidence that individuals with ASC show an atypical response pattern in this region to direct gaze, a salient ostensive cue conveying communicative intent directed at the observer. This was expressed as a gaze direction by group interaction, with typical controls showing the expected increased response in the arMFC to direct relative to averted gaze, and individuals

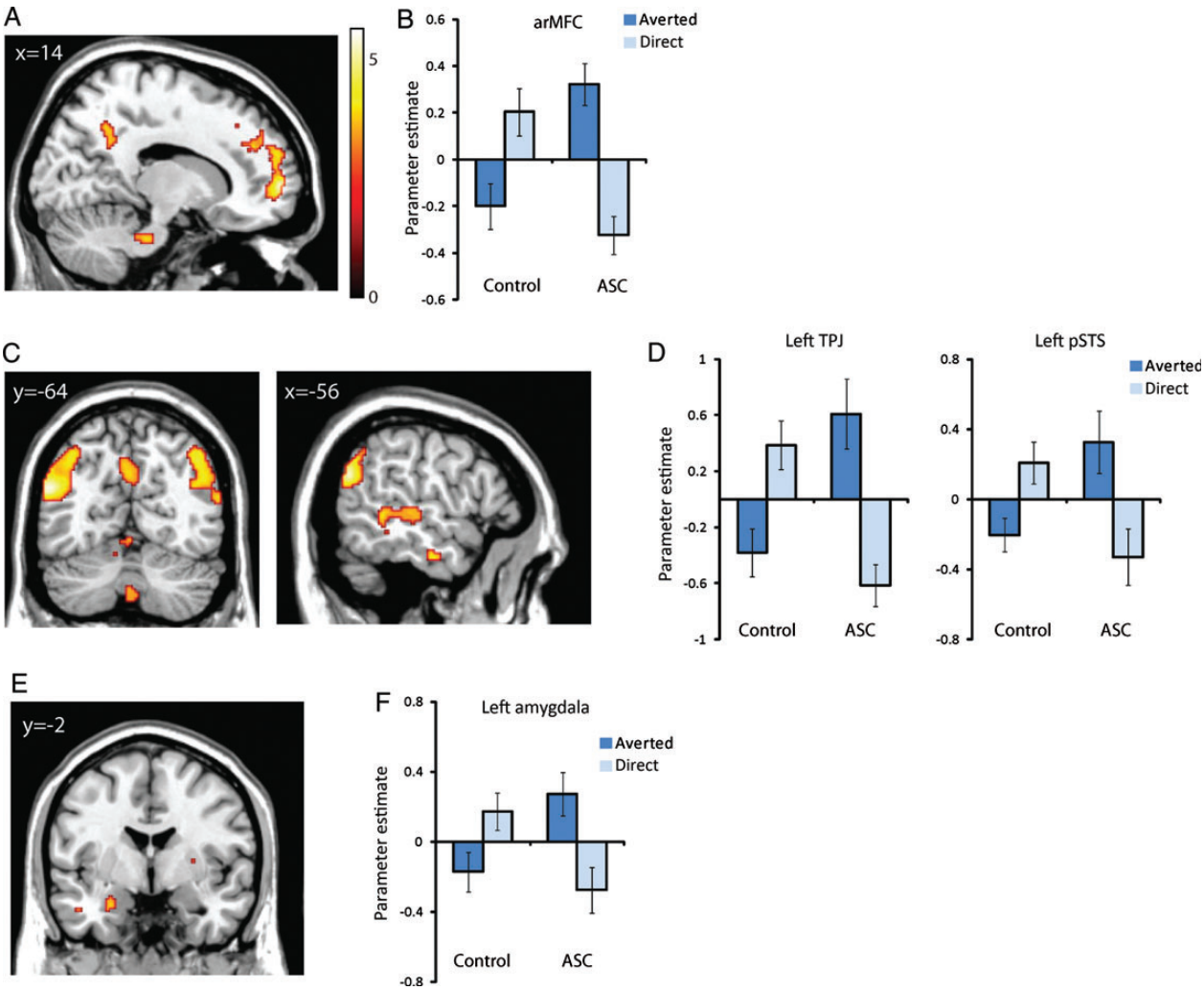

Figure 3. Areas showing a significant group by condition interaction. (*A* and *B*) arMFC; (*C* and *D*) left TPJ and left pSTS; (*E* and *F*) left amygdala. Graphs represent the parameter estimates at the peak voxel for averted and direct gaze. Error bars represent the standard error of the mean. Brain images are displayed at a threshold of $P < 0.001$ uncorrected for visualization purposes.

Table 2

Coordinates and *P*-values for group (control and ASC) by gaze direction (direct vs. null and averted vs. null) interaction, controls direct gaze > averted gaze, and ASC averted gaze > direct gaze

	Hemisphere	*F*	*P*-value[a]	MNI coordinates		
				x	*y*	*z*
Group × gaze direction interaction						
arMFC	R	28.02	0.001	14	60	2
TPJ	L	28.13	0.001	−52	−64	24
TPJ	R	20.61	0.01	54	−56	18
pSTS	L	15.25	0.07	−56	−42	0
MTG/pSTS	R	17.27	0.04	62	−46	−6
Amygdala	L	14.45	0.008	−26	−2	−24
Amygdala	R	8.95	0.07	28	−2	−26
Controls, direct > averted						
arMFC	R	3.92	0.04	14	58	2
TPJ	L	4.59	0.005	−58	−62	26
Amygdala	L	3.86	0.003	−26	−4	−24
Amygdala	R	3.36	0.02	32	4	−20
ASC, averted > direct						
arMFC	R	4.64	0.004	10	56	18
TPJ	L	3.72	0.06	−40	−68	20
TPJ	R	3.88	0.04	46	−58	20
Amygdala	L	2.76	0.06	−24	0	−14

[a]Small-volume corrected for multiple comparisons using the FWE correction.

with ASC showing the opposite pattern. This same pattern was mirrored across other regions of the ToM network, specifically the TPJ, amygdala, and pSTS. Our results suggest that gaze directed toward the self does not convey the same communicative salience in individuals with ASC as it does in typical controls. These group differences occurred despite the faces' gaze being incidental to the experimental task, which involved in categorizing the face's sex. Our study therefore suggests that individuals with ASC show atypical spontaneous or implicit processing of eye gaze in the ToM network.

Given the evidence for the avoidance of eye contact and the eye region more generally in the ASC (Klin et al. 2002; Pelphrey et al. 2002; Dalton et al. 2005), it was important to exclude that the atypical neural response in the ASC group resulted from such different viewing patterns per se. However, our eye tracking data verify that there were no group differences in the amount of time spent looking at the eyes for either the direct or averted gaze conditions. Although eye tracking data were only available for a subset of the participants, an analysis of fMRI data for this subgroup supported the findings from the entire sample. The contrasting activation patterns we observed in the control and ASC groups are

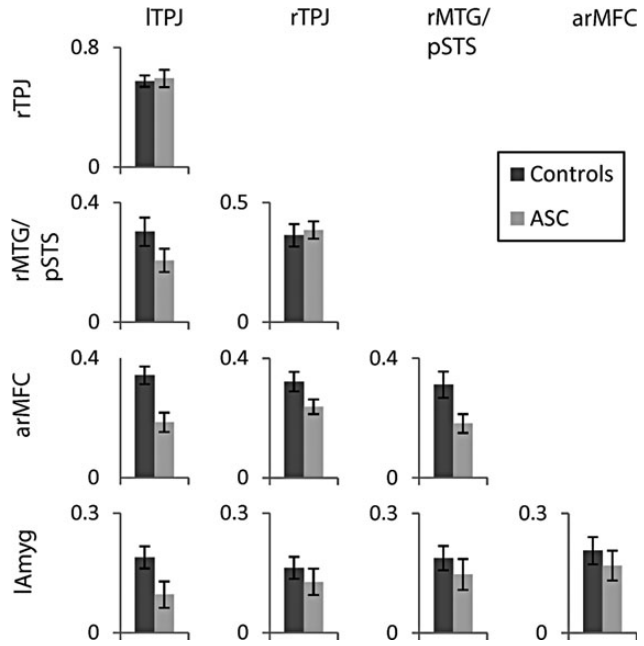

Figure 4. Mean Fisher Z-transformed correlations for control and ASC groups for the fMRI time series between regions with a significant group by gaze direction interaction: arMFC, left and right TPJ, right MTG (extending into pSTS), and left amygdala.

therefore unlikely to reflect differences in time spent looking at the eyes.

The results confirm our hypothesis that individuals with ASC show abnormal activation of the ToM network when viewing direct gaze. However, given that the pattern of activation to both direct and averted gaze is reversed in the ASC group (averted > direct) relative to the controls (direct > averted), it is clear that the same brain regions show an atypical response to both direct and averted gaze in ASC. Note that the ToM regions (arMFC, TPJ, pSTS, and amygdala) also showed no main effect of group, indicating that it is the relative response to both direct and averted gaze that is atypical in ASC, rather than the overall extent to which these regions are engaged. Whether it is meaningful that individuals with ASC show an increased response to averted gaze in the ToM network is unclear. For instance, it may be that, in ASC, averted gaze is a more salient or a preferred mode of social interaction and therefore engages the ToM network in a similar way to direct gaze in typical individuals. At present, however, our study shows that the relative response to direct and averted gaze in these regions is atypical in individuals with ASC. And more specifically, individuals with ASC do not show the previously established increased response to direct gaze in the arMFC found in typical individuals (Kampe et al. 2003; Schilbach et al. 2006).

The absence of an increased response to direct gaze in the arMFC and other ToM regions is consistent with the hypothesis that individuals with ASC are not attributing intentions to direct gaze faces in the same way as controls (e.g. he is interested in me, he wants to talk to me). Previous fMRI studies have found that individuals with ASC show reduced response in ToM regions relative to typical individuals when the task is designed to elicit the attribution of intentionality, for instance to moving shapes (Castelli et al. 2002). Similarly, Pelphrey et al. (2005) found that unexpected gaze shifts away from an object, seen as a violation of subjects' expectations, did not elicit an increased response in pSTS in individuals with ASC, suggesting that they had not formed any expectations about the intentionality of the gaze shift. Although our paradigm is very different and did not involve gaze shifts toward or away from an object, the observed reduction to direct gaze in individuals with ASC relative to controls can also be interpreted as atypical extraction of intentionality in the ASC group, that is, direct gaze does not signal the same communicative intent to individuals with ASC. However, it is unclear whether the increased response to averted gaze in ASC might reflect an increased attribution of intentionality, for instance, because averted gaze signals greater communicative intent or salience to the observer with ASC.

It is worth noting that averted gaze can also convey communicative intent, particularly in joint attention scenarios where the gaze cue is designed to draw the observer's attention toward, for example, an object in the environment. However, our stimuli were presented in the absence of an explicit target and did not involve gaze shifts toward or away from the observer or an object, making it unlikely that our averted gaze condition elicited joint attention mechanisms. We also found no regions with an increased response to averted gaze in our control group, again suggesting joint attention mechanisms were not significantly engaged (Williams et al. 2005; Redcay et al. 2010). Although initiating and responding to bids of joint attention have been shown to elicit atypical brain responses in individuals with ASC (Redcay et al. forthcoming), our results suggest that atypical processing of gaze in ASC is present even in the absence of a joint attention style format.

The results of our connectivity analysis demonstrate that, relative to the controls, individuals with ASC showed decreased connectivity among the regions of the ToM network that showed a significant group by gaze direction interaction (arMFC, TPJ, pSTS, and amygdala). Note that the connectivity analyses looked at the correlations among these regions across the entire time series comprising direct gaze, averted gaze, and null events. It was not a psychophysiological interaction between stimulus type and connectivity. Hence, the reduced connectivity in the ASC individuals is not explained simply by the reverse patterns of local activation to direct and averted gaze in the control and ASC groups. Importantly, the change in correlations is also not explained by differences in overall engagement of these regions in the 2 groups, as there was no significant main effect of group in the analysis of regional effects. Finally, connectivity analyses of 2 further networks, a motor network and a visual network as well as a combined visuo-motor network, suggest that the connectivity differences observed in the ToM network are specific to that network rather than reflecting an overall reduction in connectivity in ASC.

To our knowledge, only one other study has looked at differences in the neural processing of direct gaze in ASC relative to typical individuals (Pitskel et al. 2011). Consistent with the present study, they found a significant group by gaze direction interaction in the right TPJ, with controls showing greater activity in this region to direct relative to averted gaze, and the opposite pattern in ASC; however, they did not find differences in activation in the arMFC and other regions of the ToM network identified in our current study. Neither did

Pitskel et al. (2011) find that these regions, including the TPJ, showed main effects of gaze direction in separate analyses of the control and ASC groups. The discrepancies with our current study might be explained by a number of factors. Pitskel et al. (2011) used a very different design to our own in which the stimuli consisted of a video clip of a man walking toward the viewer while looking at or away from them, so there were no changes or shifts in the person's gaze. Inclusion of the man's entire body and the background context may also have encouraged the participants to focus on parts of the stimuli other than the face. In the absence of eye tracking data, it is also unclear whether the observed differences could be attributed to atypical looking behavior in ASC. It is also worth noting that the TPJ showed the largest mean difference in activation for direct relative to averted gaze in both groups in our study, hence Pitskel et al.'s (2011) study may underestimate the extent of the atypical processing of direct gaze direction in ASC, identifying only regions with the largest amplitude difference.

Limitations

Although our gaze stimuli created an illusion of movement and are therefore more typical of eye gaze encountered during social interactions than static images, our faces were computer generated. Hence, future research should determine whether similar findings are found for real-life videos. It is also worth noting that our participants with ASC consisted primarily of individuals with Asperger syndrome, and all of our participants were high functioning with IQs of 85 or higher. It remains to be seen, therefore, whether the current findings generalize to lower-functioning forms of ASC. In addition, our participants were explicitly instructed to look at the eye region of the face, a behavior that may not come naturally to some individuals with ASC (Klin et al. 2002; Pelphrey et al. 2002; Dalton et al. 2005). While this instruction helps discount that a failure to look at the eyes in the direct or averted gaze conditions underlies the different neural patterns in the control and ASC groups, it is unclear whether asking ASC participants to look at faces in a potentially unnatural way may have contributed to our results. Finally, recent work has highlighted contributory artifacts to connectivity measures, particularly differences in motion (Satterthwaite et al. 2012; Van Dijk et al. 2012). We cannot wholly exclude this possibility, but note that the sum of movement displacements (of any amplitude) did not differ between the groups, indicating no systematic difference in head motion. We also modeled motion parameters in the first level, corrected for motion parameters when extracting the regional time series, and found that connectivity differences were not restricted by connection length (a feature of motion-induced artifactual connectivity changes).

In conclusion, we have shown that individuals with ASC show distinct response patterns to dynamic changes in direct and averted eye gaze relative to controls. Although the controls displayed an increased response to direct relative to averted gaze in the arMFC and other areas of the ToM network, the ASC group showed the opposite pattern. Individuals with ASC also showed significantly reduced connectivity between brain areas showing a group by gaze direction interaction. Thus, in individuals with ASC, areas of the ToM network show both atypical localized changes in processing gaze direction and atypical communication. We suggest that direct gaze does not convey the same communicative intent for individuals with ASC as it does for controls, and that averted gaze may be a more socially meaningful stimulus in ASC. Whether the increased activation in the ToM network in ASC in response to averted gaze fulfills a similar role to direct gaze in typical individuals remains to be seen.

Supplementary Material

Supplementary material can be found at: http://www.cercor.oxfordjournals.org/

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