

Effective Connectivity of Brain Networks Responsible for
Impaired Joint Attention in Individuals with Autism

Catherine Hanson^{1,3} Stephen José Hanson¹ Joseph Ramsey² Clark Glymour²

¹ Rutgers University
Department of Psychology, Smith Hall
101 Warren St.
Newark, NJ 07102

² Carnegie Mellon University
Department of Philosophy
Baker Hall 135
Pittsburgh, PA 15213

³*Correspondence should be addressed to:*

Dr. Catherine Hanson
Rutgers University
Smith Hall, Psychology Department
101 Warren St.
Newark, NJ 07102

email: cat@psychology.rutgers.edu
tel: 973-353-3396
fax: 973-353-1171

Running head: Connectivity of Brain Networks

Abstract

Failing to engage in joint attention is a strong marker of impaired social cognition associated with autism spectrum disorder (ASD). Our goal in this study was to localize the source of impaired joint attention in individuals with ASD by examining both behavioral and fMRI data collected during various tasks involving eye gaze, directional cuing, and face processing. The tasks were designed to engage three brain networks associated with social cognition (face processing, Theory of Mind, and action understanding). The behavioral results indicate that even high functioning individuals with ASD perform less accurately and more slowly than neurotypical (NT) controls when processing eyes, but not when processing a directional cue (an arrow) that did not involve eyes. Behavioral differences between the neurotypical and ASD groups were consistent with differences in the effective connectivity of FACE, TOM, and ACTION networks. We used IMaGES (Ramsey et al., 2010) to examine these brain networks and found that whereas neurotypicals produced stable patterns of response across tasks designed to engage a given brain network, ASD participants did not. Moreover, ASD participants recruited all three networks in a manner highly dissimilar to that of neurotypicals.

Following the eye gaze of another individual occurs reflexively for most people (Friesen & Kingstone, 1998) from early childhood. Eye gaze may be especially potent in capturing attention (Driver et al., 1999; Langton, Watt, & Bruce, 2000) even when the one doing the gazing is a member of a different species (Deaner & Platt, 2003; Ricciardelli et al., 2002). The ability to follow gaze underlies fundamental social skills and impaired gaze following is viewed as an early sign of autism spectrum disorders (ASD) as well as being predictive of impaired language skills (Mundy et al., 1990).

Impairments in gaze following and language skills often accompany deficits in other forms of social communication. Children with ASD have difficulty engaging in symbolic play (Sigman & Ungerer, 1984) and are less likely to use conventional gestures such as waving (Hobson & Lee, 1998) or pointing (Hobson & Meyer, 2005; Landry & Loveland, 1988). Impaired social cognition has been attributed to deficits in: 1) Theory of Mind (Baron-Cohen, Leslie, & Frith, 1985; Baron-Cohen, 1995; Leslie, Friedman, & German (2004); Siegal & Varley, 2002), 2) face processing (Dawson et al., 2005; Grelotti, et al., 2002; Schultz, 2005), and 3) action understanding (Boria, et al., 2009; Gallese et al., 2009; Ecker et al., 2010).

The evidence that impaired social cognition is associated with poor Theory of Mind (Baron-Cohen, Leslie, & Frith, 1985; Baron-Cohen, 1995; Siegal & Varley, 2002) or mind-reading (Baron-Cohen et al., 1997; Golan et al., 2006; Pellicano et al., 2005; Ponnet et al., 2008; Roeyers et al., 1998) skills is extensive. From this perspective, failure to follow eye gaze, as observed in individuals with ASD, can be seen as failure to understand another's intention or to empathize with another's interest.

Impaired joint attention in individuals with ASD has also been attributed to difficulty processing faces (Dawson et al., 2005; Grelotti et al., 2002; Schultz, 2005). Some researchers have argued that impaired face processing stems from atypical brain response in areas such as fusiform gyrus (Dawson et al., 2005) and amygdala (Baron-Cohen et al., 2000), or the connectivity between the two structures (Schultz, 2005).

A third explanation that has been offered for impaired social cognition in individuals with ASD focuses on action understanding (e.g., Gallese et al., 2009). The argument is that appropriate social interchange is highly dependent on successful imitation of others, and impaired imitation can be traced to atypical mirror neuron activation. Mirror neurons were first discovered in nonhuman primates, but human analogues have been identified, particularly in IFG (see Rizzolatti et al. 2004 for a review). Moreover, there is evidence that individuals with ASD exhibit a pattern of response in the brain areas associated with action understanding that differs from that for neurotypicals (Ecker et al., 2010).

Our goal in the present study was to determine if and how recruitment of the three brain networks associated with Theory of Mind (TOM), face processing (FACE), and action understanding (ACTION) might differ between individuals with ASD and neurotypicals. We presented our participants with five different visual stimuli, each designed to engage one or more of the three brain networks. We then compared behavioral performance (RT and accuracy), brain activation (using GLM analysis), and effective connectivity (using IMAGES) across tasks and participants.

Method

Participants

Participants ranged in age from 18-35 years and were fluent in English. None of the participants had a major medical illness or a history of seizures for the previous two years. None had embedded metal such as surgical pins or electronic devices such as a pacemaker. All participants signed a consent form in compliance with HIPPA regulations and were paid for their participation.

ASD participants were recruited from the Autism Center of the University of Medicine and Dentistry of New Jersey/New Jersey Medical School (UMDNJ-NJMS) and included nine males. Based on assessment using the Autism Diagnostic Interview - Revised (ADI-R) and the Autism Diagnostic Observation Schedule (ADOS-G), four participants were found have autism and four to have autism spectrum disorder. IQ scores (as tested on the Wechsler Abbreviated Scale of Intelligence - WASI) ranged from 77 to 129 with a mean of 104. NT participants included nine males with IQ scores (WASI) ranging from 88 to 127 and a of mean 110.

Many individuals with autism spectrum disorders were taking psychotropic medication (for example selective serotonin reuptake inhibitors and atypical neuroleptics) for symptoms and behaviors related to these disorders. We did not ask subjects on medication to discontinue these in order to qualify for inclusion in the study. This decision was made on the basis of: (a) the ethical concerns about withdrawing people from medication (especially in a study which includes no direct therapeutic benefit to subjects), (b) the pervasive social communication deficits that persist despite being on these medications and (c) the finding by

Schultz et al (2000) of no significant differences of any fMRI activation variables between autism subjects taking psychotropic medication versus those not taking medication.

Scanning Information

Imaging was performed using an Allegra 3T (Siemens, head only model) system for all scans. Participants were scanned in a prone position and a standard quadrature head coil was used. Foam cushioning was used to stabilize head position and minimize head movement. The stimuli were presented using the software E-Prime under the Windows XP operating system projected onto a back-projection screen placed at the rear of the scanner bore. Participants viewed the screen by looking in a mirror attached to the head coil. The mirror was adjusted individually to maximize viewing comfort of the participants. An mri compatible two-button mouse was used for responses. Scanning was synchronized with stimulus presentation through a trigger pulse sent to the Eprime software.

T1-weighted axial anatomical scans (TR = 2000ms, TE = 4.38ms, 204x256 matrix, FOV = 22cm, slice thickness 2mm, 0mm gap, 80 slices) were obtained prior to the experimental trial sequence. These anatomic scans were used to register the functional imaging data. Functional imaging was done using an echo planar gradient echo imaging sequence and axial orientation and were obtained using the following parameters: TR = 2000ms, TE = 30ms, 64x64 matrix, FOV = 22cm, slice thickness 4mm, 0mm gap, 32 slices.

Stimuli and design

Five types of stimuli were used: Arrow-Object, Eyes-Object, Eyes-LeftRight, Eyes-OpenClosed, and Mouth-OpenClosed. Arrow-Object stimuli displayed an arrow centrally

located on the screen and pointing either left or right. Two different objects, one positioned at either end of the arrow, such that the arrow was pointing toward one object and away from the other, were displayed concurrently with the arrow. The Eyes-Object stimuli were similar to the Arrow-Object stimuli, although for these stimuli the arrow was replaced by a person shown facing toward the viewer, with eyes averted toward one of the objects (see Figure 1).

The three remaining types of stimuli displayed a person facing the viewer as in the Eyes-Object stimuli. The Eyes-LeftRight included a person whose eyes were averted to the left or to the right as in the Eyes-Object stimuli, but in this case there were no objects. For the Eyes-OpenClosed stimuli the eyes of the displayed person were either open (and not averted) or closed. Finally, the Mouth-OpenClosed stimuli displayed a person whose eyes were not averted, but whose mouth was either open or closed. These stimuli are shown in Figure 7.

The experiment consisted of having participants make simple, two-alternative forced-choice decisions (“yes” or “no”) about the presented stimuli. For the Arrow-Object and Eyes-Object conditions, the task was to decide if the arrow (or eye gaze) was indicating a predesignated target. For the Eyes-LeftRight condition subjects were asked either “Is the person looking right?” or “Is the person looking left?” The Eyes-OpenClosed and the Mouth-OpenClosed conditions required subjects to determine if the eyes (Eyes-OpenClosed) or mouth (Mouth-OpenClosed) of the person in the picture were open or closed. A typical trial sequence is shown in Figure 2.

The stimuli were drawn from a pool of 8 different objects and 10 different faces (half male and half female) and are shown in Figures 3 and 4. For each trial a stimulus was generated online with the following constraints: (1) all objects and all faces were presented with the same probability across trials, (2) objects appeared on the left and right an equal

number of times, (3) for the Arrow-Object and Eyes-Object trials the direction of the arrow or eye gaze was to the left and right equally often, and (4) for half of all trials in a given condition the correct response was “yes” and for the remaining half it was “no.” A unique set of experimental trials was generated for each subject.

Stimuli were presented in blocks of 24 trials. All stimuli in a given block tested the same condition (e.g. Arrow-Object or Mouth-OpenClosed). Two blocks of each type were presented and the order of the blocks was randomized for each subject. Thirty seconds of rest, in which the subject was not required to make any judgment or response, preceded each block of trials.

Before entering the magnet, each subject practiced each type of task using stimuli similar to those that would be presented during the experiment. Practice continued until both the subject and the experimenter felt confident that the task and experimental procedure were well understood. Following these practice trials, the subject was prepared for scanning and placed in the magnet. Once the experimental trials were completed, the subject was removed from the magnet and paid for his/her participation. Any questions or comments about the experiment that the subject may have had were addressed at this time.

Behavioral analysis

Both judgment accuracy and response times (RT) were collected on every trial. Mean accuracy (percentage of correct trials) was calculated for each participant in each condition. Mean RT was calculated by averaging over trials in a given condition and was also performed for each subject individually. Mean performance (accuracy and RT) for each condition was calculated separately for ASD and NT subjects by averaging individual subject means.

fMRI analysis

Analysis was carried out using FEAT (FMRI Expert Analysis Tool) Version 5.4, part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). Individual subject data was motion corrected and spatial smoothing (Gaussian kernel FWHM 5 mm) was applied. Comparisons between stimulus conditions were performed by subtracting out activation patterns from a condition that was similar in all features except the contrast of interest. So, for example, in order to compare the effect of eye gaze as a directional indicator relative to an arrow, activation recorded during the Arrow-Object condition was subtracted from (i.e., contrasted with) activation during the Eyes-Object condition. In this way, all aspects of the task and stimulus were identical with the exception of the factor of interest, which in this example was the type of directional indicator (arrow or eye gaze) that was presented. This allowed us to focus on the factor that differentiated two conditions and eliminate activation that was common to both (e.g., response generation, number of components in the display, type of judgment required).

These individual contrasts were then used to compare ASD and neurotypical subjects using FEAT (FMRI Expert Analysis Tool) Version 5.90, part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). So, for example, to see how brain activation of ASD and neurotypical subjects differed when eye gaze was used as a directional indicator, we subtracted (contrasted) the average activation obtained from the individual Eye-Object > Arrow-Object contrasts in one group from that obtained from the individual Eye-Object > Arrow-Object contrasts in the other. These higher-level analyses were carried out using a

fixed effects model, by forcing the random effects variance to zero in FLAME (FMRIB's Local Analysis of Mixed Effects) [Beckmann 2003, Woolrich 2004].

Effective Connectivity Analysis

Discovery of network graphs is not possible with confirmatory methods such as DCM or SEM which require prior specification of the graph model, nor is it possible with methods for determining functional connectivity (e.g., Granger Causality, seed Pearson R correlations) which can do neither model specification nor search. Thus, we used a recently developed effective connectivity method, IMaGES (Independent Multiple-sample Greedy Equivalence Search). IMaGES is based on a modification of the Greedy Equivalence Search (GES; Meek, 1997). It was designed with the specific goal of avoiding the spurious statistical dependencies that can arise when directly combining datasets, and has the advantage over other approaches (e.g., SEM or DCM) in that it discovers an equivalence class of models that fit the data rather than providing a goodness of fit score for an experimenter provided model.

IMaGES restricts the pool of potential graph candidates by using a parallel Bayesian search to exploit the constraints imposed by multiple subjects doing the same task. IMaGES has been validated over a large set of benchmarks (Ramsey, Hanson, & Glymour, 2012; Smith et al., 2011) by demonstrating over 90% recall and precision in known graphs of various sizes.

The time series of voxel activation was extracted for each voxel in each ROI for each participant. The mean time series for a given ROI and a given participant was then calculated. These time series data were then submitted to IMaGES using a modeling tool TETRAD (www.phil.cmu.edu/projects/tetrad). Graphs with the highest goodness of fit based

on the graph's BIC (Bayesian Information Criterion) score (Schwarz, 1978) were chosen for each subject population and task. For a more detailed description of this method and the rationale for using IMaGES see Ramsey et al., (2010).

Results

Separate analyses were conducted to compare ASD and NT participants in the five stimulus conditions. For the behavioral analyses, we examined response time (RT) and accuracy to determine if and how ASD and NT participants differ in performing the various tasks. We used a GLM analysis to identify significant activation of ROIs associated with the FACE, TOM, and ACTION networks. Finally, we compared effective connectivity of the three networks using IMaGES. The results are discussed separately in the following sections.

Behavioral Data

In general, ASD subjects tended to be both less accurate and slower than NT subjects across all five conditions, but still performed well above chance. Thus, whereas ASD subjects appeared to be impaired relative to NT subjects, they clearly had little difficulty understanding and complying with the task requirements.

Comparison of Eyes-Object and Arrow-Object stimuli. Arrows, like eye gaze, can initiate reflexive orientation of attention in both neurotypical subjects (Bayliss & Tipper, 2005; Ristic, Friesen, & Kingstone, 2002; Tipples, 2002) and ASD subjects (Swettenham et al., 2003; Kylliainen & Hietanen, 2004). Moreover, for individuals with ASD, eye gaze and arrows appear to be equally effective in orienting attention (Senju et al., 2004; Vlamings et al., 2005). In order to determine if ASD subjects had a general problem following directional indicators

we compared response accuracy and reaction time by ASD and NT subjects on the Eyes-Object (EO) and Arrow-Object (AO) tasks. Because these tasks differed only in the type of directional indicator that was used (arrows in the AO task, eye gaze in the EO task), a comparison of performance on these tasks would allow us to determine if ASD subjects are generally impaired relative to NT subjects in processing directional indicators. Moreover, a comparison of responses in the AO and EO tasks would allow us to determine if any discrepancy in performance between the two groups reflected a general difference in processing, or was specific to a particular directional indicator.

An analysis of variance was conducted on the percentage of correct responses, with Subject Type (ASD, NT) as the between-subject factor and Stimulus Type (AO, EO) as the within-subject factor. A main effect for Subject Type ($F(1, 32) = 18.75, p < .001$) was found reflecting the superior accuracy of NT subjects in both tasks. Stimulus Type was also found to be significant ($F(1,32) = 5.64, p < .05$), suggesting that both subject groups found the AO task to be easier than the EO task. Finally, the interaction between the two factors was also significant ($F(1,32) = 5.03, p < .05$), reflecting the greater difference in performance between the AO and EO tasks for ASD subjects relative to NT subjects. Pairwise comparisons (Tukey's HSD test) confirmed these conclusions. Whereas ASD subjects were significantly more accurate on AO stimuli than on EO stimuli ($p < .02$), the accuracy of NT subjects did not differ between the two conditions ($p > .99$). Moreover, NT subjects were significantly more accurate than ASD subjects in the EO task ($p < .0001$), but did not differ from ASD subjects on the AO task ($p > .46$).

Response times followed the same pattern observed in the accuracy data (see Table

1), although an analysis of variance performed on the response times did not yield any significant differences. As with the analysis of response times, we used Subject Type as the between-subject factor and Stimulus Type as the within-subject factor. The results of the analysis of variance on response times revealed no significant effect for Subject Type ($F(1, 32) = 3.33, p > .08$), Stimulus Type ($F(1,32) = .81, p > .38$), or the interaction of the two factors ($F(1,32) = .04, p > .84$). Given that the trend of the response time data followed that of the accuracy data, we attribute the lack of significance found in the response time analysis to the greater variance we observed in response times relative to mean accuracy.

Comparison of Eyes-OpenClosed and Mouth-OpenClosed stimuli. The comparison of performance on EO and AO stimuli strongly indicates that ASD subjects are disadvantaged relative to NT subjects when processing eye gaze. However, the difference in response to the EO and AO stimuli by ASD subjects could reflect a general difficulty processing eye gaze in particular or face processing in general. To test this possibility, we compared accuracy and response times of both subject groups while performing the EOC (Eyes-OpenClosed) or MOC (Mouth-OpenClosed) tasks. The two tasks required subjects to determine whether the target feature (eyes in the EOC task or mouth in the MOC task) was open or closed. Thus, the two tasks both used face stimuli and required the same type of judgment to be made, but allowed us to determine if eyes were particularly difficult for ASD subjects relative to NT subjects.

We performed an analysis of variance using Subject Type as the between-groups factor and Stimulus Type as the within-groups factor as we had in the AO-EO comparison. The analysis yielded a significant main effect for Subject Type, $F(1,32) = 9.51, p < .01$,

reflecting the generally higher mean accuracy scores achieved by NT subjects. Neither the main effect for Stimulus Type, $F(1,32) = 1.38, p > .25$, or the interaction between Subject Type and Stimulus Type, $F(1,32) = .91, p > .35$, were significant. Pairwise comparisons (Tukey's HSD test) revealed that NT subjects were significantly more accurate than ASD subjects on the EOC task ($p < .04$), but not significantly different from ASD subjects on the MOC task ($p > .44$). It appears that eyes, and not faces in general, posed a problem for our ASD subjects.

We replicated the analysis of variance with the response time data and found, as we did in the analysis of mean accuracy, a Subject Type main effect, $F(1,32) = 4.61, p < .04$. As with the accuracy data, neither the Stimulus Type, $F(1,32) = .66, p > .47$, nor the interaction between the two main factors, $F(1,32) = .00, p > .97$, was significant. Pairwise comparisons (Tukey's HSD test) revealed no difference between ASD and NT subjects on either the EOC task ($p > .45$) or the MOC task ($p > .43$).

Comparison of eyes-LeftRight and Eyes-OpenClosed. A comparison of mean accuracy between ELR (Eyes-LeftRight) and EOC (Eyes-OpenClosed) was made to determine if the perception of averted eyes differed between ASD and NT subjects. As in the comparisons described earlier, an analysis of variance was conducted using Subject Type as the between-groups factor and Stimulus Type as the within-groups factor. Subject Type was found to be significant, $F(1,32) = 8.88, p < .01$, although neither Stimulus Type, $F(1,32) = 1.00, p > .32$, nor the interaction between the two factors, $F(1,32) = .54, p > .47$, were significant. Pairwise comparisons (Tukey's HSD test) found NT subjects to be more accurate on ELR tasks than ASD subjects ($p = .06$), but not to differ from ASD subjects on the EOC

task ($p > .40$).

A similar comparison using response time data found a significant effect of Subject Type, $F(1,32) = 5.63$, $p < .03$, and no significant effect of either Stimulus Type, $F(1,32) = .61$, $p > .44$, or the interaction between Subject Type and Stimulus Type, $F(1,32) = .00$, $p > .95$.

Pairwise comparisons (Tukey HSD test) revealed no significant difference between NT and ASD subjects on either the ELR task ($p > .37$) or the EOC task ($p > .33$).

Comparison of Eyes-Object and Eyes-LeftRight stimuli. From the comparison of AO (Arrow-Object) and the EO (Eyes-Object) stimuli, we learned that the EO stimuli were more difficult to process for ASD subjects than were the AO stimuli. The comparison of EOC and MOC tasks verified that ASD subjects had difficulty processing eye gaze, not just face stimuli. In this comparison between EO (Eyes-Object) and ELR (Eyes-LeftRight), we examined whether the problem ASD subjects demonstrated in the EO task could be due to the presence of potential targets. Specifically, we wondered if ASD subjects have difficulty maintaining attention between eye gaze and object, or if they have difficulty simply perceiving the direction of averted eyes. To answer this question, we compared accuracy and response times for ASD and NT subjects performing the EO and ELR tasks. The tasks were identical with the exception that EO stimuli included objects that could be potential targets.

We used analysis of variance to compare performance between ASD and NT subjects on the EO and ELR tasks using Subject Type as the between-subject factor and Stimulus Type as the within-subject factor. A main effect for Subject Type was found for both accuracy, $F(1,32) = 12.49$, $p < .002$, and response time, $F(1,32) = 5.85$, $p < .05$, reflecting the tendency of NT subjects to respond not only more accurately than ASD subjects, but also to

respond more quickly. Stimulus Type was not significant for either the accuracy measure, $F(1,32) = .36, p > .55$, or the response time measure, $F(1,32) = .69, p > .41$, and no significant interaction was found for either accuracy, $F(1,32) = .13, p > .71$, or for response time, $F(1,32) = .27, p > .86$. These results suggest that tasks involving eyes are particularly difficult for ASD subjects whether or not eyes are used to indicate an object.

We wondered if the inferior performance of ASD subjects relative to NT subjects was restricted to stimuli in which attention needed to follow eye gaze toward an object (EO task), or if performance would be impaired for both tasks relative to NT subjects. Pairwise comparisons (Tukey's HSD test) found that NT subjects were more accurate than ASD subjects on the ELR task ($p < .05$), but did not differ significantly from that of ASD subjects on the EO task ($p > .13$). Similar pairwise comparisons on the response time data did not yield any significant differences for either the ELR task ($p > .40$) or the EO task ($p > .28$).

GLM Analysis

Figure 5 displays statistically significant contrasts for ROIs in the FACE, TOM, and ACTION networks. The activation shown reflects contrasts between conditions (e.g., Eyes-Object > Arrow-Object) averaged independently over ASD and NT subjects. Details about these results are described in the following sections.

Eyes-Object contrasted with Arrow-Object. We first subtracted AO activation from EO activation individually for each subject. Because the EO and AO conditions differed only in the use of eye gaze (EO) or an arrow (AO), the subtraction of AO from EO provided the means of examining brain activity associated specifically with processing eye gaze as a

directional indicator. These first level analyses were then used to perform the group analysis contrasting ASD and NT subjects in order to determine how these two groups differed in processing eye gaze. A listing of activated areas yielded by the EO > AO contrast for ASD and NT subjects is shown in Table 1.

Eyes-OpenClosed contrasted with Mouth-OpenClosed. This contrast was performed to determine if brain activation differences could be detected between ASD and NT participants as a function of whether eyes were targeted by the task. Both the EOC and the MOC conditions required face processing, however, only the EOC condition required specific focus on eyes. Consequently, this analysis was conducted to provide information about how processing of eyes, in particular, affect brain activation. Significantly activated areas for the EOC > MOC contrasts for ASD and NT subjects is shown in Table 3.

Eyes-LeftRight contrasted with Eyes-OpenClosed. This contrast focused on how averted gaze, specifically, would affect brain activation between the subject groups. Both the ELR and the EOC conditions targeted eye processing, with the difference being that the ELR condition involved averted gaze. See Table 4 for a comparison of ASD and NT subjects with this contrast.

Eyes-Object contrasted with Eyes-LeftRight. The aim of this contrast was to determine how the presence of an object could mediate processing of averted gaze. Both EO and ELR stimuli involved averted gaze, with the only difference between the two conditions being the presence of additional objects. Table 5 displays the results of the EO > ELR contrast for ASD and NT subjects.

Effective Connectivity Analysis

Face processing. We chose the ELR, EOC, and MOC conditions to compare face processing in ASD and NT participants. The EO condition was not included because of the presence of objects in the stimulus. Shown in Figure 6 are the graphical models of the face processing network for ASD and NT participants. NT subjects demonstrated similar patterns for the EOC and MOC conditions, but a different pattern for the ELR condition. Specifically, in the ELR condition, an additional edge was observed between pSTS and fusiform gyrus. Activation for all three conditions in ASD subjects was similar to that of the NT subjects. This result suggests that ASD subjects engaged the FACE network in a manner similar to that for NT subjects.

Theory of Mind. We used the EO and ELR conditions to assess the effective connectivity of the TOM network (see Figure 9). We chose these conditions as being most similar to situations involving joint attention insofar as they involved averted eyes. As was found for the face processing network, the NT participants showed highly similar activation patterns for both conditions. In contrast, the pattern observed for ASD subjects was markedly different between the two conditions. Moreover, neither pattern found for the ASD subjects was similar to that seen for the NT group. A notable difference for ASD subjects in the ELR is the absence of an edge between amygdala and paracingulate gyrus. Which is seen in the EO condition for ASD subjects and both the ELR and EO conditions for NT subjects.

Action understanding. For this analysis we compared the AO, EO, and ELR conditions. These conditions were chosen because they each depicted directionality, an implied correlate of movement or action. The graphical models obtained for the ACTION

network are shown in Figure 1. As was found for the FACE and TOM networks, NT subjects showed similar patterns across the three stimulus conditions whereas ASD subjects had markedly different connectivity patterns across the same conditions. The ASD group did exhibit a connectivity pattern similar to that of the NT group, but only for the AO condition. This similar connectivity pattern is consistent with the behavioral data showing little difference between ASD and NT subjects. Once again, the greatest difference between the ASD and NT groups was found for the ELR condition.

General Discussion

Three brain networks have been implicated in impaired social cognition: 1) face processing, 2) Theory of Mind, and 3) action understanding. This study examined how the recruitment of these three networks differ between individuals with ASD and neurotypicals when engaged in various tasks related to social cognition.

The behavioral results affirm that individuals with ASD, even those who are high functioning, have difficulty processing social cues relative to neurotypicals. ASD participants were slower to respond and less accurate than were neurotypicals particularly when the task required attention to eyes (EO, ELR, and EOC). ASD participants did not differ significantly from neurotypicals in tasks that did not require eye processing (AO, MOC). These results suggest that individuals with ASD do not have difficulty processing a nonsocial directional cue such as an arrow, nor are they impaired in a face processing task that does not involve attention to eyes. However, our ASD participants were particularly impaired when processing averted gaze (EO, ELR). To the extent that joint attention requires the ability to follow averted

eye gaze, it is not surprising that individuals with ASD have difficulty engaging in joint attention.

In order to map brain activation to the behavioral differences we observed between ASD and NT participants, we took two approaches to examining the fMRI data. The first approach was to conduct a GLM analysis in which brain activation patterns were contrasted between tasks and between our subject groups. Specifically, we compared the activation in ROIs related to the three networks associated with social cognition (FACE, TOM, ACTION). The GLM analysis revealed differential recruitment of brain areas by ASD and NT participants. In general, NT participants appeared to engage brain areas associated with the three networks to a greater extent than did ASD participants. The exception to this pattern appeared in ROIs associated with the TOM network. ASD participants demonstrated significantly more activation of the TOM network than did NT participants for EO>ELR and ELR>EOC contrasts. This result is consistent with research suggesting connectivity abnormalities in ASD brains (Belmonte & Yurgelun-Todd, 2003; Rubenstein & Merzenich, 2003) and may explain why the tasks involving the processing of averted gaze (EO, ELR) were performed least well by ASD participants.

The GLM analysis provided evidence that the activation of ROIs differed across tasks for ASD and NT participants. However, GLM analysis provides no understanding of the neural networks underlying cognitive performance. To this end, we conducted graph analyses of each network (FACE, TOM, ACTION) for each task and subject group. We found that NT participants demonstrated similar connectivity in a given network across tasks used to recruit that network. On the other hand, for the ASD participants, connectivity patterns differed not only from NT participants, but also differed across tasks used to recruit the same network.

This pattern in ASD participants was particularly evident for the TOM and ACTION networks. ASD recruitment of the FACE network did not differ greatly from that of NT subjects. It should be noted that the greatest difference between ASD and NT subjects was found for the ELR condition, the condition that also resulted in the poorest behavioral performance for ASD subjects.

Taken together, the behavioral, GLM, and effective connectivity analyses indicate that the source of social cognitive impairment in individuals with ASD is not isolated to processing faces, or engaging in Theory of Mind, or understanding action. Rather, the effective connectivity analyses indicate that individuals with ASD recruit the brain networks associated with social cognition very differently than do neurotypicals. Additional research should focus on identifying the extent to which individuals with ASD differ from neurotypicals in recruiting other brain networks such as those associated with attention, memory, or reward. It is possible that atypical effective connectivity in individuals with ASD is restricted to networks associated with social cognition. However, it is also possible that atypical recruitment of social cognition networks will be seen in other networks not exclusively associated with social cognition. This atypical recruitment might arise from a more general connectivity problem of brain response in individuals with ASD (e.g., Belmonte & Yurgelun-Todd, 2003; Rubenstein & Merzenich, 2003). Support for this argument is found in recent work (Assaf et al., 2010) that found evidence of abnormal functional connectivity in the default mode network of individuals with ASD.

Funding

Funding from The NJ Governor's Council for Medical Research and Treatment of Autism and the James S. McDonnell Foundation.

Acknowledgements

The authors would like to thank Dr. Charles Cartwright for his recruitment and psychiatric assessment of the participants with autism spectrum disorder.

References

- Assaf, M., Jagannathan, K., Calhoun, V.D., Miller, L., Stevens, Michael C., Sahl, R., O'Boyle, J.G., Schultz, R.T., Pearlson, G.D. Abnormal functional connectivity of default mode sub-networks in autism spectrum disorder patients. *Neuroimage*, 2010; 53(1), 247-256.
- Baron-Cohen, S., Leslie, A., & Frith, U. Does the autistic child have a "theory of mind"? *Cognition*, 1985; 21(1): 37-46.
- Baron-Cohen, S. *Mindblindness: An essay on autism and theory of mind*. Cambridge, MA: MIT Press; 1995.
- Bayliss, A., & Tipper, S. Gaze and arrow cueing of attention reveals individual differences along the autism spectrum as a function of target context. *Br J Psychol*, 2005; 96(Pt 1): 95-114.
- Belmonte, M.K. & Yurgelun-Todd, D.A. Functional anatomy of impaired selective attention and compensatory processing in autism. *Brain Research*, 2003; 17(3): 651-664.
- Dawson, G., Webb, S., & McPartland, J. Understanding the nature of face processing impairment in autism: Insights from behavioral and electrophysiological studies. *Dev Neuropsychol*, 2005; 27(3) 403-424.
- Deaner, R., & Platt, M. Reflexive social attention in monkeys and humans. *Curr Biol*, 2003; 13(18): 1609-13.

- Driver, J., Davis, G., Ricciardelli, P., Kidd, P., Maxwell, E., & Baron-Cohen, S. Gaze perception triggers visuospatial orienting by adults in a reflexive manner. *Vis Cogn*, 1999; 6: 509-540.
- Friesen, C., & Kingstone, A. The eyes have it!: Reflexive orienting is triggered by nonpredictive gaze. *Psychon B Rev*, 1998; 5: 490-495.
- Gallese V., Rochat M., Cossu G., Sinigaglia C. Motor Cognition and its role in the phylogeny and ontogeny of intentional understanding. *Dev Psychol*, 2009, 45:103-113.
- Golan, O., Baron-Cohen, S., & Hill, J. The Cambridge Mindreading (CAM) Face-Voice Battery: Testing complex emotion recognition in adults with and without Asperger syndrome. *J Autism Dev Disord*, 2006; 36(2): 169-83.
- Grelotti, D.J., Gauthier, I., & Schultz, R.T. Social interest and the development of cortical face specialization: what autism teaches us about face processing. *Dev Psychobiol*, 2002; 40(3): 213-25.
- Hobson, R., & Lee, A. Hello and goodbye: a study of social engagement in autism. *J Autism Dev Disord*, 1998; 28(2): 117-27.
- Hobson, R., & Meyer, J. Foundations for self and other: a study in autism. *Dev Sci*, 2005; 8(6): 481-91.

- Kylliäinen, A., & Hietanen, J. Attention orienting by another's gaze direction in children with autism. *J Child Psychol Psyc*, 2004; 45(3): 435-44.
- Landry, S., & Loveland, K. Communication behaviors in autism and developmental language delay. *J Child Psychol Psyc*, 1998; 29(5): 621-34.
- Langton, S., Watt, R., & Bruce, I. Do the eyes have it? Cues to the direction of social attention. *Trends Cogn Sci*, 2000; 4(2): 50-59.
- Leslie, A.M., Friedman, O., & German, T.P. (2004). Core mechanisms in 'theory of mind'. *Trends in Cognitive Sciences*, 8, 528–533.
- Meek, C. Graphical Models: Selecting causal and statistical models. PhD thesis. Carnegie Mellon University; 1997.
- Mundy, P., Sigman, M., & Kasari, C. A longitudinal study of joint attention and language development in autistic children. *J Autism Dev Disord*, 1990; 20(1): 115-28.
- Pellicano, E., Maybery, M., & Durkin, K. Central coherence in typically developing preschoolers: does it cohere and does it relate to mindreading and executive control? *J Child Psychol Psyc*, 2005; 46(5): 533-47.
- Ramsey, J. D., Hanson, S. J., & Glymour, C. Multi-subject search correctly identifies causal connections and most causal directions in the DCM models of the Smith et al. simulation study. *Neuroimage*, 2011; 58(3): 838-48.

Ricciardelli, P., Bricolo, E., Aglioti, S., & Chelazzi, L. My eyes want to look where your eyes are looking: exploring the tendency to imitate another individual's gaze. *Neuroreport*, 2002; 13(17): 2259-64.

Ristic, J., Friesen, C., & Kingstone, A. Are eyes special? It depends on how you look at it. *Psychon B Rev*, 2002; 9(3): 507-513.

Roeyers, H., Van Oost, P., & Bothuyne, S. Immediate imitation and joint attention in young children with autism. *Dev Psychopathol*, 1998; 10(3): 441-50.

Schultz, R.T. (2005). Developmental deficits in social perception in autism: the role of the amygdala and fusiform face area. *Int J Dev Neurosci*, 23, 125-141.

Schultz, R.T., Gauthier, I., Klin, A., Fulbright, R., Anderson, A., Volkmar, F., Skudlarski, P., Lacadie, C., Cohen, D., & Gore, J. Abnormal ventral temporal cortical activity during face discrimination among individuals with autism and Asperger syndrome. *Arch Gen Psychiat*, 2000; 57(4): 331-40.

Senju, A., Tojo, Y., Dairoku, H., & Hasegawa, T. Reflexive orienting in response to eye gaze and an arrow in children with and without autism. *J Child Psychol Psyc*, 2004; 45(3): 445-58.

Siegal, M., & Varley, R. Neural systems involved in 'theory of mind'. *Nat Rev Neurosci*, 2002; 3:463-471.

Sigman, M., & Ungerer, J. Attachment behaviors in autistic children. *J Autism Dev Disord*, 1984; 14(3): 231-44.

Schwarz, Gideon E. Estimating the dimension of a model. *Annals of Statistics*, 1978; 6(2): 461–464.

Swettenham, J., Condie, S., Campbell, R., Milne, E., & Coleman, M. Does the perception of moving eyes trigger reflexive visual orienting in autism? *Philos T Roy Soc B*, 2003; 358(1430): 325-34.

Vlamings, P., Stauder, J., van Son, I., & Mottron, L. Atypical visual orienting to gaze- and arrow-cues in adults with high functioning autism. *J Autism Dev Disord*, 2005; 35(3): 267-77.

Table 1. Behavioral performance by ASD and NT participants.

Task Type	Subject Type	Accuracy		Response Time	
		Mean %	SE	Mean (ms)	SE
AO	ASD	.92	.02	655.00	94.41
	NT	.99	.02	484.29	56.95
EO	ASD	.81	.04	738.53	68.58
	NT	.97	.01	585.23	76.56
ELR	ASD	.76	.09	679.54	38.54
	NT	.96	.03	545.84	45.09
EOC	ASD	.85	.05	728.64	63.85
	NT	.97	.01	587.26	76.41
MOC	ASD	.92	.03	676.28	72.58
	NT	.98	.01	530.68	51

Table 2. Shown is the cluster extent (number of voxels) exceeding the cluster corrected threshold $p < .001$ for regions associated with Theory of Mind, Face Processing, and Action Understanding networks. Data is shown for ASD and NT subjects in the EO > AO condition and includes the coordinates (mm) and z score of the maximally activated voxel.

Network	Region	x	y	z	Cluster extent	Max Z
ASD						
Theory of Mind	temporoparietal junction	-38	-58	16	44	2.06
	paracingulate cortex	-6	30	30	44	1.44
	posterior cingulate gyrus	-4	-42	12	28	1.52
	precuneus	-8	-60	62	230	2.16
Face Processing	middle fusiform gyrus	42	-42	-20	116	2.05
	inferior occipital gyrus	-34	-84	2	227	1.99
	amygdala	28	0	-18	17	1.47
Action Understanding	frontal operculum	44	18	-2	27	1.67
	posterior STS	64	-10	0	47	2.00
	inferior parietal lobule	-42	-42	22	18	1.73
NT						
Theory of Mind	temporoparietal junction	-58	-56	18	1013	2.44
	paracingulate cortex	4	42	34	1926	2.65
	posterior cingulate gyrus	0	-28	38	951	2.52
	precuneus	2	-42	70	605	2.06
Face Processing	Middle fusiform gyrus	-40	-52	-12	580	2.34
	inferior occipital gyrus	-34	-84	-10	410	2.21
	amygdala	22	-8	-10	149	2.42
Action Understanding	frontal operculum	40	24	-2	416	2.37
	posterior STS	-50	-38	2	878	2.71
	Inferior parietal lobule	-36	-44	24	274	2.43

Middle fusiform = temporal occipital fusiform

ipl = parietal operculum

Table 3. Shown is the cluster extent (number of voxels) exceeding the cluster corrected threshold $p < .001$ for regions associated with Theory of Mind, Face Processing, and Action Understanding networks. Data is shown for ASD and NT subjects in the EOC > MOC condition and includes the coordinates (mm) and z score of the maximally activated voxel.

Network	Region	x	y	z	Cluster extent	Max Z
ASD						
Theory of Mind	temporoparietal junction	56	-58	20	47	1.80
	paracingulate cortex	4	46	2	45	1.67
	posterior cingulate gyrus	-14	-40	34	22	1.42
	precuneus	10	-52	58	544	2.33
Face Processing	middle fusiform gyrus	-38	-42	-12	234	2.45
	inferior occipital gyrus	-28	-88	0	127	1.98
	amygdala	6	-2	-20	26	1.97
Action Understanding	frontal operculum	34	22	6	5	1.46
	posterior STS	66	-28	4	26	1.43
	inferior parietal lobule	64	-20	18	70	1.55
NT						
Theory of Mind	temporoparietal junction	-54	-58	28	90	1.58
	paracingulate cortex	12	26	38	389	2.18
	posterior cingulate gyrus	18	-48	8	472	2.27
	precuneus	-4	-56	56	1269	2.39
Face Processing	middle fusiform gyrus	38	-52	-8	306	2.07
	inferior occipital gyrus	-40	-68	-10	79	1.81
	amygdala	30	-4	-26	27	1.50
Action Understanding	frontal operculum	34	12	14	96	2.10
	posterior STS	64	-28	20	57	1.42
	Inferior parietal lobule	40	-30	26	307	2.13

Table 4. Shown is the cluster extent (number of voxels) exceeding the cluster corrected threshold $p < .001$ for regions associated with Theory of Mind, Face Processing, and Action Understanding networks. Data is shown for ASD and NT subjects in the ELR > EOC condition and includes the coordinates (mm) and z score of the maximally activated voxel.

Network	Region	x	y	z	Cluster extent	Max Z
ASD						
Theory of Mind	temporoparietal junction	50	-52	44	1052	2.58
	paracingulate cortex	8	48	16	1672	2.99
	posterior cingulate gyrus	-10	-42	38	1887	2.54
	precuneus	10	-70	44	2782	2.84
Face Processing	middle fusiform gyrus	30	-50	-14	269	2.06
	inferior occipital gyrus	-38	-74	12	496	2.49
	amygdala	32	2	-16	34	1.42
Action Understanding	frontal operculum	-44	18	-2	274	2.28
	posterior STS	-50	-40	8	364	2.19
	inferior parietal lobule	-62	-30	18	131	2.20
NT						
Theory of Mind	temporoparietal junction	-44	-60	20	365	2.15
	paracingulate cortex	10	26	38	238	1.94
	posterior cingulate gyrus	-4	-46	44	361	1.92
	precuneus	-8	-70	50	747	2.06
Face Processing	middle fusiform gyrus	34	-56	-16	43	1.82
	inferior occipital gyrus	32	-80	2	177	1.87
	amygdala	16	0	-16	43	1.93
Action Understanding	frontal operculum	32	18	16	35	2.02
	posterior STS	64	-26	0	75	1.88
	Inferior parietal lobule	-42	-40	26	235	2.06

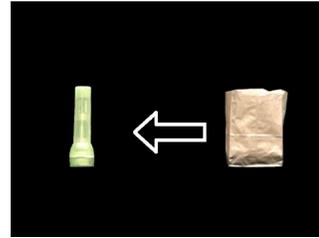
Table 5. Shown is the cluster extent (number of voxels) exceeding the cluster corrected threshold $p < .001$ for regions associated with Theory of Mind, Face Processing, and Action Understanding networks. Data is shown for ASD and NT subjects in the E0 > ELR condition and includes the coordinates (mm) and z score of the maximally activated voxel.

Network	Region	x	y	z	Cluster extent	Max Z
ASD						
Theory of Mind	temporoparietal junction	-36	-60	20	47	1.82
	paracingulate cortex	-6	54	6	181	2.80
	posterior cingulate gyrus	-8	-54	6	289	2.33
	precuneus	24	-58	8	1179	2.67
Face Processing	middle fusiform gyrus	48	-48	-24	463	2.42
	inferior occipital gyrus	34	-76	2	345	2.20
	amygdala	30	-6	-20	3	1.16
Action Understanding	frontal operculum	-36	14	14	16	1.53
	posterior STS	62	-36	10	16	1.37
	inferior parietal lobule	42	-22	20	17	1.33
NT						
Theory of Mind	temporoparietal junction	58	-56	18	105	1.78
	paracingulate cortex	0	42	34	224	1.81
	posterior cingulate gyrus	-8	-40	40	116	1.80
	precuneus	-	-	-	-	-
Face Processing	Middle fusiform gyrus	-40	-52	-12	311	2.13
	inferior occipital gyrus	-38	-76	2	207	2.18
	amygdala	22	-2	-20	24	1.36
Action Understanding	frontal operculum	44	24	6	9	1.32
	posterior STS	-50	-22	-2	143	1.73
	Inferior parietal lobule	62	-34	30	3	1.51

Table 6. Behavioral performance by ASD and NT subjects in each stimulus condition.

<i>Task Type</i>	<i>Subject Type</i>	<i>Accuracy</i>		<i>Response Time</i>	
		Mean %	<i>SE</i>	Mean (ms)	<i>SE</i>
AO	<i>ASD</i>	.92	.02	655.00	94.41
	<i>NT</i>	.99	.02	484.29	56.95
EO	<i>ASD</i>	.81	.04	738.53	68.58
	<i>NT</i>	.97	.01	585.23	76.56
ELR	<i>ASD</i>	.76	.09	679.54	38.54
	<i>NT</i>	.96	.03	545.84	45.09
EOC	<i>ASD</i>	.85	.05	728.64	63.85
	<i>NT</i>	.97	.01	587.26	76.41
MOC	<i>ASD</i>	.92	.03	676.28	72.58
	<i>NT</i>	.98	.01	530.68	51.68

Arrow-Object (AO)



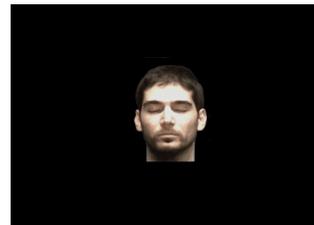
Eyes-Object (EO)



Eyes-LeftRight (ELR)



Eyes-OpenClosed (EOC)



Mouth-OpenClosed (MOC)

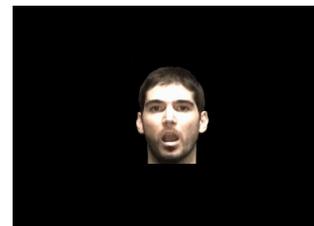


Figure 1. Example stimulus used in each condition.

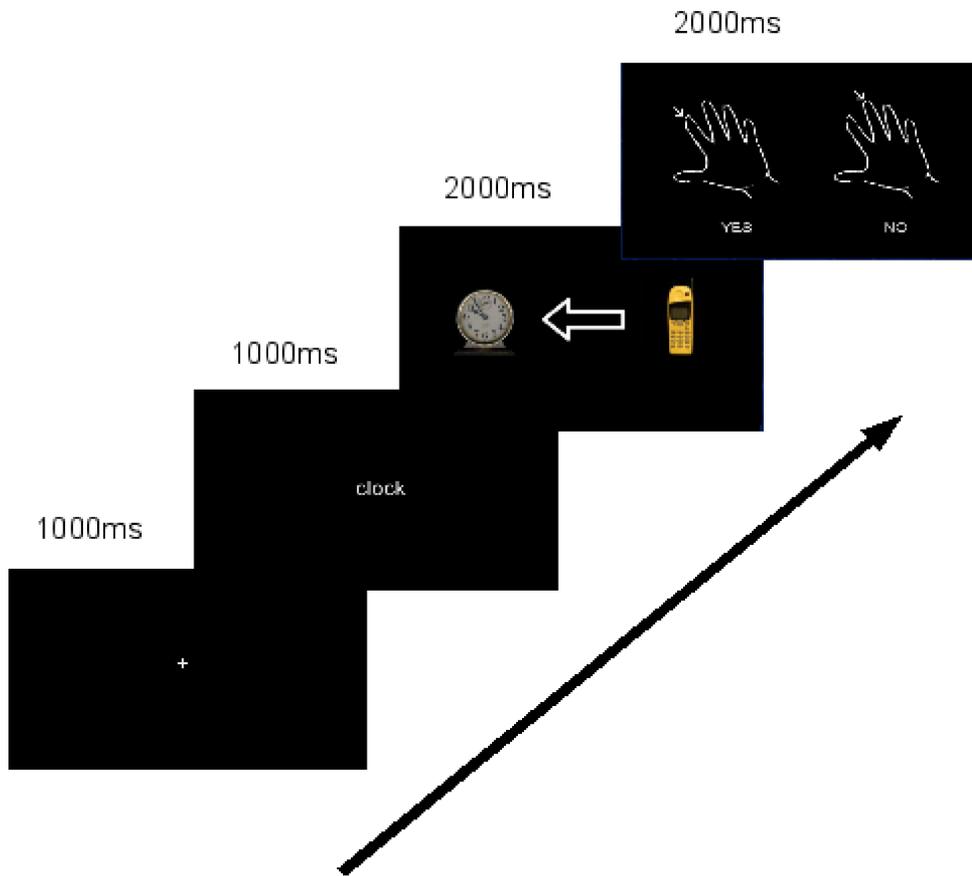


Figure 2. Timing and progression of a standard trial.



Figure 3. Objects used in the EO and AO conditions.



Figure 4. Faces used in the EO, ELR, EOC, and MOC conditions.

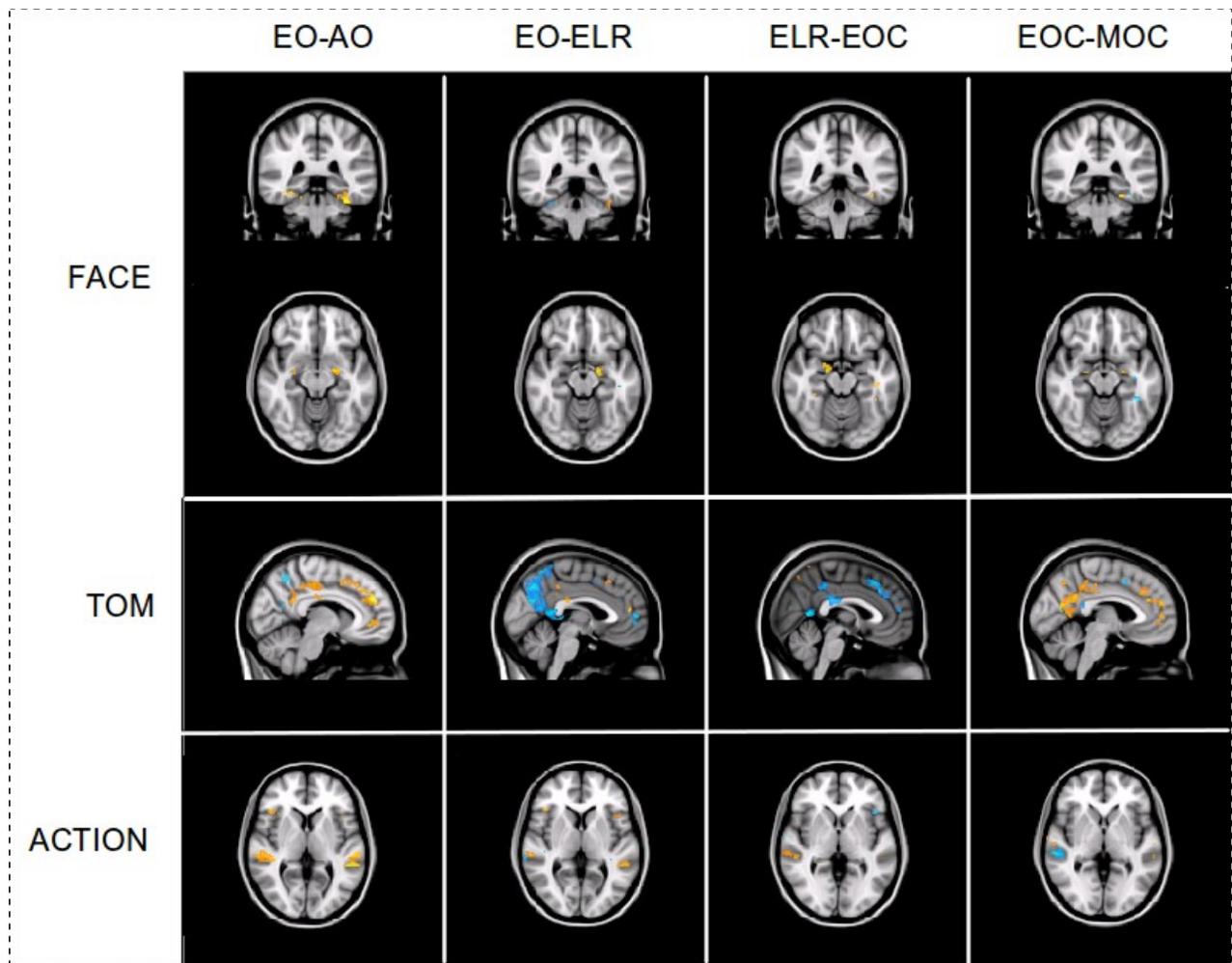


Figure 5. Significant activation for ROIs in the FACE, TOM, and ACTION networks as a function of task contrasts. Activation is based on contrasts between ASD and NT subjects. Activation in yellow indicates activation for NT > ASD contrasts. Activation in blue indicates activation for ASD > NT contrasts.

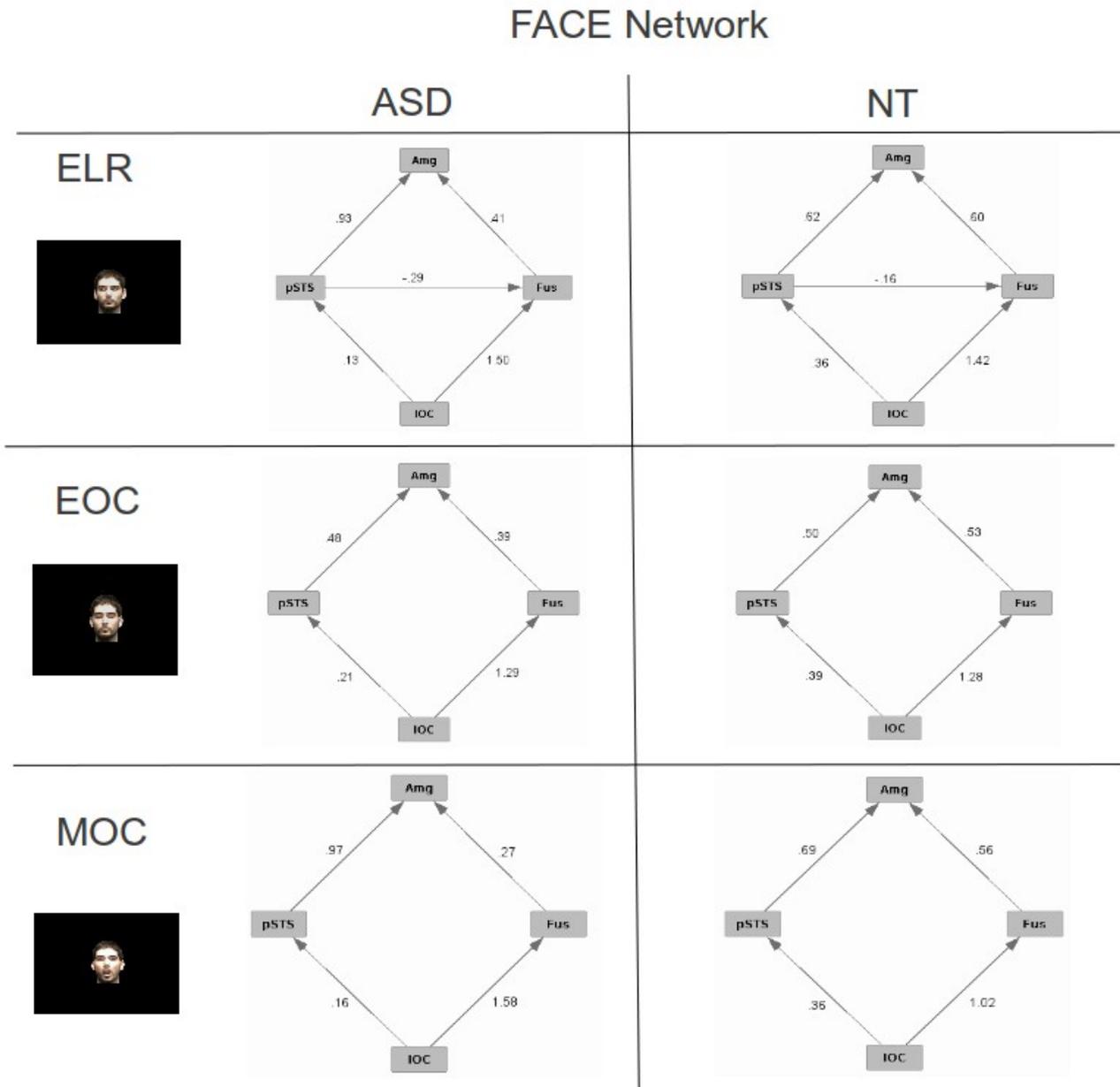


Figure 6. Effective connectivity of the FACE network for ASD and NT subjects for tasks designed to engage face processing. Numbers on the edges reflect the regression values for those edges.

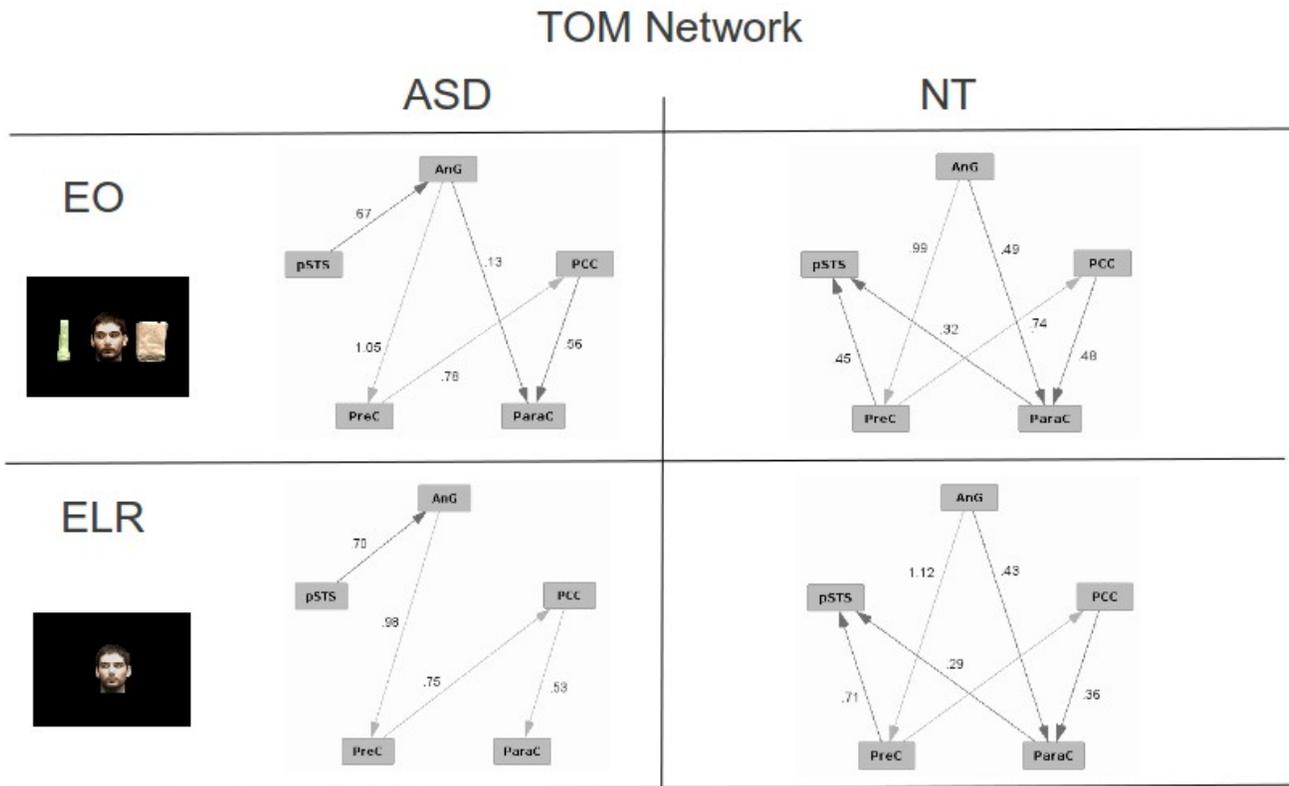


Figure 7. Effective connectivity of the TOM network for ASD and NT subjects for tasks designed to engage Theory of Mind. Numbers on the edges reflect the regression values for those edges.

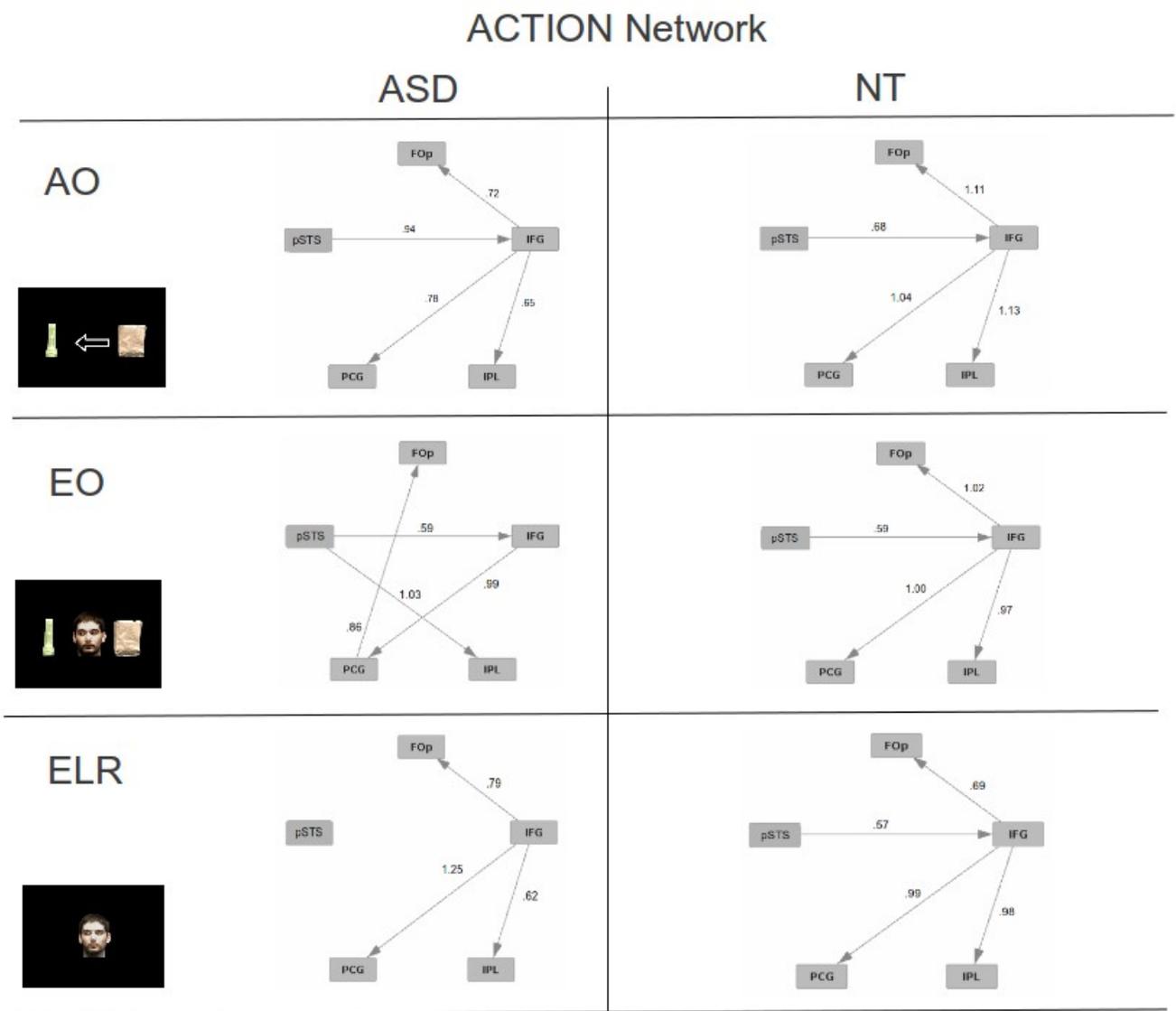


Figure 8. Effective connectivity of the ACTION network for ASD and NT subjects for tasks designed to engage action understanding. Numbers on the edges reflect the regression values for those edges.