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Reduced neural sensitivity to online social interactions in autism

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Abstract

Difficulty with social interactions is a hallmark characteristic of autism spectrum disorders. While many studies have investigated the neural mechanisms underlying atypical social cognition, the methods used have rarely involved social interaction, relying instead on offline reasoning about a character. In the current study, we examined whether and which brain systems are sensitive to online social interactions in individuals with autism. We compared functional MRI data collected from 15 neurotypical (NT) and 15 autism spectrum disorder (ASD) participants during live real-time interactions (Live) and during a video replay of the same interaction (Recorded-Same) and a novel interaction (Recorded-Novel). Whole brain analyses demonstrated a significantly greater response to Live than Recorded conditions, in NT vs ASD, within left posterior superior temporal sulcus (pSTS) and regions of the cerebellum bilaterally. Region of interest analyses revealed that right posterior temporal regions were differentially recruited during online social interactions in the ASD and NT groups. Also, regions commonly associated with personal salience (i.e., dorsal anterior cingulate and bilateral insula) were sensitive to online social interactions in NT, but to novelty in the ASD group. These data suggest reduced and atypical neural sensitivity to online social interactions in individuals with autism.

Keywords: social interaction; autism; fMRI.

Introduction

Social interactions provide a rich opportunity to learn from others beginning early in infancy and continuing throughout one’s life. Individuals with autism engage in fewer interactions than their typically developing peers and reduced social engagement predicts later delays in language and social abilities (e.g., Mundy, Sigman, & Kasari, 1990). A central question in the study of autism is what underlies this reduced engagement in social interactions. Some have proposed that social interactions are inherently rewarding, and thus motivating, for neurotypical (NT) individuals but not for those with autism spectrum disorders (ASD) (e.g., Chevallier, Kohls, Troiani, Brodkin, & Schultz, 2012; Dawson et al., 2002). Similarly, others suggest that, unlike NT individuals, social stimuli fail to capture the attention of those with autism (e.g., Klin, Jones, Schultz, & Volkmar, 2003). Others still suggest difficulties with social interactions arise from impairments in theory of mind, or reasoning about another person’s thoughts (Baron-Cohen, Leslie, & Frith, 1985).

While evidence exists to support each of these claims, most of the empirical data come from studies using proxies for social interactions, such as a picture, video, or vignette of a person or characters. While important, these offline methods may be missing the processes at the root of ASD, namely social interactions or engagement with others. For example, difficulties interpreting or predicting a social partner’s behavior are thought to underlie real-world difficulties in communication; however, offline tasks in which individuals must predict a fictional character’s action based on false beliefs often fail to find differences between autism and neurotypical groups in behavioral reports (e.g., Senju, Southgate, White, & Frith, 2009) and brain activation patterns (Dufour et al., 2012). Interestingly, while offline reasoning processes appear to be relatively intact, individuals with autism fail to spontaneously anticipate the location of an actor’s reach based on a false belief (Senju et al., 2009) – a process more akin to real-world use of belief inferences to predict behavior. Furthermore, even for neurotypical individuals, social or communicative behavior in the context of an interaction, as compared to mere observation, may be quantitatively and/or qualitatively different from offline social communication (e.g., Clark & Brennan, 1999; Pökkänen, Alhoniemi, Leppänen, & Hietanen, 2011; Redcay et al., 2010; Risko et al., 2012; Schilbach et al., 2012; Sebanz, Bekkering, & Knoblich, 2006; Shimada & Hiraki, 2006) Thus, like others (e.g., Schilbach et al., 2012), we argue for a second-person neuroscience approach to understand core difficulties with social interaction in individuals with autism.

Using a novel method for collecting fMRI data during an online social interaction, we previously demonstrated that brain systems supporting reward processing, social cognition, and attention were engaged more when interacting with another person in a real-time face-to-face interaction (i.e. the Live condition) than during a video replay of the experimenter from the same interaction (Recorded-Same condition) or video replay of the experimenter taken from a different scan session (Recorded-Novel condition) (Redcay et al., 2010). Thus, this paradigm provides a method to examine the extent to which reward, attention, and social-cognitive systems are engaged during simple social interactions in individuals with autism, and as such can provide insight into the proposed mechanisms underlying atypical social interactions.
The goals of the current study were to 1) replicate findings from Redcay et al., (2010) in a new neurotypical sample, 2) determine what is driving the difference between live and recorded conditions (i.e., novelty or social contingency), and 3) examine whether reward, attention, or social-cognitive systems (or some combination) show an atypical response profile in individuals with autism. To investigate these questions, we examined the response profiles for each condition of interest (Live, Recorded-Same, Recorded-Novels) within the regions of interest identified in the previous study for the contrast of Live vs. Recorded conditions (Redcay et al., 2010). A greater response to Live interactions as compared to the same video replay (Recorded-Same) may simply be due to the novelty of the interaction. Thus, the critical comparison to isolate brain regions sensitive to contingent social interaction, independent of novelty, is Live vs. Recorded-Novels. In both of these conditions, the participant sees the experimenter moving and talking in novel ways with novel objects; the only difference is that in the Live condition, the experimenter’s actions are contingent on real-time communication with the participant. Based on our previous study, we predicted that regions within social, attention, and reward networks would be differentially recruited during the Live condition in the NT group. Given the hypotheses discussed above, we predicted reduced differentiation between Live and Recorded conditions in the ASD group within regions associated with reward and social cognition.

Methods

Participants

All participants provided written, informed consent as approved by the Committee on the Use of Humans as Experimental Subjects (COUHES) at the Massachusetts Institute of Technology and were compensated monetarily for their participation. Participants were excluded if they had a history of neurological or psychiatric disorders or any contraindication for MRI scanning. IQ data were collected using the Kaufman Brief Intelligence Test (K-BIT).

Table 1: Participant Information.

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>FIQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASD</td>
<td>15</td>
<td>28.4±7.1</td>
<td>11M</td>
<td>119.5±14.8</td>
</tr>
<tr>
<td>NT</td>
<td>15</td>
<td>27.4±6.2</td>
<td>11M</td>
<td>117.5±12.3</td>
</tr>
</tbody>
</table>

Participants with Autism Eighteen adults with high-functioning ASD participated in the current experiment. All participants met criteria for ASD (autism or spectrum) on the Autism Diagnostic Observation Schedule (ADOS), Module 4. Three participants were excluded because of an inability to perform the task (2) or excessive movement during the scan (criteria described below).

Neurotypical Participants Fifteen NT participants were recruited to match the ASD participants on age and sex. Verbal, nonverbal, and full-scale IQ scores did not differ significantly between ASD and NT participants (IQ data from 1 ASD and 4 NT are missing).

Study Design

Prior to each scanning session the experimenter administered consents, screening forms, and IQ assessments in order for all participants to have some familiarity with the same experimenter in the face-to-face fMRI task.

Live face-to-face set-up During fMRI data acquisition participants were able to see and hear an experimenter in the control room. For extensive details on the audio-visual set-up see Redcay et al., 2010. Briefly, during the Live conditions, a real-time video and audio feed of the experimenter was provided to the participant. For all conditions, the experimenter viewed a real-time video feed of the participant’s eye through use of a camera from an eye-tracker at the back of the scanner bore. With this dual video set-up both experimenter and participant could interact in real-time. The timing of dual video capture and presentation was implemented using Psychtoolbox extensions in Matlab 7.8 (Brainard, 1997; Pelli, 1997). This dual video capture capability allowed for post-scan coding of the participants eye-movements as well as with the experimenter’s actions throughout the experiment.

Social Interaction Task During fMRI data collection, participants engaged in a social interaction task, in which the experimenter prompted them to choose one of two buckets (via eye movements) in the context of a highly-scripted interaction (Figure 1). During ‘Live’ conditions these interactions occurred in real-time while ‘Recorded’ conditions involved video replays. Participants were told whether they were in the Live or Recorded conditions both via a green or red square around the screen, respectively, and a text prompt before the start of the block and above the video of the experimenter throughout the block. Importantly, they were told to play along with the experimenter’s requests during the Recorded conditions even though she could not see them. During the Recorded-
same condition, the same video of the experimenter from the previous Live condition was replayed to the participant, serving as a perfect control for perceptual complexity. During the Recorded-Novel condition a novel video from a previous interaction with a different participant was presented, controlling for the novelty of the live interaction.

**fMRI design** Conditions were presented in a blocked design with each block lasting 40 seconds. Each run contained two repetitions of each condition (i.e., Live, Recorded-Same, Recorded-Novel) alternating in a pseudo-counterbalanced order (with the caveat that Live had to precede Recorded-Same). To allow for the opening and closing of video capture devices, the first and last 2.5 seconds of each block were modeled but not analyzed. Runs contained 3 blocks of a 20-second resting baseline at the beginning, middle, and end of each run. All participants completed four experimental runs except for one participant in the ASD group who completed 3.

**Data acquisition and analyses**

**Data acquisition** Data were collected on a 3T Siemens Tim Trio scanner at the Athinoula A. Martinos Imaging center at the McGovern Institute for Brain Research at the Massachusetts Institute of Technology. Functional imaging data were collected using a T2*-weighted gradient echo-planar image sequence with a voxel resolution of 3.1x3.1x4.0 mm (TR=2s, TE=30ms, 32 slices). Siemens PACE online motion correction was used to adjust for head movement (<8mm). T1-weighted structural images were collected with 128 slices axially (TE=3.39 ms, TR=2530 ms, 1.3 mm isotropic voxels).

**fMRI analyses** fMRI data were analyzed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm) and in-house Matlab scripts. Preprocessing steps included 1) realignment of all data to the first volume of the first run using a 6-degree rigid spatial transformation, 2) spatial smoothing with a 5 mm full width half maximum Gaussian filter, 3) spatial normalization to a standard EPI template in Montreal Neurological Institute (MNI) space using a 12-parameter affine transformation. A high pass filter of 260 s (1/260 Hz) was applied to the functional data to model low-frequency signals unrelated to the task. 260 seconds was chosen because it is the length from the beginning of the first block to the end of the last in each run. Motion artifacts were estimated using the artifact detection toolbox (ART). A volume exceeding 1 mm (across rotational and translational directions) of movement between timepoints or intensity greater than 3 SD was marked as an outlier. Participants with more than 15% outlier timepoints across any experimental run were removed (1 ASD participant).

Whole-brain first-level analyses were performed within each subject using the general linear model. The model included conditions of interest (Live, Rec-Same, Rec-Novel) as well as conditions not of interest (the 2.5 seconds at the beginning and end of each block and the text prompt preceding each block). Nuisance regressors included the degree of deviation at each time point for the 6-motion directions (roll, pitch, yaw, x,y,z) and any outlier timepoints identified. Contrasts of interest included each condition of interest vs. fixation as well as the Live condition compared to Rec-Same and Rec-Novel separately and compared to both recorded conditions combined (Recorded). Contrasts of Rec-Novel to Rec-Same were also included and all reverse contrasts were modeled (e.g., Recorded vs. Live).

Second level random effects analyses were conducted via voxel-wise whole-brain t-tests (within and between sample) for each contrast of interest and region of interest analyses. All within-sample whole-brain tests were corrected at p<.05 using nonparametric permutation analyses (snpm5b). All between-group whole-brain tests were thresholded at p<.001 (uncorrected) with a cluster correction corresponding to p<.05 (k=192 mm²). Cluster size was determined using AFNI’s 3dClustSim program (Cox, 1996).

Region of interests were created from previously published data using this same social interaction task (Redcay et al., 2010). These data included a sample of 16 typically developing adults (7 male; 18-29 years) who were not part of the sample in the current study. Region of interests included voxels that were significantly more engaged during the Live than Recorded conditions (p<.05, corrected) and intersected with a sphere (6 mm radius) surrounding the peak coordinate for each region identified in the group contrast of LiveRecorded (Redcay et al., 2010). Parameter estimates from the first-level analyses for each condition of interest from each subject were extracted from each of these 21 regions of interest. Repeated-measures ANOVAs were run for each ROI with condition (Live, Rec-Same, Rec-Novel) as the repeated measure and group (ASD, NT) as the between-subjects measure. The Greenhouse-Geisser correction was used when the assumption of sphericity was violated. For all regions showing a significant effect of condition or significant group x condition interaction, follow-up paired t-tests were conducted within each group for the contrasts Live vs. Rec-Same, Live vs. Rec-Novel, and Rec-Novel vs. Rec-Same.

**Post-scan video coding** Following data collection, videos from 9 ASD and 10 NT participants were coded for several behavioral variables, including the onset and duration of eye movements during the event periods in which the experimenter requested a response from the participant. Videos from the remainder of the participants were lost or not collected at the time of the fMRI session due to technical difficulties in video recording. The number and duration of eye movements were compared between groups and between conditions using separate two-way repeated measures ANOVAs.

**Results**

**Eye movements do not differ by condition or group** No significant main effects or interactions were found for either the total number or duration of eye movements during the
Replication of previous study in new TD sample Whole-brain and ROI analyses comparing the Live and Recorded conditions revealed many similarities but also some differences from the sample published in a previous paper (Redcay et al., 2010). In general a smaller number of areas were recruited during the Live vs. Recorded contrast than reported in the previous study. Specifically, subcortical regions associated with reward and anterior temporal regions did not show differential recruitment during the Live condition. However, regions within dorsal medial prefrontal cortex (dMPFC), which did not meet threshold for significance in the 2010 paper, were significant in the current NT sample. Regions showing a greater response to Live than Recorded conditions (in both samples) included bilateral posterior STS, dorsal anterior cingulate (dACC), dorsal medial prefrontal cortex (dMPFC), thalamus, and left cerebellum (Figure 2, top).

Next, we compared parameter estimates for Live and Recorded conditions within the ROIs from the previous study using one-way paired samples t-tests (p<.05, Bonferroni corrected). Nine of the 21 regions revealed a pattern of significantly greater activation in Live as compared to Recorded conditions: dorsal anterior cingulate (dACC) t(14)= 2.95, p<.011, anterior cingulate cortex/medial prefrontal cortex (ACC) t(14)=3.26, p<.006, left cerebellum (L CBLM) t(14)=3.68, p<.002, left lingual gyrus t(14)=3.01, p<.009, left insula t(14)=4.96, p<.0001, left middle temporal gyrus (L MT) t(14)=2.7, p<.017, right insula t(14)=3.61, p<.003, right posterior superior temporal sulcus (RpSTS) t(14)=5.65, p<.000, right temporoparietal junction (RTPJ) t(14)=3.30, p<.005, and supplementary motor area (SMA) t(14)=3.58, p<.003.

Whole brain comparisons between ASD and NT Only the right pSTS showed a significantly greater response during the Live as compared to Recorded conditions in the ASD group (Figure 2, bottom). Direct statistical comparison of the Live vs. Recorded contrast between groups revealed significantly greater activation in the NT group in the left posterior STS and bilateral cerebellum. Significantly greater activation was seen in the ASD than NT group for the Live-Recorded contrast within the left angular gyrus (AG) and right putamen; however, this effect was driven by greater deactivation in the NT group during Live conditions rather than differential engagement of these regions in ASD.

Region of interest analyses Two-way repeated measures ANOVA for each of the 21 ROIs revealed significant main effects of condition (Live, Rec-Same, Rec-Novel) in nine of the ten regions as reported above (dACC, ACC, L CBLM, LIns, RIns, RpSTS, RTPJ, SMA, LMT) and a significant group by condition interaction in one region, the anterior cingulate cortex (F(1.6,30)=6.1, p<.008) (Figure 3).

Within-group condition comparisons allowed for investigation of whether regions were sensitive to the social contingency of a live interaction (i.e. Live>Recorded-Novels and Live>Recorded-Same) or to the novelty of the interaction (i.e. Live>Recorded-Same or Recorded-Novels>Recorded-Same).

Salience network sensitive to online interactions in NT but novelty in ASD Within the NT group, 6 regions showed a pattern of sensitivity to Live as compared to Recorded-Novels and Recorded-Same conditions, suggesting
these regions are sensitive to online social interaction. These regions included those associated with the salience network (e.g., Seeley et al., 2007), namely the dorsal anterior cingulate (dACC), bilateral insula, and supplementary motor area (SMA), as well as regions associated with social cognition including the RpSTS extending into the RTPJ. Of these six regions, the ASD group demonstrated no difference between conditions within left insula and dACC (Figure 3, top left) and a pattern of sensitivity to novelty but not social interaction in the right insula, SMA, and ACC (Figure 3, top right). Like the NT group, the ASD group showed a significant effect of social interaction (i.e. Live>Recorded-Novel and Live>Recorded-Same) in the right pSTS/RTPJ (Figure 3, bottom left).

Three regions were sensitive to novelty but not live interaction specifically in both ASD and NT groups. Within the NT group, the left cerebellum, left middle temporal gyrus (MT), and left anterior STS (aSTS) demonstrated a pattern of sensitivity to novelty (i.e. Live>Recorded-Same and Recorded-Novel>Recorded-Same) that was not specific to online interactions (i.e. Live is not different from Recorded-Novel). Left MT and left aSTS demonstrated a pattern consistent with novelty in the ASD group in that Recorded-Novel was greater than Recorded-Same. Further, the region within the left cerebellum showed a greater response to Live than Recorded-Same in ASD (Figure 3, bottom right).

Discussion

The goals of the current study were to replicate previous findings using a novel interactive method and to determine whether reward, attention, and/or social-cognitive networks in autism showed a lack of sensitivity to online social interactions. We replicated the finding of a greater response to Live than Recorded conditions in many regions associated with social cognition and attention, as previously seen. Surprisingly, however, reward-related regions were not differentially sensitive to live interactions in the current sample of NT or ASD participants.

Social-cognitive areas show typical response in ASD Our hypothesis was that regions associated with social cognition, such as bilateral TPJ, posterior STS, and amygdala would not be modulated by condition in the ASD group. Some support for this hypothesis was found in the whole-brain between-group comparisons (Figure 2). The left pSTS was recruited significantly more for Live than Recorded conditions in NT than ASD groups. However, whole-brain and region of interest analyses revealed no differences between groups within right posterior superior temporal cortex (RpSTS cluster extending into RTPJ). For both NT and ASD groups this region was recruited across all three conditions but the greatest response was seen in the Live condition and no differences were found between the Recorded conditions. It is possible (and indeed likely) that group differences might have emerged if the social interaction had required mental state inferences and/or been less predictable. Nonetheless, these findings suggest that in a simple social interaction, posterior superior temporal regions are sensitive to social contingency in both NT and ASD samples.

Salience network sensitive to live interactions in NT, but not ASD Regions within attention networks, specifically the salience network, revealed the greatest differences between groups in the region of interest analyses. We found a significantly greater response in the Live condition as compared to both Recorded conditions within regions thought to be part of a personal salience network, including bilateral insula and dorsal anterior cingulate (e.g., Seeley et al., 2007) in NT individuals but not individuals with ASD. In fact, within the dorsal anterior cingulate cortex a significant group x condition interaction revealed sensitivity to novelty, but not live interaction, in the ASD group. This salience network is engaged during tasks of empathy (Bernhardt & Singer, 2012), affective pain (Singer et al., 2004), error processing and task-onset (Dosenbach et al., 2006) and can be identified through task-free intrinsic connectivity analyses (Seeley et al., 2007). Seeley et al. (2007) propose that these regions are important for associating incoming sensory stimuli with “markers” to aid in the decision of what to do next through interaction with other control, attention, and emotion networks. One possibility is that in NT individuals, interaction with another person in real-time provides a salient cue to enhance attention to the stimuli or task at hand via the salience network. This is analogous to theories suggesting social interactions “gate” learning (e.g., Kuhl, 2007; Meltzoff, Kuhl, Movellan, & Sejnowski, 2009). For individuals with ASD, however, the novelty of the visual stimulus engages the salience network rather than the social contingency. These data are consistent with the proposal by Mundy and colleagues (e.g., Mundy, 2003) that atypical social-executive networks, of which the dorsal anterior cingulate plays a primary role, may characterize autism. Thus, these data may provide a neurobiological correlate for how social interactions are less “special” in individuals with autism. These findings also underscore the importance of examining the interaction of social and attention processes, instead of treating them as separate processes and systems.

Future Directions

While the results are intriguing, the current study has several limitations that need to be addressed in future work. First, the interaction was highly scripted and simplified. Future studies should examine whether increasing the unpredictability or required mental state inferences within the interaction would lead to greater differences between groups within social-cognitive brain regions. Similarly, future studies should explicitly engage reward systems during real-time social interaction to help explain the discrepancy in activation of reward systems between these studies. Finally, it will be critical to examine the
developmental trajectory of atypical responses to social interactions within the salience network to determine whether reduced neural sensitivity underlies the emergence of the autistic phenotype.

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