Neural and cortisol responses during play with human and computer partners in children with autism

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Children with autism spectrum disorder (ASD) exhibit impairment in reciprocal social interactions, including play, which can manifest as failure to show social preference or discrimination between social and nonsocial stimuli. To explore mechanisms underlying these deficits, we collected salivary cortisol from 42 children 8–12 years with ASD or typical development during a playground interaction with a confederate child. Participants underwent functional MRI during a prisoner’s dilemma game requiring cooperation or defection with a human (confederate) or computer partner. Search region of interest analyses were based on previous research (e.g., insula, amygdala, temporal parietal junction—TPJ). There were significant group differences in neural activation based on partner and response pattern. When playing with a human partner, children with ASD showed limited engagement of a social salience brain circuit during defection. Reduced insula activation during defection in the ASD children relative to TD children, regardless of partner type, was also a prominent finding. Insula and TPJ BOLD during defection was also associated with stress responsivity and behavior in the ASD group under playground conditions. Children with ASD engage social salience networks less than TD children during conditions of social salience, supporting a fundamental disturbance of social engagement.

Keywords: autism, insula; social exchange; prisoner’s dilemma; fMRI; temporal parietal junction

INTRODUCTION

Social cognition requires the ability to interpret another person’s behavior, interact in complex social groups, empathize and predict how others will feel, think and act (Baron-Cohen et al., 1985). Impairment in social cognition is a distinguishing feature of autism spectrum disorders (ASD) (APA, 2000). Children with ASD have reduced social engagement with peers during play (Hauck et al., 1995; Corbett et al., 2010) especially under conditions of solicited cooperative play by a peer (Corbett et al., 2014). In addition to reduced reciprocal social interaction during play, engaging with typically developing peers is often accompanied by increased physiological arousal as indexed by elevated cortisol responses (Corbett et al., 2010; Schupp et al., 2013). While play is a fundamental milestone in childhood, facilitating the development of important cognitive and social skills (Boucher, 1999), it is often an area of significant delay and impairment in children with ASD (e.g., Hauck et al., 1995; Farmer-Dougan and Kaszuba, 1999; Macintosh and Disanayake, 2006; Ingram et al., 2007; Schupp et al., 2013).

The psychobiological investigation of play allows for study of brain networks involved in social behaviors (Panksepp et al., 1984). Various disciplines have used social exchange games to explore aspects of human social behavior, such as motivation, reward and cooperation (Panksepp et al., 1984; Rilling et al., 2002, 2004, 2007; Sally, 2003; King-Casas et al., 2005). The prisoner’s dilemma (PD) provides a well-established paradigm for reciprocal interactions (Axelrod and Hamilton, 1981; Rilling et al., 2002; Patel et al., 2006; Deykin et al., 2007). The PD relies on either cooperation or defection with partners, rendering four possible outcomes. Cooperation is associated with positive feelings of trust and friendship, while defection is associated with negative feelings including anger or contempt. In situations where the responses of the players are conflicting, the cooperator often feels anger or frustration, while the defector may experience feelings of guilt, anxiety or alternatively, happiness.

Exchange games such as the PD have been used with fMRI to explore the correlates of social cognition (Rilling et al., 2002; Patel et al., 2006). In typical populations, these paradigms frequently recruit limbic and striatal brain regions involved in reward [e.g. anterior cingulate cortex (ACC)], learning (e.g. caudate) and affective processing (e.g. amygdala, insula) (Delgado et al., 2005; King-Casas et al., 2005; Tomlin et al., 2006). Recruitment of brain regions varies by player choice; cooperative play has been associated with activity in the nucleus accumbens, caudate, orbital frontal cortex, dorsolateral prefrontal cortex and rostral ACC (Rilling et al., 2002, 2007), whereas defection tends to recruit the amygdala and anterior insula (Rilling et al., 2002; Sanfey et al., 2003). However, activation patterns are highly dependent on the opponent player (e.g. human vs computer partner) (Kircher et al., 2009; McClure-Tone et al., 2011; Suzuki et al., 2011). Game playing can also be enhanced through the use of putative human partners that are presumed to be playing outside the scanner (e.g. Rilling et al., 2008a).

These paradigms have been employed in studies of children, adolescents and adults with ASD to elucidate behavioral patterns and neural networks implicated in the neuropathology of the disorder. For example, Sally and Hill (2006) demonstrated that children with autism had difficulty shifting strategy compared with the control group during the PD (Sally and Hill, 2006). In a study of monetary reward processing, adult males with ASD showed enhanced activation of left rostral ACC during monetary vs social reward, which may reflect enhanced performance monitoring to achieve a goal-directed behavior (Schmitz et al., 2008).

The aim of the investigation was to examine behavioral, physiological and neural patterns of play to elucidate elements of social cognition in autism. We employed a playground peer interaction paradigm to allow for examination of physiological response and...
behavioral variables during natural play with a peer (Corbett et al., 2014). Subsequently, we utilized the PD game with human and computer partners during fMRI to examine whether deficits in peer interactions were related to alterations in the neural circuitry involved in social decision making. To ascertain the response to social and non-social partners, we explicitly modeled the outcome phase of the task. Based on previous child studies (McClure-Tone et al., 2011), relevant brain search regions of interest (ROIs) were identified and included the ACC, insula, medial prefrontal cortex, TPJ, caudate and prefrontus.

Based on failure to show preference for social stimuli (Klin, 1991; Dawson et al., 2002; Riba and Hancock 2008; Wilson et al., 2010) and greater self-play (Corbett et al., 2014), it was hypothesized that children with ASD would show a similar behavioral response regardless of whether they were playing with a human or computer partner. In line with previous findings of atypical response to social stimuli in ASD (Chiu et al., 2008; Corbett et al., 2009), we hypothesized that children with ASD compared with peers would show differences in social salience circuitry, including the amygdala, insula, temporal cortex, precuneus and ACC, reflecting reduced recruitment for social stimuli during both cooperation and deflection trials. Conversely, it was hypothesized that neurotypical children would show a pattern of activations similar to healthy adult participants, such as recruitment of the insula during deflection, and greater activity in the ACC, amygdala, caudate and temporal cortex during play with a human partner (Rilling et al., 2004, 2008b). Finally, based on our previous studies (Kidd et al., 2012; Corbett et al., 2014), exploratory analyses were conducted to determine if elevated cortisol levels in children with ASD would be associated with activation in social salience brain regions, such as the insula, TPJ and amygdala.

**METHODS**

**Participants**

Participants were recruited from study registries, clinics and schools. Inclusion criteria for all participants were: IQ ≥80 (Wechsler, 1999), prepubertal development (Petersen et al., 1988) and an absence of known neurological, psychiatric or medical conditions based on semi-structured parental interview. Scanning required having no major contraindication for MRI (e.g. metal implants, seizures, claustrophobia). Only participants meeting all of the following three criteria were included in the ASD group: (i) confirmed diagnosis of an ASD based on diagnostic criteria (APA, 2000), (ii) clinical judgment (B.A.C) and (iii) current assessment with Autism Diagnostic Observation Schedule (Lord et al., 1999). In addition to the ADOS, the Social Communication Questionnaire (SCQ; Rutter et al., 2003) was used to rule out autism for the typical children (score >10 excluded).

Our initial sample consisted of 42 (21 children with ASD, 21 TD) medication-free, prepubescent, right-handed children (five females) between 8 and 12 years. Fourteen children (nine ASD, five TD) were excluded from the fMRI analyses due to excessive motion and failure to complete the task resulting in an attrition rate of 30%, which is comparable to pediatric fMRI studies (Yerys et al., 2009). There were no differences in symptom severity between those children who were excluded due to motion and those who were not. The final fMRI analyses were conducted on 28 children (12 ASD and 16 TD). Demographic and psychological characteristics of the sample are presented in Table 1.

The Institutional Review Board of Vanderbilt University approved the study and procedures were followed consistent with the Declaration of Helsinki (BMJ 1991; 302: 1194). Parents completed written informed consent and children assented to participate. Participants received compensation for participating in the playground study visit as well as gift cards, the value of which was based on dollars earned during the fMRI task.

**Procedures.** The study required three visits to the University over 1 month: (i) diagnostic and psychological assessment, (ii) the peer interaction playground with confederate child and (iii) fMRI Prisoner’s dilemma paradigm.

**Visit 1**

*Diagnostic and Neuropsychological Methods*

Autism Diagnostic Observation Schedule (ADOS; Lord et al., 1999) is a semi-structured interview designed to assess behaviors indicative of autism, which was administered by an ADOS trained, research-reliable psychologist.

Social Communication Questionnaire (SCQ; Rutter et al., 2003) was used as a screening tool for ASD (scores of ≥15 is suggestive of ASD). The exclusion criteria for a typically developing child was a score ≥10; however, no TD participants exceeded this score.

Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999) was used to obtain an estimate of each child’s intellectual functioning. An estimated IQ ≥80 was required for participation in the study.

**Visit 2**

Peer Interaction Playground Paradigm: The naturalistic playground paradigm includes two research participants (a child with ASD, and a TD child) and a confederate child of the same age and gender who provided structure to the otherwise natural interaction. The paradigm is fully described elsewhere (Corbett et al., 2010; Schupp et al., 2013) and in Supplementary materials. Briefly, the 20-min play is subdivided into periods of prescribed free and cooperative play facilitated by a confederate child on the playground communicating with the research staff via concealed audio technology. Interactions were video recorded using state-of-the-art equipment.

Observer XT Version 8.0 software was used for the collection and analysis of the interaction observational data (Noldus, 2008). Data were analyzed based on a predefined list of operationalized behaviors (Corbett et al., 2010; Schupp et al., 2013).

**Physiological Arousal During Play.** Salivary samples were obtained to measure cortisol, a primary stress hormone, in order to assess physiological arousal in response to the social interaction at the beginning (20 min) and end (40 min) of play (there is a 20-min lag in the detection of cortisol in saliva which guides the collection of saliva in 20 min intervals). Our established methods for home and protocol collection

<table>
<thead>
<tr>
<th>Table 1 Demographic between group data</th>
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<tbody>
<tr>
<td>Demographic Mean (SD)</td>
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<tr>
<td>------------------------</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Verbal IQ</td>
</tr>
<tr>
<td>Performance IQ</td>
</tr>
<tr>
<td>Estimated full IQ</td>
</tr>
<tr>
<td>SCQ</td>
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<tr>
<td>SRS</td>
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</tbody>
</table>

Note: SD = Standard Deviation, IQ = Intellectual Quotient, SCQ = Social Communication Questionnaire, SRS = Social Responsiveness Scale. There were three TD females in the final analysis.
Visit 3

Participants engaged in the fMRI study described below. Importantly, the confederate from the playground was the same child that participants were told they would play with during a game in the scanner.

**Subject Preparation for MRI scanning.** Subjects underwent preparatory procedures designed for children. As part of the training on the PD paradigm immediately prior to the actual scan, children were tested for their understanding of the task and appreciation for the concept of money. Scans were conducted following same-day mock scanner exposure to minimize anticipatory stress (Corbett et al., 2008). The mock scanner exposure occurs ~30 min prior to starting the actual scan. The actual scan lasted ~45–60 min, including prep time.

We followed the general fMRI design used by Rilling (Rilling et al., 2002; Patel et al., 2006). The paradigm was simplified, colored and shortened to be more appropriate for children. Each round consisted of 20 rounds lasting ~8 min and there were two runs. The order of the runs was counterbalanced across subjects.

At the start of each round, the Payoff Matrix (Figure 1A) was back-projected onto a translucent screen placed near the end of the MRI gantry and viewed through a periscope prism system attached to the head coil.

The payoff matrix was displayed for 4 s during the decision portion of the task, followed by a 4-s fixation, a white cross hair on a black background. The outcome matrix was presented at 8 s and remained on the screen for 4 s followed by a 4-s fixation (Figure 1B). The outcome was revealed by highlighting each player’s choice and the resulting payoff for that round. Four possible outcomes per round exist: Players A and B cooperate (CC), Player A cooperates and Player B defects (CD), Player A defects and Player B cooperates (DC) or Players A and B defect (DD). Each round lasted 16 s. Scan acquisition parameters are detailed in the Supplemental materials.

**Data analysis**

**Behavioral data**

Between group difference of the behavioral data for response choices and reaction time were calculated using independent sample t tests using SPSS 18.0 (SPSS, Inc., 2009, Chicago, IL, USA, www.spss.com).

**fMRI data**

**fMRI Data Preprocessing.** Data were preprocessed using SPM8 (Wellcome Department of Neurology, http://www.fil.ion.ucl.ac.uk/ spm8) and Matlab (Version 7.1, The Mathworks, Inc., Natick, MA, USA). Data were slice-time corrected, motion-corrected by alignment to the mean image across runs, and co-registered with the structural scan. Images were normalized to the MNI T1 template and resampled to 1-mm³ voxels. Data were smoothed using a 6-mm FWHM Gaussian kernel. All participants included for analysis had translation <3 mm and rotation <3°. Functional images were analyzed for BOLD response to both outcome and decision (Figure 1B) such that each epoch of the decision (0–8 s) and outcome (9–16 s) were analyzed separately. Reaction time, choices and outcome variables were convolved with the hemodynamic response function. The aim of the study was to ascertain responses to partner actions both on the playground and in the scanner; therefore, we focused on differences during the outcome phase of the paradigm.

We used the general linear model in SPM8 for first level statistical analysis. Separate regressors were constructed modeling each of the four task outcomes. Because of the low number of CC trials in both groups, CC and DC trials were combined to create a ‘Co-Player Cooperation’ contrast, and CD and DD trials were combined to create a ‘Co-Player Defection’ contrast (McClure-Tone et al., 2011). The subsequent responses were examined for both the computer co-player and the human co-player runs. These first (participant)-level contrast images were then used for second (group)-level analyses.

Within-group activation was examined by separate analyses of each contrast (Co-Player Defected, Co-Player Cooperated) for both the computer and human runs, in each group (ASD and TD). We then compared activation between the groups for both co-player conditions, for a total of four comparisons, in a set of a priori search ROIs thought to represent a social salience network, including the precuneus (Assaf et al., 2010), ACC (Watanabe, 2012), insula (Pfeifer et al., 2013), amygdala, temporal pole (Carter et al., 2012a), and caudate as defined by the aal atlas. We also performed spherical ROI analyses in SPM8 for the mPFC and temporal parietal junction (TPJ), as defined by McClure-Tone; the TPJ ROI consisted of a sphere with a radius of 15 mm, centered at coordinates 48, −54, 27, the peak that corresponded best to those used in prior PD game studies (McClure-Tone et al., 2011). These regions have all shown enhanced activation or activation differences during performance of the prisoner’s dilemma task in previous studies of various populations, including healthy adults (Singer et al., 2004; Patel et al., 2006; Suzuki et al., 2011; Emonds et al., 2012), adults with varying degrees of pro-social personality traits (Emonds et al., 2014), adolescents with without anxiety disorders (McClure-Tone et al., 2011), and adults with and without psychopathic traits (Rilling et al., 2007, for review see Stallen and Sanfey, 2013) and are thought to represent a network for detection of socially salient stimuli. In order to be comprehensive, and in line with previous fMRI studies in pediatric psychiatric samples (McClure-Tone et al., 2011; Cascio et al., 2013), we initially collected results from all search ROI analyses at uncorrected P < 0.05. Subsequently, to obtain an extent-based cluster threshold for each ROI, the statistical significance of these clusters was determined based on simulations performed with AlphaSim (http://afni.nimh.nih.gov/pub/dist/doc/manual/AlphaSim.pdf); which indicated that a family-wise error rate of α = 0.05 was achieved.
with the following cluster sizes for our search ROIs: 132 voxels for the precuneus, 90 voxels for the insula, 127 voxels for the temporal pole, 34 voxels for the amygdala, 118 voxels for the TPJ and 105 voxels for the caudate. In order to correct for multiple comparisons in our ROI analyses, we used the Bonferroni–Holm method (Holm, 1979). Bonferroni-Holm is similar to a traditional Bonferroni correction procedure, in that it provides sufficient control for avoidance of Type I Error without the great sacrifice of power that occurs with traditional Bonferroni correction. In Bonferroni–Holm, tests are conducted in a sequential, step-down manner such that the tests are ordered by significance and tested with a step-wise adjustment of the alpha levels on the basis of the number of remaining tests.

We conducted-between-group whole brain analyses to identify other regions that may be involved in social salience processing during the PD (topologically FDR corrected $q<0.01$) (Chumbley and Friston, 2009).

**RESULTS**

**Behavioral performance**

Using independent sample $t$ tests, behavioral response patterns between children with ASD and TD children were examined based on whether the participant chose to Cooperate (C), Defect (D) or not respond (NR). As shown in Table 2, there were no significant between group differences for behavioral response patterns or reaction time for Cooperate (CC and CD) or Defect (DC and DD) when playing with either Human or Computer partners (all $P>0.05$). There were no significant differences between the groups based on NR trials when playing with either partner type (all $P>0.05$). On average the children with ASD cooperated roughly a third of the time for the Computer (30.5%) and Human (29.7%) conditions; whereas they defected two-thirds of the time for both the Computer (66.4%) and Human (66.6%) conditions, respectively. The typically developing children had a similar profile for cooperation with the Computer (28%) and Human (37.6%) and defected twice as much for Computer (69%) and Human (64.8%) partners. Because so few participants chose to cooperate, we were underpowered to detect between or within group differences for cooperation trials and therefore only discuss the results of defection trials.

<table>
<thead>
<tr>
<th>Group</th>
<th>Computer Co-Player defection</th>
<th>Peak Voxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASD</td>
<td>2009)</td>
<td></td>
</tr>
<tr>
<td>ASD</td>
<td>Coop: (C) Computer</td>
<td>6.11</td>
</tr>
<tr>
<td>TD</td>
<td>Defect (D) Human</td>
<td>1026.01</td>
</tr>
<tr>
<td>ASD</td>
<td>Defect (D) Computer</td>
<td>1088.07</td>
</tr>
<tr>
<td>TD</td>
<td>Cooperate (C) Human</td>
<td>1101.37</td>
</tr>
<tr>
<td>ASD</td>
<td>Cooperate (C) Human</td>
<td>125</td>
</tr>
<tr>
<td>TD</td>
<td>Defect (D) Human</td>
<td>126</td>
</tr>
<tr>
<td>ASD</td>
<td>Person co-player defection</td>
<td>1026.01</td>
</tr>
<tr>
<td>TD</td>
<td>temporal pole</td>
<td>158</td>
</tr>
<tr>
<td>ASD</td>
<td>Temporal Pole (R)</td>
<td>158</td>
</tr>
<tr>
<td>TD</td>
<td>Caudate (L)</td>
<td>158</td>
</tr>
<tr>
<td>ASD</td>
<td>Caudate (R)</td>
<td>158</td>
</tr>
<tr>
<td>TD</td>
<td>Defect (D)</td>
<td>158</td>
</tr>
</tbody>
</table>

Note ASD = autism spectrum disorder; TD = typically developing, SD = standard deviation, ms = milliseconds.

**Table 2 Behavioral response choices and reaction time between the groups**

<table>
<thead>
<tr>
<th>Group</th>
<th>Cooperate (C) Computer</th>
<th>Defect (D) Computer</th>
<th>Cooperate (C) Human</th>
<th>Defect (D) Human</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASD</td>
<td>6.11 (4.11)</td>
<td>13.28 (4.07)</td>
<td>5.94 (3.91)</td>
<td>13.33 (3.91)</td>
</tr>
<tr>
<td>TD</td>
<td>5.6 (3.71)</td>
<td>13.8 (3.58)</td>
<td>6.52 (4.21)</td>
<td>12.96 (4.25)</td>
</tr>
</tbody>
</table>

**Table 3 Within group search ROI brain findings**

Money earned

Amounts earned across the runs were computed and children received half of the money earned across 40 trials. Earnings were rounded to the nearest $.5 denomination and given in the form of gift cards. The average amount earned was $40.00 and there were no significant differences between children with ASD or TD ($P>0.05$) suggesting that both groups perceived money to be a salient reward.

**Social and reward circuitry activation**

**Computer partner**

Defection (DD and CD). Within-Group: There were no significant findings for the ASD search ROI within-group analyses. Whole brain analysis showed significant activation of the R cerebellar lobe, L sensorimotor cortex, and R globus pallidus/putamen (Table 3 and Supplemental Table S1). The TD group showed activation in the R TPJ and bilateral precuneus. TD whole brain analyses identified additional significant regions including L putamen with submaxima extending to somatosensory and motor cortices, R insula with submaxima extending to the globus pallidus and putamen, and R motor cortex.

Between-Group: Search ROI comparisons revealed that, when playing with a Computer partner during Defection trials, ASD participants showed significantly less activation than the TD children in the R insula (Figure 2, Table 4). The whole brain analyses revealed statistically significant R insula activation (ASD<TD) (cl = 77, $t = 5.16$; 51,11,1, Supplemental Table 2).

**Human partner**

Defection (DD and CD). Within-Group: Strikingly, the ASD group did not show any significant search ROI or whole brain BOLD signal activity during defection with a human partner. The TD group displayed significant activations in the R temporal pole, R TPJ, L insula and bilateral caudate. TD whole brain analyses identified significant areas of activation in bilateral DLPFC, bilateral putamen, bilateral parietal cortex, L motor cortex, L dorsal medial cingulate cortex, R fusiform gyrus and R cerebellar lobe.
Between-Group comparisons showed that during defection trials with a putative human partner, the ASD group demonstrated significantly less activation than the TD children in left insula and TPJ, as well as the bilateral caudate (Figure 3). The amygdala was also less active in ASD participants compared to TD, although this finding was just under cluster extent thresholding (cl = 30). There were no findings in which ASD children showed more activation (Table 4). Whole brain analyses (ASD < TD) revealed significant differences in the R caudate, L angular gyrus, L insula/putamen, L supplementary motor area and R motor cortex (Supplemental Table S2).

We also performed analyses comparing human to computer co-player trials. When collapsing across co-player conditions, there were no significant differences between activation in the human vs computer conditions, either within or between groups. Taken together, the results show that when children with ASD played the PD game with the Human partner, they showed a lack of engagement of prototypical social salience regions during defection, including the insula and TPJ.

### Summary of BOLD findings that meet cluster extent thresholding criteria

In this study, TD participants recruited the bilateral precuneus and caudate, as well as the right TPJ during defection with a computer co-player. During defection with a human co-player TD participants recruited the left insula, and right temporal pole, in addition to the bilateral caudate and right TPJ. Between-group contrasts show significantly less activation of the right insula during computer defection trials in the ASD group compared with the TD group. During human defection trials, there was significantly less activation of the left insula and bilateral TPJ in the ASD group compared to the TD group.

### Neural–behavioral correlational analyses

Significant behavioral differences between the ASD and TD groups have been consistently reported during the peer interaction paradigm in cooperative play, verbal interaction and self-play (all \( P < 0.05 \)) (Corbett et al., 2010, 2014). Associations between these play behavior variables and the ROI activations for the total group (ASD and TD) were investigated using Pearson product correlations (Table 5). For Human Defection, significant correlations were observed for the R insula and bilateral TPJ and self-play.

### Neural–physiological correlational analyses

Significant differences between the groups were found on salivary cortisol during play with the confederate child (\( P < 0.05 \)) showing higher arousal for the ASD group (Corbett et al., 2014). Using exploratory Pearson product partial correlational analyses controlling for baseline cortisol levels, we examined whether activation magnitudes for significant ROI regions during social processing were related to physiological arousal during the playground interaction with peer confederates (Figure 4). Total-group comparisons are presented in Table 5.

### DISCUSSION

We examined the neural, behavioral and physiological patterns of play during defection with human and computer partners in an effort to...
elucidate aspects of social salience in autism. Regarding behavioral responses, both groups showed comparable reaction time and earned essentially the same amount of dollar rewards. ASD and TD children showed similar response patterns during the PD paradigm, with both groups engaging in competitive play twice as much as cooperative play. Preadolescents tend to be more competitive than younger children in the PD game (Tedeschi et al., 1969). This bias for defection has also been reported for adolescents with and without anxiety during the PD paradigm (McClure-Tone et al., 2011). Due to insufficient power to interpret cooperative trial findings, we only discuss defection trials below.

Regarding neural activation, there were significant group differences based on partner type (Human vs Computer). Children with ASD are characterized by impairment in reciprocal social interaction, which may be attributed to limited social motivation or salience (Chevallier et al., 2012). Thus, it was hypothesized that children with ASD would show differential recruitment of social salience circuitry compared with typically developing children during defection conditions, which is supported in part by the findings detailed below. The results are explained based on brain structure and their relationship to physiological arousal and playground behavior when playing with the confederate outside of the scanner.

**Insula**

During both the Computer and Human co-player defection contrasts, the ASD group showed less activation in the insula than TD children. The insula is involved in aspects of self-awareness (Craig, 2004), as well as interoceptive awareness enhanced by interpersonal and negative emotional experiences (Critchley et al., 2004). In the PD task, the TD children recruited the insula during defection in response to social partners, suggesting self-reflection amidst a mildly negative or frustrating outcome. Engagement of the insula under co-player defection conditions for the TD children replicates previous findings in adults (Rilling et al., 2008b) and supports our hypothesis predicting similar activation in salience regions between TD children and adults.

The contrast between the groups based on partner demonstrates atypical and opposing responsiveness of networks underlying reciprocal social exchange. This notion is supported by a recent investigation in which youth with ASD exhibited hypoactivation of the anterior insula during self-appraisal and greater activation of the insula during ‘other’ appraisal (Pfeifer et al., 2013). Other studies show that insula activity in ASD is heightened in response to rewarding stimuli, such as food and objects, related to restricted interests suggesting altered salience or reward processing specific to nonsocial stimuli.

### Table 5 Total group correlations between neural activations, cortisol and play behavior

<table>
<thead>
<tr>
<th>Partner and contrast</th>
<th>Cortisol S1 stress</th>
<th>Cortisol S2 stress</th>
<th>Self-play</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human defection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insula (L)</td>
<td>r = −0.37(^T)</td>
<td>r = 0.40</td>
<td></td>
</tr>
<tr>
<td>Insula (R)</td>
<td></td>
<td>r = 0.41*</td>
<td></td>
</tr>
<tr>
<td>TPJ (L)</td>
<td>r = −0.48*</td>
<td>r = −0.38(^\dagger)</td>
<td>r = 0.43*</td>
</tr>
<tr>
<td>TPJ (R)</td>
<td></td>
<td>r = −0.46*</td>
<td>r = 0.44*</td>
</tr>
</tbody>
</table>

Note: Partial correlations controlled for baseline cortisol level during play with confederate. L = left; R = right; TPJ = temporal parietal junction. S1 = cortisol level during initial exposure to confederate, S2 = cortisol level at end of 20-min play with confederate. Self-Play = percentage of time engaged in self-play on playground with confederate. *P < 0.05, \(^\dagger\) = trend (P = 0.06).
There is evidence that activation of anterior insula is positively associated with social anxiety and self-awareness (Terasawa et al., 2013). Individuals with ASD often exhibit heightened autonomic arousal and increased stress during face-to-face encounters and reduced stress during self-play (Hirstein et al., 2001; Corbett et al., 2010; Schupp et al., 2013). In this study, insula activation was strongly correlated with self-play, suggesting that children who engaged in more self-play demonstrated enhanced recruitment of the insula when defecting with human partners. These relationships contributed to the Neural–Behavioral-Physiological Model presented in Figure 5. Taken together, the findings suggest aberrant functioning of prototypical networks underlying social exchange, salience and self-perception.

Temporal parietal junction (TPJ)
The TPJ is part of a social cognition network (Assaf et al., 2009), and may have a specialized role in predicting behavior in social situations (Frith and Frith 2003; Carter et al., 2012b). In this study, TD children showed greater activation of the TPJ than ASD children during defection with the human partner. TPJ recruitment seems to be especially sensitive in individuals showing a strong preference for human over computer partners (Carter et al., 2012b); enhanced activation of TPJ in the TD group during defection trials may be related to greater self-reflection in the TD group relative to the ASD participants. Adults with ASD do not recruit the TPJ; similar to ASD children in this study (Lombardo et al., 2011). In our study, bilateral TPJ BOLD was positively associated with enhanced self-play, which corroborates the ASD profile of reduced mentalizing ability, increased independent play and less social interaction with others. Taken together, our findings of reduced activity in the TPJ in our ASD participants relative to TD children support the idea that the TPJ may be a critical region of interest in elucidating social salience deficits in autism.

Caudate
In this study, the caudate was less active in the ASD group compared with the TD group during defection with a human, but not a computer, partner. Previous findings have indicated decreased activity of the dorsal striatum in ASD compared with TD during processing of...
social reward (Delmonte et al., 2012) although other studies found no differences between participants with ASD and TD groups (Cascio et al., 2012; Dichter et al., 2012b). Although the caudate is commonly associated with reward processing, it has a more generalized function of stimulus valuation and motivated behavior via projections from the amygdala (Zorrilla and Koob, 2013) which may help to explain our findings during defection trials.

The amygdala is another brain structure that subserves social and emotional salience and processing, including the ‘motivational value of stimuli’ (Zald, 2003). Engagement of the amygdala during defection is a common finding in PD paradigms when playing with human partners (e.g. Rilling et al., 2007). During the human co-player defection, children with ASD recruited the right amygdala less than the TD children suggesting that they processed the defection outcome with a human partner to be less salient or less negatively arousing than TD children. However, this finding was just under cluster extent thresholding.

Our findings illustrate a disturbed social salience network in children with ASD, demonstrated by diminished and atypical recruitment of regions implicated in a social salience network in interpersonal exchanges. The most prominent finding in this study is reduced insula activity during defection trials in ASD relative to TD, in both social and non-social conditions, which is consistent with previous reports (for review see Dichter, 2012a). Also in line with our exploratory corticolimbic regression analyses, there is evidence that individuals with ASD exhibit heightened autonomic arousal during face-to-face encounters (Corbett et al., 2014), which has been interpreted to reflect a strong negative response to social stimuli (Hirstein et al., 2001). In this investigation, associations were observed between heightened cortisol levels and decreased activation of the left insula and bilateral TPJ. Thus, it may be that social interaction with others is not simply less salient to children with ASD (e.g. Dawson et al., 1998; Weigelt et al., 2012), but that it may be aversive. It is also likely that a history of difficulty engaging with peers and experiencing social rejection may contribute to heightened negative reactivity during social interaction (Church et al., 2000). These negative social experiences can exacerbate social anxiety and stress especially with peers (Bellini, 2006; White and Roberson-Nay, 2009; White et al., 2009; Corbett et al., 2010; Schupp et al., 2013).

Our findings contribute to the expanding literature showing dysfunction of social salience and motivational valuation systems in both children (Scott-Van Zeeland et al., 2010; Kohls et al., 2013) and adults with ASD (Dichter et al., 2012b). The fact that there is relative similarity across studies despite differences in design and subject characteristics, lends credence to the replicated findings and interpretation. Whereas some find disruption primarily for social rewards (Scott-Van Zeeland et al., 2010), others have reported disruption for nonsocial (Schmitz et al. 2008; Dichter et al., 2012b) or both reward types (Kohls et al., 2013). There is a convergence of data supporting disturbed salience networks in children with ASD. The findings support the idea that engaging with social agents is less intrinsically salient for individuals with ASD. However, the data are unable to answer whether this may be due to limited social motivation (Chevallier et al., 2012), aberrant salience processing (Scott-Van Zeeland et al., 2010) or to a history of negative social exchanges with peers (e.g. White et al., 2009; Humphrey and Symes, 2011). Nevertheless, the results add to the growing literature showing diminished responsivity to social stimuli in children with ASD relative to typically developing children.

As part of the PD paradigm, this study incorporated money earned during the game in the form of gift cards. While some studies have shown disruption in BOLD signal in response to monetary stimuli in ASD (Kohls et al., 2013), there were no significant differences between the groups based on money earned suggesting that both were incentivized by financial reward. A recent investigation of adults with low empathy suggests heightened activation of putative reward regions in response to monetary incentives vs social stimuli (Gossen et al., 2013). To date, only one study of children with ASD has compared brain reward system activity to primary (i.e. food) vs secondary (i.e. monetary) rewards, as well as to social and non-social rewards, finding similar activation patterns between ASD and TD groups for monetary rewards but increased activity to primary rewards compared with TD controls (Cascio et al., 2012). Given these mixed findings, the relative salience of secondary rewards such as monetary rewards in ASD warrants further investigation. In this study, qualitative observations before and after the scan related to the promise of earning money suggest participants were equally enthusiastic across the groups. However, the design of this study does not allow for the interpretation of the relationship of the reported findings to monetary reward processing. Future fMRI studies should investigate monetary vs social salience processing in people with ASD. Unique features of the study pertain to the inclusion of a confederate child, which the participants actually engaged with on a playground paradigm and thereby served as a known social partner during the PD. While enhancing ecological validity, it likely contributed to the believability that participants were actually playing with a human partner. Moreover, the children were all medication-free; therefore, confounding influences that disturb the regulation of corticolimbic activity were removed (e.g. Rubia et al., 2009).

Limitations
Despite these strengths there are several limitations to acknowledge. There were significantly fewer cooperative than competitive trials, making negative findings in cooperative tasks less interpretable. However, this preponderance for defection has also been observed in other studies (McClure-Tone et al., 2011). Importantly, interpretations regarding social cooperation were less tenable than more general interpretation about salience processing differences (both social and non-social) between our ASD and TD groups. The study was limited by a small sample size, especially in the ASD group. While the attrition rate is comparable to other pediatric studies (Yerys et al., 2009), it may have contributed to Type II error. Salivary cortisol was measured during a previous peer interaction exchange with the human confederate rather than on the scan day. Our research measuring biobehavioral profiles provides some assurance that these values reflect a strong measure of physiological arousal status during natural social play conditions (Corbett et al., 2010, 2014; Schupp et al., 2013). Even so, it is unclear if elevated BOLD activity can be reliably compared with states of physiological arousal in a trait-like manner. Finally, the study involved multiple comparison analyses, which were not corrected because the groups were not identical; we were interested in the results of individual hypotheses, and the correlational analyses were deemed exploratory.

SUMMARY
Children with ASD demonstrate a lack of engagement of social salience networks during play with social agents, yet engage such structures with non-human partners. It remains unclear the degree to which the behavioral and neural response patterns of social salience are modifiable and if so, under what conditions. Future studies are needed to explore the saliency of social and non-social stimuli, the distinction between perceptual and motivational factors in social exchange, and the plasticity of social salience circuitry in response to treatment for persons with ASD.