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Atypical Neural Processing of Ironic and Sincere Remarks in Children and Adolescents with Autism Spectrum Disorders

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Abstract

Individuals with ASD show consistent impairment in processing pragmatic language when attention to multiple social cues (e.g., facial expression, tone of voice) is often needed to navigate social interactions. Building upon prior fMRI work examining how facial affect and prosodic cues are used to infer a speaker's communicative intent, the authors examined whether children and adolescents with ASD differ from typically developing (TD) controls in their processing of sincere versus ironic remarks. At the behavioral level, children and adolescents with ASD and matched TD controls were able to determine whether a speaker's remark was sincere or ironic equally well, with both groups showing longer response times for ironic remarks. At the neural level, for both sincere and ironic scenarios, an extended cortical network—including canonical language areas in the left hemisphere and their right hemisphere counterparts—was activated in both groups, albeit to a lesser degree in the ASD sample. Despite overall similar patterns of activity observed for the two conditions in both groups, significant modulation of activity was detected when directly comparing sincere and ironic scenarios within and between groups. While both TD and ASD groups showed significantly greater activity in several nodes of this extended network when processing ironic versus sincere remarks, increased activity was largely confined to left language areas in TD controls, whereas the ASD sample showed a more bilateral activation profile which included both language and “theory of mind” areas (i.e., ventromedial prefrontal cortex). These findings suggest that, for high-functioning individuals with ASD, increased activity in right hemisphere homologues of language areas in the left hemisphere, as well as regions involved in social cognition, may reflect compensatory mechanisms supporting normative behavioral task performance.

Social communication and language impairments are at the core of Autism Spectrum Disorders (ASD). In particular, language delay is a defining feature of this disorder, and almost always the first sign that a child may be on the spectrum (Howlin, 2003; Kurita, 1985; Lord & Paul, 1997). Even individuals with high cognitive abilities who do eventually acquire language may have persisting deficits in semantics, syntax, and pragmatics (e.g., Frith & Happé, 1994; Kjelgaard & Tager-Flusberg, 2001). For instance, impairments in semantic processing in ASD include misuse of proper vocabulary (e.g., Howlin, 2003), failure to correctly interpret metaphor (e.g., Happé, 1993; but see Giora, Gazal, Goldstein, Fein, & Stringaris, this issue), difficulties in semantic integration (e.g., Gold, Faust, & Goldstein, 2010), and superior processing of perceptual information in written speech as opposed to the competing linguistic message (e.g., Järvinen-Pasley, Pasley, & Heaton, 2008). Similarly, individuals with ASD show problems with both production of complex grammatical structure (e.g., Bartolucci, Pierce, & Streiner, 1980) and syntactic comprehension (e.g., Kjelgaard et al., 2001).

In line with the deficits observed in autism in Theory of Mind abilities (i.e., the capacity to attribute mental states, such as beliefs, desires and goals, to others; e.g., Baron-Cohen, Leslie, & Frith, 1985; Baron-Cohen, 1988; Castelli, Frith, Happé, & Frith, 2002; Happé, 1993), one of the most severely affected language domains in ASD is pragmatics, or the appropriate use of language in a social context (Boucher, 2003; see Groen, Zwiers, van der Gaag, & Buitelaar, 2008, for review). Prosody—the rhythm, stress or intonation of speech—plays an important role in language pragmatics as it provides important cues about a speaker's communicative intent. Prior studies have reported difficulties with both production and comprehension of prosody in individuals with ASD. For instance, after controlling for verbal mental age, high-functioning children with ASD have shown difficulties with the production of appropriate speech prosody (McCann, Peppé, Gibbon, O'Hare, & Rutherford, 2007). These deficits, seen in both children and adults with ASD, extend to prosodic speech comprehension, affecting the ability to infer others' mental state by relying on their vocal intonations (e.g., Golan, Baron-Cohen, Hill, & Rutherford, 2007; Peppé, McCann, Gibbon, O'Hare, & Rutherford, 2007; Rutherford, Baron-Cohen, & Wheelwright, 2002). Impairments in processing prosodic cues, as well as difficulties in the ability to integrate a speaker's tone of voice with other social cues, may hinder both the understanding of others' mental states and the comprehension of non-literal speech, such as irony and metaphor, (e.g., Martin & McDonald, 2004) when the intended meaning of an utterance differs from its literal meaning.

Paralleling the difficulties observed at the behavioral level, a growing literature suggests abnormalities in language relevant neural networks in individuals with ASD. A number of studies have shown structural abnormalities in language relevant brain regions (Bigler et al., 2007; De Fossé et al., 2004; Herbert et al., 2002; Herbert et al., 2005; Rojas et al., 2002). Likewise, studies using functional MRI (fMRI; Gaffrey et al., 2007; Harris et al., 2006; Redcay & Courchesne, 2008; Tesink et al., 2009) as well as functional connectivity (Just, Carpenter, Keller, Eddy, & Thulborn, 2004; Kana, Keller, Cherkassky, Minshew, & Just, 2006) have also shown abnormal language processing in individuals with ASD. Several fMRI studies examining a variety of language functions have reported a more bilateral or right-lateralized pattern of activity in both adults (Kleinhans, Müller, Cohen, & Courchesne, 2008; Mason, Williams, Kana, Minshew, & Just, 2008; Tesink et al., 2009) and children (Knaus, Silver, Lindgren, Hadjikhani, & Tager-Flusberg, 2008; Redcay & Courchesne, 2008) with ASD. Some investigations have shown both hyperactivation (Wang, Lee, Sigman, & Dapretto, 2006), as well as hypoactivation (Gaffrey et al., 2007; Wang, Lee, Sigman, & Dapretto, 2007) in language relevant cortices. Furthermore, other studies report both decreased frontal activity and simultaneous increased recruitment of posterior temporal regions (Harris et al., 2006; Just, Cherkassky, Keller, & Minshew, 2004). While these

somewhat discrepant results may be attributable to different task demands and subject populations (e.g., children versus adults), taken together these findings indicate that the neural networks engaged during language processing in individuals with ASD may differ from those in neurotypical individuals.

Relatively few studies have focused on the neural underpinnings of higher-level language functions such as language pragmatics or the role of prosodic cues in language comprehension. For instance, Tesink et al. (2009) explored the neural correlates of pragmatic language by examining brain activity in adults with ASD while they made inferences about a speaker's characteristics (i.e., gender, age, social background) by integrating voice-based cues with the content of the speaker's message. Despite similar behavioral performance between the two groups, they found increased activity of the right inferior frontal gyrus (rIFG) in the ASD group (as compared to neurotypical controls), suggesting a compensatory mechanism for making inferences based on prosodic cues. Another recent study investigating the neural correlates of prosodic speech comprehension (Hesling et al., 2010) found a greater reliance on the left supramarginal gyrus when processing prosodic information in individuals with ASD relative to controls.

Two other studies have focused on the neural correlates of understanding communicative intent, using ironic speech as a test case. In the first study (Wang et al., 2006), we examined the neural circuitry involved when using context and prosodic cues to infer a speaker's intent in typically developing children (TD) and children with ASD. While the TD and ASD groups recruited overall similar neural networks, the ASD group showed hyperactivity in the rIFG and bilateral temporal regions whereas the TD group showed greater recruitment of the medial prefrontal cortex (MPFC) when processing potentially ironic remarks. The increased cortical recruitment of right frontal and bilateral temporal regions in children with ASD was interpreted as reflecting a compensatory mechanism and/or increased neural effort needed to perform the task at equivalent level of accuracy as observed in TD children. In a later study (Wang et al., 2007), we then explored the role of attention to facial cues and tone of voice while processing potentially ironic speech. We found that explicit instructions to attend to a speaker's facial expression and tone of voice elicited significantly greater activity in the MPFC in children with ASD than neutral instructions to just pay attention; in contrast, TD children showed significant MPFC activity irrespective of instructions, consistent with evidence that this region is recruited automatically when processing cues that convey communicative intentions (Kampe, Frith, & Frith, 2003) in neurotypical individuals but not in individuals with ASD. As both of these studies focused on the role of facial and prosodic cues in inferring a speaker's communicative intent, the study designs did not allow us to examine brain activity specifically associated with processing ironic versus sincere remarks.

The goal of this study was to expand upon our prior work in this area (Wang et al., 2006, 2007) to directly examine the neural underpinnings of ironic speech comprehension. More specifically, in this study we used the same audio-visual stimuli as those employed in our prior study (Wang et al., 2007) but in the context of a new fMRI paradigm, one that allowed us to separately examine neural responses to sincere versus ironic remarks. Based on our prior findings (Wang et al., 2006, 2007), we expected the two groups *not* to differ at the behavioral level, with both groups performing well above chance. In contrast, we expected the two groups to show significant differences at the neural level, with greater MPFC activity in TD children than in children with ASD, and increased recruitment of the right hemisphere homologues of canonical language regions in the ASD group.

METHODS

Participants

Our sample consisted of 16 high-functioning children and adolescents with ASD (14 males; all right-handed) and 16 TD control children and adolescents matched by gender, handedness, age (TD: $M = 13.15$, $SD = 2.18$; ASD: $M = 14.27$, $SD = 2.5$), IQ (TD: $M = 109$, $SD = 13$; ASD: $M = 108$, $SD = 13$) and amount of head motion (TD: $M = 0.32$, $SD = .22$; ASD: $M = 0.45$, $SD = .32$) while in the MRI scanner (see Table 1). For the ASD sample, a prior clinical diagnosis of autism was confirmed at the UCLA Autism Evaluation Clinic using the Autism Diagnosis Observation Schedule (ADOS: Lord et al., 2000) or Autism Diagnostic Interview (ADI; Lord, Rutter, & Le Couteur, 1994), as well as expert clinical opinion based upon DSM-IV criteria (American Psychiatric Association, 1994). All participants with ASD had fluent language skills and full scale IQ > 75 , based on either the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999) or the Wechsler Intelligence Scale for Children (Wechsler, 1991). Of ASD participants, 11 were not currently taking any medications. Of the remaining five ASD participants, two were taking a selective serotonin reuptake inhibitor only, one was taking a combination of atypical antipsychotic, SSRI and antidepressant, one was taking an atypical antipsychotic, SSRI and a central adrenergic agonist, and one was taking an atypical antipsychotic, a central adrenergic agonist and a selective norepinephrine reuptake inhibitor. While it is not known how these medications may impact brain function, the level of activity observed in these five participants in regions where significant between-group differences were observed (for the main comparison of both activation conditions vs. resting baseline) was well within the range of that observed in the 11 ASD participants who did not report any medication use, thus suggesting that this variable did not meaningfully affect our findings. All participants reported no history of neurological conditions or known genetic disorders. Typically developing individuals had no history or current diagnosis of developmental, learning, psychiatric or neurological disorders. Written informed consent was obtained from all participants and their parents according to the specifications of the UCLA Institutional Review Board.

Stimuli

Each experimental condition involved the presentation of short cartoon scenarios which participants viewed while listening to a speaker's commentary (see Figure 1). Stimuli were the same as those used in Wang et al. (2007). Each scenario had a sincere version and an ironic version that shared the same neutral setup. Sincere scenarios ended with a positive outcome and a final remark made in a genuinely sincere (and positive) tone of voice. Ironic scenarios ended with an undesirable outcome and a final remark uttered in a clearly ironic (and negative) tone of voice. For instance, one scenario showed a girl and boy going to the beach with the following neutral set-up "John and Linda want to go swimming at the beach." The sincere version then continued with "When they get there, the sky is blue and sunny. John says, 'What a perfect day!'", whereas the ironic version of this scenario continued with "When they get there, the sky turns dark and rainy. John says, 'What a perfect day. . .'" Finally, a prompt followed either version asking participants to determine if the character making the final remark meant what he/she said (e.g., "Did John mean what he said?"). All scenarios included information about event outcome (positive vs. negative) as well as strong facial expression cues (happy vs. sad/upset) and prosodic cues (sincere or ironic tone of voice) to aid participant's interpretation of the speaker's communicative intent. The availability of the multiple sources of information has proved successful in insuring minimal differences in behavioral performance, thus mitigating the potential confound of task difficulty when interpreting any between-group differences observed at the neural level. As described in Wang et al. (2007), a sample of 12 adults validated the stimuli in order to

ensure that the final comments truly sounded sincere or ironic. All versions of the scenarios were matched in terms of syntactic structure, semantic complexity and length.

fMRI Paradigm

Eighteen different scenarios, each lasting 15 seconds, were presented during the fMRI scan. Scenarios with either ironic or sincere endings were presented in a pseudo-randomized order, subject to the constraint that there were no more than two sincere or ironic scenario occurring in a row. In order to further minimize any possible order effects, different orders were created whereby for any given scenario set-up, we used its sincere ending in one order and its ironic ending in the other; these different presentation orders were used equally often across participants within each group. Furthermore, while each participant only saw one ending for a given scenario, to avoid any specific item effects, each scenario was used equally often with its sincere and ironic ending across participants within each group. The scan started with 30 seconds of rest and 8 additional resting blocks were interspersed with the scenarios throughout the run. The entire paradigm lasted a total of 7 minutes and 15 seconds. Participants were instructed to “pay attention” at the end of each block of rest.

The software program MacStim 3.2.1 (White Ant Occasional Publishing, West Melbourne, Australia) was used to present vignettes and record response time (RT) and accuracy data. Visual stimuli were presented through magnet-compatible goggles and responses were collected from a magnet-compatible button box (Resonance Technology, Northridge, CA). The button box remained in the right hand of the participant while they lay in a supine position in the scanner. Participants conveyed whether the speaker was sincere or ironic by pressing down their index or middle finger, respectively. The participants were instructed that “yes” indicated the speaker meant what was said (i.e., the speaker's intent was literal and sincere), whereas “no” meant the speaker meant the opposite of what was said (i.e., the speaker's comment was ironic). Prior to the actual fMRI scan, all participants first practiced with two scenarios not used in the scanner (one sincere and one ironic example) and were allowed to repeat the practice trials until they were comfortable with the task.

fMRI Data Acquisition

Images were acquired using a Siemens Trio 3.0 Tesla MRI scanner at the UCLA Ahmanson-Lovelace Brain Mapping Center. A T2-weighted volume (TR = 5000 ms, TE = 28 ms, flip angle = 90) with 34 4 mm thick transverse slices covering the whole brain, a 128×128 matrix, and an in-plane resolution of 1.5 mm $\times$ 1.5 mm was acquired co-planar to the functional scan in order to ensure identical distortion characteristics to the fMRI scan. Each functional run involved the acquisition of 145 EPI volumes (gradient-echo, TR = 3000 ms, TE = 28 ms, flip angle = 90), each with 34 transverse slices, 4 mm thick, and a 64×64 matrix yielding an in-plane resolution of 3 mm $\times$ 3 mm.

Imaging Data Analysis

Analyses were performed using FSL Version 4.1.4 (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). Preprocessing included motion correction to the mean image, spatial smoothing (Gaussian kernel FWHM = 6 mm), and high-pass temporal filtering ($t > 0.01$ Hz). Functional data were linearly registered to a common stereotaxic space by first registering to the in-plane T2 image (6 degrees of freedom) then to the MNI152 T1 2 mm brain (12 degrees of freedom).

Statistical analysis was carried out using FEAT (FMRI Expert Analysis Tool) Version 5.98, part of FSL. Fixed-effects models were run separately for each subject, then combined in a higher-level mixed effects model to investigate within and between-group differences. We modeled the BOLD response using a separate explanatory variable for each of the two

conditions, sincere and ironic. Higher-level group analyses were carried out using FSL's FLAME (FMRIB's Local Analysis of Mixed Effects State) stage 1 and stage 2 (Beckmann, Jenkinson, & Smith, 2003; Woolrich, 2008; Woolrich, Behrens, Beckmann, Jenkinson, & Smith, 2004). Within-group Z statistical images for each condition (vs. resting baseline) were thresholded at $Z > 2.3$ ($p < .01$) with correction for multiple comparisons applied at the cluster level ($p < .05$; Worsley, 2001). These initial analyses focused on the extensive bilateral networks where we previously observed significant task-related activity in both typically developing controls as well as children with ASD using these exact stimuli (Wang et al., 2007); more specifically, these regions of interest (anatomically defined according to the Harvard Oxford Cortical and Subcortical Structural Atlases, 25% probability) included canonical language areas in the frontal, temporal and parietal regions (inferior frontal gyrus, superior and middle temporal gyrus, as well as supramarginal and angular gyrus) and their right hemisphere homologues, as well as the medial prefrontal cortex (both dorsal and ventral), the temporal pole, and the fusiform gyrus. All between-group comparisons, as well as direct comparisons between the two conditions within each group, were then performed within a functionally defined mask which included all regions where significant task-related activity was observed for each condition (vs. resting baseline) in either the TD and ASD group in the current study. These contrasts were also thresholded at $Z > 2.3$ ($p < .01$), with a minimum cluster size > 10 voxels. Response times were regressed out in all between-group analyses, as well as in the within-group/between-condition contrast, because RTs differed significantly between groups and conditions (the respective average group RTs for the sincere and ironic conditions were assigned to the one ASD and one TD subject for whom RT data were not available).

RESULTS

Behavioral Results

Table 2 lists percent accuracy and response times for each condition (sincere and ironic) in both groups (TD and ASD). Due to computer malfunction, behavioral data from two participants (one in each group) were not available. Both groups performed well above chance in both sincere and ironic conditions. There was no significant main effect of groups for accuracy, $F(1, 28) = .871$, $p = .359$; and no between-group differences in accuracy for either the sincere, $F(1, 28) = .147$, $p = .704$; or ironic condition, $F(1, 28) = 2.465$, $p = .128$. Additionally, no differences in accuracy were observed between the sincere and ironic conditions in either the TD, $F(1, 28) = .438$, $p = .514$; or ASD group, $F(1, 28) = 2.734$, $p = .109$. The group $\times$ condition interaction for accuracy was also not significant, $F(1, 28) = .492$, $p = .489$.

With regard to response times, a significant main effect of condition was observed such that, across groups, RTs were slower for the ironic than sincere condition, $F(1, 28) = 17.25$, $p < .001$; this effect held in both the TD, $F(1, 28) = 10.203$, $p = .003$; and the ASD group, $F(1, 28) = 7.179$, $p = .012$. A significant main effect of group was also observed such that RTs were significantly slower in the TD than the ASD group, $F(1, 28) = 5.979$, $p = .021$; this effect held for both the sincere, $F(1, 28) = 4.83$, $p = .036$; and ironic condition, $F(1, 28) = 5.567$, $p = .026$. There was no significant group $\times$ condition interaction, $F(1, 28) = .133$, $p = .719$.

Functional Magnetic Resonance Imaging Results

To allow for a comparison with previously reported findings (Wang et al., 2007), we first examined the pattern of regional activity observed in each group when summing across the sincere and ironic conditions (see Figures 2 and 3, Table 3). Consistent with our previous findings, the TD group showed robust activation in canonical language networks in the left

hemisphere (LH)—as well as in homologue regions in the right hemisphere (RH)—which included the inferior frontal gyrus (IFG; pars orbitalis, triangularis, and opercularis), the middle and superior temporal gyri (MTG and STG), the transverse temporal gyrus (TTG), as well as the supramarginal and angular gyri (SMG and AG), further extending into the superior parietal lobule (SPL); in addition, significant task-related activity was also observed in visual cortices (fusiform gyrus, FG), the temporal poles, and the medial prefrontal cortex (MPFC). The ASD group also showed significant activity in all of these regions, albeit to a somewhat reduced extent. As shown in Figure 4 and Table 3, a direct statistical comparison between the two groups revealed that the TD group showed significantly greater activity than the ASD group in several nodes of this large scale network including the IFG (left pars opercularis, bilateral pars triangularis), left AG, bilateral MTG and STG, bilateral temporal pole and FG, as well as dorsal MPFC. The ASD group did not show any significantly greater activity than the TD group.

To a considerable extent, each group showed significant activation in the same extended network described above when we examined the pattern of brain activity specifically associated with scenarios ending with sincere vs. ironic remarks (see Table 4 and Table 5, respectively). For each condition examined separately, the TD group again showed significantly greater activation than the ASD group in a similar set of regions as described above (i.e., dorsal MPFC, IFG, MTG, STG, SMG, and FG). However, while the ASD group did not show any significantly greater activity than the TD group for the sincere condition, significantly greater activity in the ASD than TD group was observed for the ironic condition in MPFC as well as in the left temporal pole.

Despite the overall similar networks activated across the two conditions in both groups, significant modulation of activity was nevertheless detected when we directly compared activity between the sincere and ironic conditions in each group, as well as between groups. Only a few regions showed increased activity for sincere as compared to ironic remarks (Table 6). More specifically, in both groups, significantly greater activity for sincere than ironic remarks was only detected in the right MTG and FG (left FG in the TD, right FG in the ASD). For the reverse comparison (ironic > sincere), increased activity was observed in a more extensive set of regions in both groups (see Table 6 and Figure 5). More specifically, the TD group showed greater activation for ironic versus sincere scenarios in a left-lateralized network, which included the IFG (both pars triangularis and pars opercularis), STG, SMG, and temporal pole, with two additional clusters also observed in the right STG and temporal pole. The ASD group also showed stronger activation in response to ironic than sincere scenarios but in a wider and more bilateral network of areas which included bilateral IFG (pars orbitalis, triangularis, and opercularis) and right SMG, MTG, left STG and temporal pole, as well as MPFC and dorsal MPFC (see Figure 5). A significant group $\times$ condition interaction confirmed that, as compared to the TD group, the ASD group showed greater signal increases for ironic versus sincere scenarios in the right IFG (pars triangularis), right MTG, STG, and SMG (see Table 7).

DISCUSSION

The results of the current study extend our prior work on the neural correlates of understanding communicative intent in typical development (Wang et al., 2006) and autism (Wang et al., 2006, 2007) by examining how the brain may differentially process sincere and ironic remarks. Rather than focusing on how attention to facial expression and tone of voice may aid in the interpretation of a speaker's communicative act, here we used the same exact stimuli as in Wang et al. (2007) in a novel design that allowed us to directly compare neural activity associated with sincere versus ironic utterances. In line with our prior findings (Wang et al., 2007), as well as those of other investigations on the neural correlates of irony

and sarcasm in neurotypical individuals (e.g., Eviatar & Just, 2006; Uchiyama et al., 2006), when we first examined activity across both types of scenarios (as compared to resting baseline), we observed strong activity within a large scale network that encompassed canonical language areas in frontal, temporal, and inferior parietal regions in the left hemisphere and, to a lesser degree, their right hemisphere counterparts, in addition to activity in visual cortices (including the fusiform face area), and MPFC. While TD children and children with ASD showed remarkably similar activation profiles, direct between-group comparisons revealed that the TD group did show significantly greater activity than the ASD group in several nodes within this larger network. Replicating the results observed for the neutral instructions condition in our prior study (Wang et al., 2007), regions showing stronger activity in TD children included the dorsal MPFC and bilateral temporal regions; however, significantly greater activity was also observed in language-relevant areas in frontal and parietal regions as well as in the FG. The detection of more robust activity in the TD versus ASD group in these additional regions likely reflects increased power in the current study where we examined activity in response to three times as many scenarios (as we no longer had to divide our stimuli amongst several different conditions to allow for our attentional manipulation). When we directly compared group activity observed for sincere and ironic scenarios (each versus resting baseline), an overall similar pattern emerged with TD controls showing greater activity than children with ASD in a similar set of regions (as observed when summing across sincere and ironic scenarios). However, while children with ASD did not show any greater activity than TD children when processing sincere remarks, ASD children did activate the MPFC and the left temporal pole—two regions known to be involved in mentalizing and social cognition (Mitchell, 2009; Ross & Olson, 2010)—to a greater extent than their TD counterparts when processing ironic remark.

The significantly greater activity overall observed in TD children did not predict better task performance in this group as compared to children with ASD; indeed, children in both the TD and the ASD groups were extremely accurate at discriminating sincere and ironic remarks with task performance at ceiling in both groups (see Giora et al., this issue, for additional evidence of similar behavioral performance in individuals with and without Asperger's syndrome when processing metaphors). Notably, the near perfect accuracy observed in children with ASD was seemingly not achieved via overall increased activity in either normative or alternative neural circuitry, as children with ASD showed significantly greater activity than TD controls only for ironic scenarios. In our prior study using the same stimuli (Wang et al., 2007), we had also observed very high task performance in both groups; however, children in the ASD group did have a significantly higher number of no responses, perhaps indexing some increased task difficulty. In contrast, in the present study we had very few no responses in either group (3 missed responses in 2 children with ASD and 4 missed responses in one TD child), possibly reflecting the fact that the current sample of ASD was overall less affected than our prior one as indicated by non-significant differences in verbal IQ. Furthermore, fewer children in the current sample met criteria for full autism on the ADOS (two children met criteria for autism only on the ADI and of the 14 children who met criteria on the ADOS as well, 5 met criteria for ASD but not full autism).

Irrespective of some variability in sample characteristics across the two studies, as we previously argued (Wang et al., 2007), the remarkably high performance observed in children with ASD may be attributed to the simplicity of the scenarios and, perhaps more importantly, to the fact that a clear visual depiction of the event outcome was available to guide their inference about a speaker's communicative intent. In other words, children with ASD may have come to rely upon the discrepancy between the salient negative outcome of an event (e.g., opening a present to find a pair of socks or burning a hotdog on a campfire) and the positive speaker's remark (e.g., "that's great!") in order to perform the task. In real life social interactions, however, knowledge of an event outcome is not always available and

listeners often need to rely upon additional information—such as that provided by a speaker's facial expression and tone of voice—in order to correctly infer his or her communicative intent. Accordingly, the pragmatic language deficits typically observed in individuals with ASD (e.g., Tager-Flusberg, 1981; Happé, 1993, 1994; Baron-Cohen et al., 1994; Ozonoff & Miller, 1996; Tager-Flusberg, Joseph, & Folstein, 2001; Paul, Augustyn, Klin, & Volkmar, 2005) may result from decreased attention to these critical social cues (Chawarska, Volkmar, & Klin, 2010; Jellema et al., 2009; Kikuchi, Senju, Tojo, Osanai, & Hasegawa, 2009; Lepisto et al., 2005; Whitehouse & Bishop, 2008) when navigating social interactions. In this regard, it is actually interesting that TD children actually took significantly longer to respond than children with ASD. In line with the argument presented above, the overall longer response times observed in this group may reflect the fact that—unlike children in the ASD group—TD children may automatically take the time to process the cues conveyed by a speaker's facial expression and tone of voice even when this information is not necessary to determine communicative intent. While response times were entered as a covariate in our imaging analyses, it is possible that the increased activity observed in TD children might in part still reflect the longer processing times observed in this group.

Despite the strong similarities in the neural networks activated in response to sincere and ironic remarks in both TD children and children with ASD, significant differences were nevertheless observed when we directly compared—both within and between groups—activity associated with vignettes that ended with sincere as opposed to ironic remarks. In both groups, activity in right temporal cortices was higher for sincere than ironic scenarios. Given the known role of these regions in processing the prosodic quality of speech (see Kotz, Meyer, & Paulmann, 2006, for review), this increased activity might reflect the intrinsic low-level characteristics of the speech conveying sincere remarks (e.g., higher pitch). Both groups also showed stronger activity in the fusiform gyrus for sincere as compared to ironic remarks; to the extent that we had attempted to match as closely as possible the visual stimuli presented in the two types of scenarios, greater activity in these visual areas may reflect children's tendency to pay more attention to scenarios ending with a positive outcome and/or displaying happy facial expressions. Future studies employing eye-tracking technology could help determine the extent to which the two types of stimuli may elicit different fixation patterns and how, in turn, these may influence brain activity.

By far the most notable differences in neural responses emerged when we examined activity related to processing vignettes ending with ironic remarks as compared to sincere ones. For this contrast (ironic > sincere), both groups showed significantly greater engagement of several frontal, temporal, and parietal regions within the larger network identified in the comparison of both activation conditions against resting baseline. In TD children, this heightened activity for ironic scenarios involved primarily canonical language areas in the left hemisphere; in contrast, this increased activity was considerably more bilateral in children with ASD, extending beyond language regions in the left hemisphere and their right hemisphere homologues to also encompass regions typically engaged during mentalizing tasks such as the MPFC (see Mitchell, 2009, for a review). Importantly, direct between-group comparisons on the contrast comparing activity between the two types of scenarios (i.e., the group $\times$ condition interaction effect) confirmed that children in the ASD group showed significantly greater activity than TD children for ironic (versus sincere) scenarios in the right IFG, MTG, STG, SMG as well as the MPFC. Thus, while processing irony led to increased activity in left-lateralized, language-relevant networks in both TD children and children with ASD, the two groups differed significantly in terms of both magnitude and extent of these changes which were greater, more bilaterally distributed and more widespread in children with ASD as compared to TD controls.

The enhanced activity observed in both groups for scenarios ending with ironic remarks likely reflects the increased cognitive load involved in processing multiple meanings (i.e., the literal/positive meaning of the utterance and the ironic/negative meaning intended by the speaker). Indeed, both children with ASD and TD children took longer when deciding if a speaker meant what he/she said in the case of ironic remarks. However, the fact that children in the ASD group showed significantly greater signal increases for ironic (vs. sincere) remarks than their TD counterparts suggests that understanding irony was more difficult for them, perhaps because relevant information from the social cues provided by a speaker's facial expression and tone of voice are not automatically processed when inferring a speaker's communicative intent. These results may also be due to the fact that the ASD group may find it difficult to process the conflicting information provided by the speaker's tone of voice and the knowledge of event outcome.

The notion that understanding irony may be relatively more challenging in children with ASD is supported by the more bilateral activity observed in this group in fronto-temporal and parietal regions as prior studies have demonstrated increased activity in right hemisphere homologues of left canonical language areas as a function of increased task difficulty even in neurotypical individuals (e.g., Just et al., 1996), and particularly so when coherence-seeking is required (e.g., Caplan & Dapretto, 2001; Kircher, Brammer, Tous Andreu, Williams, & McGuire, 2001; Rodd, Davis, & Johnsrude, 2005; Mason & Just, 2011; Menenti Petersson, Scheeringa, & Hagoort, 2009). The more bilateral recruitment observed in children with ASD for the more cognitively demanding process of understanding ironic speech is also in line with a growing literature suggesting a strong right-hemisphere contribution to higher-level language processing in ASD (Dawson, Finley, Phillips, & Gapert, 1986; Flagg, Cardy, Roberts, & Roberts, 2005; Gaffrey et al., 2007; Harris et al., 2006; Knaus et al., 2008; Mason et al., 2008; Tesink et al., 2009; Wang et al., 2006; but see also Gold & Faust, 2010, this issue).

In addition to displaying greater bilateral involvement than TD controls, when processing ironic remarks (vs. sincere ones), children with ASD also displayed greater engagement of the left temporal pole, a region previously implicated in understanding irony in neurotypical individuals (Uchiyama et al., 2006) and in accessing social conceptual knowledge (Ross & Olson, 2010), as well as greater recruitment of the MPFC, a region known to play an important role in understanding others' mental states (see Amodio & Frith, 2006; Mitchell, 2009). Interestingly, in our prior work using the same stimuli but collapsing across scenarios with sincere and ironic endings, as well as in the current study when we again compared group activity across both types of scenarios, it was in TD children that we observed greater activity in the dorsal MPFC. This pattern of findings then fits well with the notion that TD children may typically recruit this mentalizing region whenever attempting to infer a speaker's communicative intent, likely reflecting an implicit and automatic appraisal of the multiple social cues available during social interactions. In contrast, our findings suggest that children with ASD may recruit this region only when faced with the additional challenge of having to reconcile the discrepancy between a negative event outcome and a speaker's positive remark; the increased engagement of the MPFC in these instances may reflect the attempt to integrate prosodic and facial cues to accurately infer a speaker's intent when the literal meaning of an utterance is in conflict with other contextual information. While reduced activity in the MPFC in individuals with autism has been reported in several "Theory of Mind" tasks (e.g., Castelli et al., 2002; Happé et al., 1996; Tesink et al., 2009), the present results are consistent with prior findings indicating that normative neurocircuitry can be successfully recruited when task demands implicitly require attention to social cues in order to detect ironic intent (Wang et al., 2006) or when task instructions explicitly direct attention to such cues (Wang et al., 2007).

Taken together, the findings of the present investigation shed further light on the mechanisms involved in understanding nonliteral language in individuals with ASD and, more broadly, the neural circuitry subserving social communication. Despite the considerable overlap in the overall networks engaged in children with ASD and TD controls, a history of altered social interactions in children with ASD does seem to affect how the brain processes social cues, leading to greater recruitment of regions known to subserve language and social cognition in the neurotypical brain. Importantly, the differences we observed at the neural level did not have a direct counterpart at the behavioral level, in line with growing evidence indicating that high-functioning individuals with ASD can achieve high levels of accuracy in constrained laboratory settings even when using tasks that specifically target processes that are known to be impaired in autism (e.g., Greene et al., 2011; Hamilton, Brindley, & Frith, 2007; Tesink et al., 2009). The increasing popularity, especially among youth, of internet based social interactions—via iChat, and social networking websites—provides new opportunities to examine the neural correlates of live social interaction by imaging study participants as they interact online with peers (see Krueger et al., 2007; Redcay et al., 2010). Doing so would inherently and greatly increase the ecological validity of neuroimaging studies, and likely offer important new insight into the neural underpinnings of the socio-communicative impairments in individuals with ASD.

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FIGURE 1.

Example scenario. The setup (top picture) is shared by both sincere and ironic versions. The sincere ending is displayed in the left bottom drawing and the ironic ending is displayed in the right bottom drawing. The text represents the auditory stimuli accompanying each drawing. After viewing either the sincere outcome or ironic outcome, participants saw a blank screen and answered the question "Did John mean what he said?".

FIGURE 2.

Brain activity for the TD group summing across both sincere and ironic conditions relative to resting baseline. Activation exceeds threshold of $Z > 2.3$ ($p < .01$) with correction for multiple comparison applied at the cluster level ($p < .05$) (color figure available online).

FIGURE 3.

Brain activity for the ASD group during both sincere and ironic scenarios relative to resting baseline. Figures are thresholded at $Z > 2.3$ ($p < .01$) with correction for multiple comparison applied at the cluster level ($p < .05$) (color figure available online).

FIGURE 4.

Brain regions more strongly activated in the TD group relative to the ASD group in response to both sincere and ironic scenarios combined relative to resting baseline. Figures are thresholded at $Z > 2.3$ ($p < .01$), with a minimal cluster size of 10 voxels (color figure available online).

FIGURE 5.

Brain regions more strongly activated when comparing ironic to sincere conditions for both the TD group (shown in blue) and the ASD group (shown in yellow). Activation exceeds threshold of $Z > 2.3$ ($p < .01$), with a minimal cluster size of 10 voxels (color figure available online).

TABLE 1

Participant Demographics Listed as “Mean (Standard Deviation)”

	<i>TD Group Mean (SD)</i>	<i>ASD Group Mean (SD)</i>	<i>p Value</i>
Age, y	13.15 (2.2)	14.27 (2.5)	0.184
Full Scale IQ	109 (13)	108(13)	0.791
Verbal IQ	111 (16)	109 (15)	0.721
ADI	n/a	47.8 (9.4)	n/a
ADOS	n/a	10.2 (3.5)	n/a
Mean Head Motion	0.32	0.45	0.199

TABLE 2

Behavioral Results

<i>Condition</i>	<i>Accuracy (% Correct), Mean (SD)</i>		<i>Response Time (s), Mean (SD)</i>	
	<i>TD Group (n = 15)</i>	<i>ASD Group (n = 15)</i>	<i>TD Group (n = 15)</i>	<i>ASD Group (n = 15)</i>
Sincere	.93 (.13)	.95 (.08)	2.63 (.24)	2.40 (.32)
Ironic	.95 (.08)	.99 (.04)	2.81 (.36)	2.55 (.22)

TABLE 3

All Activation Conditions vs. Resting Baseline

Anatomical Region	Side	TD			ASD			TD > ASD		
		MNI Peak (mm)			MNI Peak (mm)			MNI Peak (mm)		
		x	y	z	x	y	z	x	y	z
Medial Prefrontal Cortex		2	54	26	4.97	0	50	32	3.96	
Dorsal Medial Prefrontal Cortex		-6	12	44	5.43	0	6	56	4.68	-6 22 36 3.82
Frontal Pole	R	44	32	-16	3.06	44	40	-16	3.2	
	L	-44	36	-16	3.55	-52	40	-14	3.33	
Frontal Orbital Cortex	R	32	12	-16	3.09	26	8	-16	3.83	
Inferior Frontal	R	46	40	-20	3.73	36	32	-6	3.75	
Gyrus, pars orbitalis	L	-40	28	-16	5.09	-40	26	-16	3.64	
Inferior Frontal	R	54	26	0	4.96	54	24	0	2.54	46 24 4 3.48
Gyrus, pars triangularis	L	-48	24	4	5.63	-52	20	14	4.29	-28 28 8 3.93
Inferior Frontal	R	42	6	30	5.03	32	12	28	4.51	
Gyrus, pars opercularis	L	-30	14	28	4.49	-58	20	22	4.07	-50 10 10 2.74
Temporal Pole	R	48	8	-20	5.42	50	16	-34	4.92	58 6 -12 3.15
	L	-26	2	-28	4.74	-54	8	-12	4.81	-50 8 -6 3.74
Inferior Temporal Gyrus	R	52	-44	-10	3.13	52	40	-12	4.04	
	L	-58	-52	-20	3.16	-52	-42	-14	3.08	
Middle Temporal Gyrus	R	44	-60	2	5.76	52	-40	-10	4.32	70 -10 -10 3.31
	L	-60	2	-14	5.63	-48	-62	12	5.84	-64 -48 -12 2.85
Superior Temporal Gyrus	R	52	-16	-2	6.74	66	-24	10	6.39	52 -20 -6 2.83
	L	-48	-14	2	6.15	-60	-20	0	6.58	-46 -32 0 3.14
Superior Temporal Gyrus, posterior	R	64	-34	14	6.15	-58	-44	8	5.73	
	L	-44	-36	2	5.41	-44	-42	2	4.86	
Planum Temporale	L	-46	-38	16	4.43	-38	-36	16	3.28	
	R	48	-34	16	4.59					
Precentral Gyrus	L	-60	6	18	2.65	-34	4	28	3.81	
Supramarginal Gyrus	R	44	-42	12	5.75	50	-42	16	5.3	44 -40 12 2.86
	L	-58	-46	30	4.71	-54	-48	30	2.59	-40 -48 38 3.58

Anatomical Region	Side	TD				ASD				TD > ASD			
		MNI Peak (mm)			Max	MNI Peak (mm)			Max	MNI Peak (mm)			Max
		x	y	z	Z	x	y	z	Z	x	y	z	Z
Angular Gyrus	R	40	-56	22	4.15	46	-48	12	4.91				
	L	-56	-58	14	5.27	-60	-58	28	3.18	-22	-56	34	2.71
Superior Parietal Lobule	R	26	-50	44	4.43								
	L	-22	-60	48	4.34								
Occipital Fusiform Gyrus	R	34	-66	-20	7.09	18	-82	-16	5.82	-26	-70	-16	2.70
	L	-42	-68	-18	6.39	-14	-90	-14	6.17	24	-92	-18	2.66

Note. Peak activation coordinates in Montreal Neurological Institute (MNI); TD = typical development; ASD = autism spectrum disorders; Thresholded at $Z > 2.3$ ($p < .01$).

TABLE 4

Sincere Scenarios vs. Resting Baseline

Anatomical Region	Side	TD			ASD			TD > ASD		
		MNI Peak (mm)	Max	Max	MNI Peak (mm)	Max	Max	MNI Peak (mm)	Max	Max
		x	y	z	x	y	z	x	y	z
Medial Prefrontal Cortex		8	48	28	5.07	-2	48	34	4.67	
Dorsal Medial Prefrontal Cortex		-2	8	54	8.44	-4	6	52	4.65	-12 16 38 3.21
Inferior Frontal Gyrus, pars orbitalis	R	46	40	-20	4.23	34	34	-4	3.38	
	L	-28	32	4	5.00	-42	32	-16	5.44	
Inferior Frontal Gyrus, pars triangularis	R	52	26	2	7.30	56	26	-6	2.73	40 26 4 2.96
	L	-42	18	14	9.07	-50	22	10	2.99	-38 20 12 3.33
Inferior Frontal Gyrus, pars opercularis	R	48	18	26	3.55	46	14	22	3.23	
	L	-52	10	28	3.96	-54	18	16	3.67	-50 12 10 3.29
Temporal Pole	R	46	10	-22	8.38	48	22	-24	5.88	
	L	-52	18	-28	6.61	-48	6	-18	6.09	-32 8 -26 3.04
Inferior Temporal Gyrus	R	52	-54	-8	4.11	52	-42	-12	5.41	
	L	-48	-54	-8	3.65	-48	-54	-8	2.82	
Middle Temporal Gyrus	R	70	-14	-12	7.63	56	-2	-24	3.94	70 -10 -10 3.19
	L	-68	-8	-16	3.81	-62	-30	-18	2.77	-62 -50 -12 2.97
Middle Temporal Gyrus, posterior	R	52	-52	4	11.28	52	-54	8	4.70	56 -54 -6 3.05
	L	-52	-54	-8	5.00	-46	-60	12	6.09	
Superior Temporal Gyrus	R	46	-20	-4	8.88	50	-10	-8	7.68	52 -18 -2 3.21
	L	-48	-4	-12	7.46	-56	-12	-8	13.92	-48 -32 0 3.05
Superior Temporal Gyrus, posterior	R	66	-20	10	6.30	68	-24	10	6.18	44 -40 12 2.74
	L	-56	-46	10	4.95	-50	-30	0	6.51	-50 -30 2 2.62
Transverse Temporal Gyrus	R	48	-34	16	5.41	46	-26	4	6.21	
Precentral Gyrus	L	-50	4	10	2.81					-52 4 10 3.33
Supramarginal Gyrus	R	54	-44	16	4.60	58	-44	14	5.56	
	L	-54	-48	28	3.61	-56	-44	16	3.63	
Angular Gyrus	R	40	-50	20	3.42	36	-44	22	4.80	
	L	-38	-48	28	5.62	-60	-58	28	3.54	

Anatomical Region	Side	TD						ASD						TD > ASD					
		MNI Peak (mm)			Max			MNI Peak (mm)			Max			MNI Peak (mm)			Max		
		x	y	z	x	y	z	x	y	z	x	y	z	x	y	z	x	y	z
Superior Parietal Lobule	R	26	-50	42	6.79														
	L	-22	-60	46	7.47									-32	-46	42	4.73		
Occipital Fusiform Gyrus	R	34	-70	-10	9.61	20	-88	-18	8.89					26	-90	-18	2.91		
	L	-34	-66	-8	7.51	-42	-70	-20	5.37					-26	-70	-16	2.91		

Note. Peak activation coordinates in Montreal Neurological Institute (MNI); TD = typical development; ASD = autism spectrum disorders. Thresholded at $Z > 2.3$ ($p < .01$).

TABLE 5

Ironic Scenarios vs. Resting Baseline

Anatomical Region	Side	TD						ASD						TD > ASD						ASD > TD					
		MNI Peak (mm)			Max			MNI Peak (mm)			Max			MNI Peak (mm)			Max			MNI Peak (mm)			Max		
		x	y	z	x	y	z	x	y	z	x	y	z	x	y	z	x	y	z	x	y	z	x	y	z
Medial Prefrontal Cortex		0	54	24	7.50	-6	54	20	5.40											8	60	6			2.95
Dorsal Medial Prefrontal Cortex		-6	26	44	7.95	-10	40	28	3.83					-4	22	38									3.92
Frontal Orbital Cortex	R							44	38	-18															
	L	-42	28	-20	6.38	-32	16	-20	3.32																
Inferior Frontal Gyrus, pars orbitalis	R	52	28	-8	4.48	52	24	-4	3.35																
	L	-42	28	-16	8.58	-36	34	-8	4.72					-44	24	0									2.70
Inferior Frontal Gyrus, pars triangularis	R	52	26	0	7.73	52	26	2	3.06																
	L	-58	20	16	7.38	-54	22	16	4.22					-56	36	2									3.11
Inferior Frontal Gyrus, pars opercularis	R	42	10	32	6.33	32	12	28	6.55																
	L	-58	20	16	7.38	-54	20	16	4.49					-52	14	4									2.71
Temporal Pole	R	50	16	-34	4.57	46	22	-32	3.96					60	10	-16									
	L	-48	12	-16	6.32	-48	8	-16	7.2											-60	12	-20			3.06
Inferior Temporal Gyrus	R	50	-52	-10	3.84	50	-56	-8	3.96																
	L	-50	-52	-8	3.01	-50	-52	-12	3.88																
Middle Temporal Gyrus	R	50	-16	-10	13.55	52	2	-30	4.89																
	L	-70	-18	-12	3.00	-66	-10	-18	4.07					-46	-30	-6									2.84
Middle Temporal Gyrus, posterior	R	68	-42	-12	3.86	46	-64	10	8.66																
	L	-54	-38	-8	5.18	-60	-44	8	5.66					-64	-46	-10									2.87
Superior Temporal Gyrus	R	70	-12	-4	6.67	64	-24	8	6.74					60	4	-12									3.09
	L	-56	-22	6	6.66	-62	-20	0	6.69																
Superior Temporal Gyrus, posterior	R	62	-34	14	8.86	60	-38	24	4.34																
	L	-58	-44	24	5.07	-58	-48	30	2.58					-54	-26	0									2.43
Transverse Temporal Gyrus	R	40	-30	18	4.32	46	-14	-8	5.25																
	L	-42	-38	18	4.10	-38	-36	20	2.87																
Supramarginal Gyrus	L	-52	-36	46	3.50																				
Angular Gyrus	R	50	-52	12	4.03	52	-56	14	4.40																

Anatomical Region	Side	TD					ASD					TD > ASD					ASD > TD				
		MNI Peak (mm)					MNI Peak (mm)					MNI Peak (mm)					MNI Peak (mm)				
		x	y	z	Max	Z	x	y	z	Max	Z	x	y	z	Max	Z	x	y	z	Max	Z
Superior Parietal Lobule	L	-36	-54	24	3.81	4.46	-46	-56	16	3.57		24	-60	32	3.64						
	R	26	-50	44	4.46							-32	-46	38	3.88						
	L	-30	-44	38	5.40																
Occipital Fusiform Gyrus	R	38	-72	-14	11.53	42	-64	-18	5.52			-26	-70	-18	2.78						
	L	-22	-82	-14	6.50	4.78	-32	-88	-14	4.78											

Note. Peak activation coordinates in Montreal Neurological Institute (MNI); TD = typical development; ASD = autism spectrum disorders; Thresholded at $Z > 2.3$ ($p < .01$).

TABLE 6

Direct Comparison Between Activation Conditions

Ironic Scenarios vs. Sincere Scenarios														Sincere Scenarios vs. Ironic Scenarios											
Anatomical Region	Side	TD						ASD						TD						ASD					
		MNI Peak (mm)			Max			MNI Peak (mm)			Max			MNI Peak (mm)			Max			MNI Peak (mm)			Max		
		x	y	z	Z			x	y	z	Z			x	y	z	Z			x	y	z	Z		
Medial Prefrontal Cortex							-10	48	18	3.85															
Dorsal Medial Prefrontal Cortex							-4	10	58	2.64															
Frontal Orbital Cortex	L						-26	12	-20	3.29															
Inferior Frontal Gyrus, pars orbitalis	R						42	26	-10	3.09															
	L						-42	32	-6	3.90															
Inferior Frontal Gyrus, pars triangularis	R						50	26	0	4.15															
	L	-50	38	2	2.82		-54	26	12	2.73															
Inferior Frontal Gyrus, pars opercularis	L	-54	18	18	3.02		-56	18	26	2.92															
Temporal Pole	R	50	16	-34	2.73																				
	L	-52	10	-20	2.80		-46	12	-16	2.38															
Middle Temporal Gyrus	R						54	-34	-4	3.40															
Superior Temporal Gyrus	R	46	-56	-28	-18	-4	4	2.58	3.21																
	L						-52	-16	-6	2.46															
Supramarginal Gyrus	R						58	-36	22	2.97															
	L	-62	-48	30	3.09		-60	-40	28	2.64															
Occipital Fusiform Gyrus	R																								
	L						-10	-88	-16	2.61															

Note. Peak activation coordinates in Montreal Neurological Institute (MNI); TD = typical development; ASD = autism spectrum disorders; Thresholded at $Z > 2.3$ ($p < .01$).

TABLE 7

Group (ASD, TD) × Condition (Sincere, Ironic) Interaction

<i>Anatomical Region</i>	<i>Side</i>	<u><i>MNI Peak (mm)</i></u>			<u><i>Max</i></u>
		<i>x</i>	<i>y</i>	<i>z</i>	<i>Z</i>
Medial Prefrontal Cortex		4	56	22	2.61
Inferior Frontal Gyrus, pars triangularis	R	52	26	−2	3.16
Middle Temporal Gyrus	R	52	−50	0	2.73
Superior Temporal Gyrus	R	68	−26	18	2.73
Supramarginal Gyrus	R	58	−34	22	2.76

Note. Peak activation coordinates in Montreal Neurological Institute (MNI); TD = typical development; ASD = autism spectrum disorders: Thresholded at $Z > 2.3$ ($p < .01$).