The neural basis of deictic shifting in linguistic perspective-taking in high-functioning autism

Akiko Mizuno¹, Yanni Liu¹, Diane L. Williams², Timothy A. Keller¹, Nancy J. Minshew³, Marcel Adam Just¹

¹Center for Cognitive Brain Imaging, Department of Psychology, Carnegie Mellon University, Pittsburgh, PA
²Department of Speech Language Pathology, Duquesne University, Pittsburgh, PA
³Departments of Psychiatry and Neurology, University of Pittsburgh School of Medicine, Pittsburgh, PA

Abstract: Personal pronouns, such as I and you, require a speaker/listener to continuously re-map their reciprocal relation to their referent, depending on who is uttering the pronoun. This process, called deictic shifting, may underlie the incorrect production of these pronouns, or pronoun reversals, such as referring to oneself with the pronoun you, which have been reported in children with autism. The underlying neural basis of deictic shifting, however, is not understood, nor has the processing of pronouns been studied in adults with autism. The present study compared the brain activation pattern and functional connectivity (synchronization of activation across brain areas) of adults with high-functioning autism and control participants using functional MRI in a linguistic perspective-taking task that required deictic shifting. The results revealed significantly diminished frontal (right anterior insula) to posterior (precuneus) functional connectivity during deictic shifting in the autism group, as well as reliably slower and less accurate behavioral responses. A comparison of two types of deictic shifting revealed that the functional connectivity between the right anterior insula and precuneus was lower in autism while answering a question that contained the pronoun you, querying something about the participant’s view, but not when answering a query about someone else’s view. In addition to the functional connectivity between the right anterior insula and precuneus being lower in autism, activation in each region was atypical, suggesting over-reliance on individual regions as a potential compensation for the lower level of collaborative inter-regional processing. These findings indicate that deictic shifting constitutes a challenge for adults with high-functioning autism, particularly when reference to one’s self is involved, and that the functional collaboration of two critical nodes, right anterior insula and precuneus, may play a critical role for deictic shifting by supporting an attention shift between oneself and others.

Keywords: autism, functional connectivity, pronoun reversal, precuneus, insula

Personal pronouns are repeated just as heard, with no change to suit the altered situation. The child, once told by his mother, "Now I will give you your milk," expresses the desire for milk in exactly the same words. Consequently, he comes to speak of himself always as "you," and of the person addressed as "I." Kanner (1943), p. 244.
Efficient communicators achieve an understanding of another’s knowledge, information, and emotion, and use this understanding to make appropriate adjustments when delivering their messages. The human neural system conducts this intricate process in an online and relatively spontaneous manner. Dysfunction of such dynamic flexibility in reciprocal communication has been delineated as a characteristic of Autism Spectrum Disorder. For example, as described in Leo Kanner’s seminal documentation of autism above, children with autism sometimes incorrectly refer to themselves by using the second-person pronoun, you, instead of the first-person pronoun, I, by repeating the pronoun they heard someone else use when referring to them. Such atypical production of personal pronouns, called pronoun reversals, has long been recognized as a common impairment in autism.

Interestingly, it is also not uncommon to observe pronoun reversals among typically-developing children (Dale & Crain-Thoreson, 1993). These authors posited that the substantial processing demand of updating the anchoring site of an utterance, and shifting the relationship between an utterance-generating speaker and a referred-to listener, a process called deictic shifting, challenges children and triggers pronoun reversals in early development. In autism, several studies have described the decrease or even cessation of the use of pronoun reversals in later childhood (Cantwell, Baker, Rutter, & Mawhood, 1989; Kanner, 1943, 1971). Both typically-developing children and children with autism eventually master correct pronominal deixis, but it is undetermined whether a neural trace of such dexis difficulty in autism remains in adulthood. Thus, although pronoun reversals are often thought of as an issue in early development, adults with high-functioning autism may also experience difficulty in transforming a personal pronoun to an appropriate form in a linguistic task that requires deictic shifting. The present study aimed to examine this process of deictic shifting in a linguistic perspective-taking task among adults with high-functioning autism whose verbal IQ is within the normal range. We employed a computerized perspective-taking task that required deictic shifting of the personal pronouns I and you, similar to a paradigm reported by Lee, Hobson, and Chiat (1994), and we collected both behavioral and neuroimaging measures of the process.

Another important component of deictic shifting, involving personal pronouns such as I or you, is relating oneself to another person, depending on who is speaking. As indicated in the term autism, derived from the Greek word autos meaning “self,” ‘concept of self” is a central element of this disorder, particularly the relation between the self and others. Individuals with autism exhibit atypical behavior regarding themselves, namely extreme self-focus and lack of higher-order understanding of self, and this phenomenon may have something in common with the deictic shifting problem (Frith & de Vignemont, 2005; Lombardo & Baron-Cohen, 2010).

Based on accumulating brain imaging studies with functional magnetic resonance imaging (fMRI) in autism, which indicate frontal-posterior functional underconnectivity theory (a lower level of synchronization of fMRI-measured activation between brain areas) (Just et al., 2004, 2007; Kana et al., 2006, 2007, 2009; Koshino et al., 2005; Mason et al., 2008; Villalobos et al., 2005), the present study hypothesized that diminished functional communication between frontal and posterior brain regions may constrain the process of deictic shifting in autism. One of the brain areas believed to be involved in the representation of self, and hence in deictic shifts involving the self, is the precuneus (Farrer & Frith, 2002; Frings et al., 2006; Ruby & Decety, 2001; Vogeley et al., 2004; Zaehle et al., 2007), situated in the medial posterior region of the parietal cortex and adjoining the posterior cingulate cortex (PCC). Regions of the posterior parietal region are believed to contribute to the dorsal visual pathway by processing both egocentric (body-dependent) and allocentric (body-independent) spatial information (Culham & Kanwisher, 2001; Marshall & Fink, 2001), and by playing a role in selective attention (Behrmann, Geng, & Shomstein, 2004). Cavanna and Trimble (2006) suggest that the integration of those
functions allows the precuneus to play an essential role in shifting attention between targets of attention. For deictic shifting, involvement of the precuneus may be critical for shifting attention between two people: a speaker and a listener. Whitney and colleagues support this view by reporting the involvement of the precuneus in shifting of person, time, location, or action in a narrative comprehension task (Whitney et al., 2009).

Another region that may be involved in deictic shifting is the anterior insula, believed to be a neural substrate of self-awareness (Craig, 2009; Critchley, 2005). The anterior insula exhibits this role in various ways, such as right-lateralized activation for interoceptive signals (temperature: Craig et al., 2000; heartbeat: Critchley et al., 2004; pain: Wager et al., 2005), visual recognition of one’s own face (Devue et al., 2007; Uddin et al., 2005), and subjective feelings (Damasio et al., 2000; Jabbi et al., 2007). By contributing to the intrinsic understanding of one’s own position in the schematic space, the right anterior insula may provide a central axis for self- and other-representations. Thus, interregional communication between the right anterior insula and precuneus might underpin a functional network involved in deictic shifting, computing where one’s self stands in the reciprocal communication with another person.

In summary, we predicted that adults with high-functioning autism would exhibit poorer behavioral performance for deictic shifting in the perspective-taking task. We employed functional connectivity analysis by using fMRI to examine the degree of BOLD signal synchronization between the precuneus and right anterior insula, the postulated underlying neural basis for suboptimal performance of deictic shifting in autism, and expected to observe diminished synchronization. This frontal-posterior network may be supporting interpersonal attention shifting.

Method

Participants

Participants were 15 adults (14 males and one female) with high-functioning autism and 15 matched controls (all males), and all participants were native-English speakers. Both groups were matched for age, Full Scale IQ (FSIQ), Performance IQ (PIQ), and Verbal IQ (VIQ) scores, which were determined by the Wechsler Adult Intelligence Scale Revised (WAIS-R). There were no significant group differences in age or in any of the any of the IQ measures (Table 1).

The diagnosis of autism was determined using the Autism Diagnostic Observation Schedule (ADOS) (Lord et al., 2000) and the Autism Diagnostic Interview-Revised (ADI-R) (Lord, Rutter, & LeCouteur, 1994), supplemented with confirmation by expert clinical opinion. Potential participants with autism were excluded if they had an identifiable cause of autism, such as fragile-X syndrome, tuberous sclerosis, and fetal cytomegalovirus infection. Potential control and autism participants were also excluded if there was evidence of birth asphyxia, head injury, or a seizure disorder. Exclusionary criteria were based on neurologic history and examination, and chromosomal analysis, or metabolic testing, if indicated.

The control participants were community volunteers recruited to match the autism participants on age, FSIQ, race, and socioeconomic status of family of origin, as measured by the Hollingshead method (Hollingshead, 1957). Potential control participants were screened by questionnaire, telephone, face-to-face interview, and observation during screening psychometric tests.

1 All the analyses reported below were repeated with the one female participant in the autism group excluded, and resulted in the same conclusions for all behavioral and fMRI measures.
Table 1

PARTICIPANTS’ CHARACTERISTICS

<table>
<thead>
<tr>
<th></th>
<th>Autism Mean ± SD</th>
<th>Control Mean ± SD</th>
<th>t(28)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>24.7 ± 7.8</td>
<td>24.7 ± 7.7</td>
<td>0.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Full Scale IQ</td>
<td>106.3 ± 10.7</td>
<td>108.7 ± 5.1</td>
<td>0.81</td>
<td>0.43</td>
</tr>
<tr>
<td>Performance</td>
<td>106.9 ± 16.1</td>
<td>107.4 ± 6.1</td>
<td>0.12</td>
<td>0.91</td>
</tr>
<tr>
<td>Verbal IQ</td>
<td>104.4 ± 12.7</td>
<td>108.0 ± 5.8</td>
<td>1.00</td>
<td>0.33</td>
</tr>
<tr>
<td>Handedness</td>
<td>Right: Left 11: 4</td>
<td>14: 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>Male: 14: 1</td>
<td>15:0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Exclusionary criteria, evaluated through these procedures, included current or past psychiatric and neurologic disorders, birth injury, developmental delay, school problems, acquired brain injury, learning disabilities, substance abuse, and medical disorders with implications for the central nervous system or those requiring regular medication. Potential control participants were also screened to exclude those with a family history (in parents, siblings, and offspring) of autism, developmental cognitive disorders, affective disorders, anxiety disorders, schizophrenia, obsessive compulsive disorder, substance abuse, or other neurologic or psychiatric disorders thought to have a genetic component. Handedness was determined with the Lateral Dominance Examination from the Halstead–Reitan Neuropsychological Test Battery (Reitan, 1985), revealing that four participants in the autism group and one in the control group were left-handed. The brain activation data from these left-handers were clearly similar to their respective groups, and therefore, the data were not separated by handedness.

This study was approved by the Institutional Review Boards of the University of Pittsburgh and Carnegie Mellon University. Participants were recruited from the participant pool of the Collaborative Program for the Autism Centers for Excellence at the University of Pittsburgh.

Experimental Paradigm

For each participant, the stimulus texts were customized to use the participant’s first name, such as John, to refer to the participant in the stimulus sentences (Table 2 & Figure 1). The other character depicted in the pictorial part of the stimuli was referred to as Sarah when a proper name was used. All participants received written instructions from the experimenter and then participated in a practice session to become familiar with the task.

In the perspective-taking task, the participants were asked to generate a response from either a first- (SELF) or second-person (OTHER) perspective. The task was composed of two different scenes (Figure 1): an opened book and a closed book. First, the opened book scene was displayed for 2s, with Sarah (the depicted
### Table 2

#### SUMMARY OF CONDITIONS

**A. MAIN TASK** ("What" Question)

<table>
<thead>
<tr>
<th>Target</th>
<th>Deixis</th>
<th>SHIFT (Pronoun)</th>
<th>FIXED (Name)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SELF (Participant’s view)</td>
<td></td>
<td>“What can you see now?”</td>
<td>“What can John see now?”</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Carrot</td>
<td>House</td>
</tr>
<tr>
<td>OTHER (Depicted person’s view)</td>
<td></td>
<td>“What can I see now?”</td>
<td>“What can Sarah see now?”</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Carrot</td>
<td>House</td>
</tr>
</tbody>
</table>

**B. MANIPULATION CHECK** ("Who" Question)

<table>
<thead>
<tr>
<th>Self (Participant’s view)</th>
<th>Pronoun</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;Who can see the carrot now?&quot;</td>
<td>You can</td>
<td>Sarah can</td>
</tr>
<tr>
<td>&quot;Who can see the carrot now?&quot;</td>
<td>I can</td>
<td>John can</td>
</tr>
</tbody>
</table>

**OTHER (Depicted person’s view) | Pronoun | Name          |
|"Who can see the house now?" | You can | Sarah can     |
|"Who can see the house now?" | I can   | John can     |

**Note.** Examples of experimental conditions when the participant’s name was John. Both tables describe the cases introduced: a picture of ‘house’ on the front cover (right-side) and a picture of ‘carrot’ on the back cover (left-side) are displayed during the 2s of ‘open book,’ while the carrot is displayed on the back cover for 5s when the book is closed (see the Fig. 1). A). Four conditions of the main task with ‘What’ questions. B). Four conditions for the manipulation check with ‘Who’ questions.
In Press, *Brain*

**NEURAL BASIS OF DEICTIC SHIFTING**

Figure 1. A schematic diagram of the experimental stimuli.

person in the scene) holding a book with two objects visible, one on the front and one on the back cover. The depicted objects were vegetables and buildings, and one of four items from each category was shown on either side. The number of appearances for each object was equated. The position (front or back cover) of the object was pseudo-randomized, as well as the pairing of the two objects. This scene acquainted the participant with the two objects involved in the task.

Following the opened book scene, the closed book scene, displayed for 5s, illustrated Sarah holding the book closed, with only one object visible, and a question about the picture with two possible answer choices. The participant could only see one side of the book with one of the two objects, while Sarah was able to see the other side of the book showing the other object. A word balloon read, “What can [the participant (SELF) or Sarah (OTHER)] see now?” The two possible answer choices were displayed on the bottom of the screen, and the participants were instructed to answer by pressing one of the two buttons as quickly and accurately as possible.

The questions were constructed using personal pronouns or proper names. Therefore, there were
two within-subject independent variables: Target (SELF vs. OTHER) and Deixis (SHIFT vs. FIXED), resulting in four conditions: SHIFT-TO-SELF, SHIFT-TO-OTHER, FIXED-SELF, and FIXED-OTHER (summarized in the Table 2A). For example, in the SHIFT-TO-SELF condition, the question was “What can you see now?” The participant had to comprehend that the personal pronoun you referred to him/her (SELF) and select the object that s/he could see. In the SHIFT-TO-OTHER condition, Sarah asked “What can I see now?” The participant had to comprehend that the pronoun I referred to Sarah (OTHER), and select the object that she was facing, but which the participant could not see. For the FIXED conditions, the questions used proper names, such as “What can John see now?” for the SELF condition, and “What can Sarah see now?” for the OTHER condition. These four conditions were pseudo-randomly presented 12 times in two separate blocks of 24 trials.

**Manipulation Check.** In addition, participants answered 48 questions that used a ‘Who’ question form in order to confirm the manipulation for deictic shifting (see the Table 2B). These questions asked who could see a particular object, the participant or Sarah, e.g., “Who can see the carrot now?” The participant indicated an answer using either pronouns or proper nouns: “I can” or “You can,” or “John can” or “Sarah can.” The aim of having two different question forms (‘What’ and ‘Who’) was to compare the conditions with and without deictic shifting (see the details in the Results and Discussion). The ‘Who’ questions were only employed for a manipulation check and were presented separately from the ‘What’ questions. They were excluded from the main analyses. In sum, the participants completed a total of 96 trials throughout the experiment, which alternated between 24-trial blocks of ‘What’ and ‘Who’ questions. After each trial, the participants saw a fixation “X” in the middle of the screen for 6s, with instructions to fixate on the “X” while relaxing their minds and waiting for the next question.

**Data Acquisition**

The scanning was conducted on a 3.0T Siemens Allegra scanner at the Brain Imaging Research Center (BIRC), jointly owned by Carnegie Mellon University and the University of Pittsburgh. Activation was measured using BOLD contrast. The stimuli were rear projected onto a semi-translucent plastic screen, and participants viewed the screen through a mirror attached to the head coil. The study was performed with a gradient echo, EPI sequence with TR = 1000 ms, TE = 30 ms, and a 60° flip angle. Seventeen oblique-axial slices were acquired; each slice was 5-mm thick with a gap of 1-mm between slices. The acquisition matrix was 64×64 with 3.125-mm×3.125×5-mm voxels.

**fMRI Analyses**

The data were analyzed using SPM2. Images were corrected for slice acquisition timing and head motion, and were normalized to the Montreal Neurological Institute (MNI) template, resampled to 2 x 2 x 2 mm voxels, and smoothed with an 8-mm Gaussian kernel to decrease spatial noise. The time-series data for each participant was high-pass filtered with a 128-sec cutoff to remove low frequency drifts. Statistical analysis was performed on individual and group data by using the general linear model as implemented in SPM2 (Friston et al., 1995). Group analyses were performed using a random-effects model. Within-group and between-group t-maps at p < 0.001 (uncorrected), and an extent threshold of ten 8-mm³ voxels was used.

**Functional Region of Interest (ROI) Definition.** The central analyses focused on the two regions of the self-processing network that we hypothesized to be critically involved in deictic shifting: the precuneus and the right anterior insula. Both functional ROIs (precuneus and right anterior insula) were defined to encompass the main clusters of activation in the group activation map for each group in the overall task versus fixation contrast. The defined centers of the ROIs (in MNI coordinates) were [x = 0, y = -64, z = 50] for the precuneus, and [x = 32, y = 26, z = 6] for the right anterior insula, and the locations were verified with reference to the parcellation of the MNI single subject T1-weighted dataset carried out by
Tzourio-Mazoyer and colleagues (Tzourio-Mazoyer et al., 2002). A sphere was defined for each cluster with a radius of 12 mm that best captured the cluster of activation in the map for each group.

**Percentage Change in Signal Intensity.** The average percent signal change (PSC) across all voxels in the right anterior insula and precuneus ROIs was computed for participants and each experimental condition relative to the fixation condition. The mean PSC of the eight images acquired with an offset of 5s from the stimulus onset (to account for the delay in hemodynamic response) is reported. These averaged data for each participant were submitted to separate mixed Analyses of Variance (ANOVAs) for each ROI. For these ROI-based analyses, effects were considered significant at \( p < 0.05 \) (uncorrected).

**Functional Connectivity.** The functional connectivity was computed (separately for each participant) as a correlation between the average time course of signal intensity of all the activated voxels of ROIs. The activation time-course extracted for each participant over the activated voxels within each ROI originated from the normalized and smoothed images, which were high-pass filtered and had the linear trend removed. One participant in the control group who did not have activation in a given functional ROI was excluded from further analysis involving that ROI. The functional connectivity correlation was computed on the images belonging only to the experimental conditions, so it reflects the synchronization of the activation between two areas while the participant is performing the task and not during the baseline condition. Fisher’s \( r \) to \( z \) transformation was applied to the correlation coefficients for each participant prior to averaging and statistical comparison of the two groups. The transformed values for each participant were submitted to mixed ANOVAs and effects were considered significant at \( p < 0.05 \).

In order to assess the robustness of any group differences in functional connectivity, two anatomical ROIs were also defined, based on peak activations reported in previous relevant self-processing experiments (for the precuneus: Farrer & Frith, 2002; Frings et al., 2006; Ruby & Decety, 2001; Vogeley et al., 2004; Whitney et al., 2009; Zaehle et al., 2007; and for the right anterior insula: Craig et al., 2000; Critchley et al., 2004; Damasio et al., 2000; Devue et al., 2006; Uddin et al., 2005). The criteria for these two anatomical ROIs were that they encompass the targeted anatomical regions comprehensively (capturing all of the activation therein), yet exclusively (excluding neighboring anatomical areas). In order to restrict the insula ROI to the anterior segment, peak-activations located posterior to \( y = 0 \) in MNI space were excluded from the calculation to determine the centroid (Craig, 2010). The average reported peak-activations of these studies were \([x = 0, y = -62, z = 54]\) for the precuneus, and \([x = 36, y = 20, z = 8]\) for the anterior insula. A sphere was defined around each of the centroids, and then further refined by masking out adjacent cortical and subcortical regions using anatomical ROIs defined by Tzourio-Mazoyer et al. (2002), in order to limit the spherical ROIs exclusively to the precuneus and anterior insula. For the precuneus, this involved removal of anterior somatosensory association cortex (BA 5), and for the right anterior insula, this involved removal of areas identified as the caudate, putamen, lateral inferior frontal cortex, and the posterior insula. In order to approximately equate the total volume of the two ROIs after removal of adjacent cortical and subcortical areas, an initial sphere with a radius of 14 mm was used for the precuneus, and one with a radius of 18 mm was used for the right anterior insula (where the activation volume was larger).

**Results**

**Overview**

Behavioral and neural activation measures provided converging evidence of the autism group’s greater difficulty in conditions involving deictic shifting. First, participants with high-functioning autism showed reliably slower and less accurate responses than the control group for the items requiring a deictic shift (SHIFT) compared to items using a fixed label (FIXED). Second, these slower and less accurate responses of the autism group were accompanied by lower functional connectivity between the right anterior insula and
precuneus only for the SHIFT condition. Functional connectivity was reliably greater for the SHIFT than FIXED condition among controls, suggesting that the autism group failed to show a typical adaptive change of insula-precuneus communication. In addition, activation in the right anterior insula was significantly greater for the SHIFT than FIXED conditions only in the autism group. Further analyses indicated that underconnectivity between the right anterior insula and precuneus was observed when transforming you to I (SHIFT-TO-SELF), but not when transforming I to you (SHIFT-TO-OTHER), and that activation in the precuneus did not change between these two conditions in the autism group, but was significantly lower for the SHIFT-TO-SELF than the SHIFT-TO-OTHER conditions in the control group. Finally, for the SHIFT-TO-SELF condition, only the autism group showed a reliable positive correlation between right anterior insula-precuneus functional connectivity and verbal IQ, and a negative correlation between right anterior insula-precuneus functional connectivity and reaction time. All the analyses of functional connectivity above were repeated using the anatomical ROIs, and the results remained the same.

**Behavioral Results**

**Response time.** The results supported the hypothesis that deictic shifting should slow the response time of autism participants more than control participants. A 2 (Group: Autism, Control) by 2 (Deixis: SHIFT, FIXED) by 2 (Target: SELF, OTHER) mixed ANOVA showed an interaction for Group and Deixis \( F(1,28) = 6.46, p = 0.02 \), as expected (Figure 2A), along with the main effects of Deixis (Deixis taking longer than the FIXED condition), \( F(1,28) = 47.99, p < 0.01 \) and Target (slower for SHIFT-TO-OTHER relative to SHIFT-TO-SELF) \( F(1,28) = 33.76, p < 0.01 \). Additional tests of the simple effect of Group within level of Deixis yielded a marginally slower response for the Autism group (2593 ms) relative to the Control group (2295 ms) in the SHIFT condition \( F(1,28) = 3.28, p = 0.08 \), but no group difference in the FIXED condition \( p = 0.35 \). Thus, the Group by Deixis interaction resulted from a relatively greater disadvantage among participants with autism when the task required processing a deictic shift, but not when the task used proper names.

**Accuracy.** The accuracy scores showed a very similar pattern to the response times. Both groups responded less accurately for SHIFT relative to FIXED and for OTHER relative to SELF. A 3-way ANOVA yielded a Group by Deixis interaction \( F(1,28) = 11.05, p < 0.01 \), a main effect of Deixis \( F(1,28) = 6.32, p = 0.02 \), and a main effect of Target \( F(1,28) = 22.48, p < 0.01 \). Tests for the simple main effect of Group within level of Deixis indicated that accuracy was reliably lower for the Autism group relative to the Control group in the SHIFT \( F(1,28) = 5.12, p = 0.03 \) but not in the FIXED condition, and tests for the simple main effect of Deixis within each group showed that accuracy was reliably lower for SHIFT (0.91) than FIXED (0.97) in the Autism group \( F(1,14) = 12.84, p < 0.01 \). The accuracy results again indicate that the Autism group had more difficulty with deictic shifting than controls.

**Manipulation check for deictic shifting.** Increased processing requirements associated with deictic shifting are postulated to be the cause of pronoun reversals (Dale & Crain-Thoreson, 1993). To compare the groups’ performance in the absence of a deictic shift, a control condition used a *Who* question form, with pronouns and names (Table 2B), to probe the understanding of the depicted situation (who can see what) without requiring any deictic shift. In this manipulation check, the use of pronouns per se should impose no greater burden on the Autism group than on the Control group, so that no Group (Autism, Control) by Label (Pronoun, Name) interaction would be expected.
Supporting this, the 2-way ANOVAs for the Who questions conducted for both reaction time and accuracy revealed no reliable interaction between these factors (Figure 2B). (For completeness, we report that the three-way ANOVAs [Group (Autism, Control) by Question (What, Who) by Label (Pronoun, Name)] show significant three-way interactions for reaction time \( F(1,28) = 6.58, p = 0.02 \) and accuracy \( F(1,28) = 9.89, p < 0.01 \), resulting from the difference between the What and Who conditions. Figure 2 displays the reaction time data for both conditions). Thus, the observed increase in reaction time and decreased accuracy for What questions in the main conditions with pronouns (SHIFT), compared to those with names (FIXED), is consistent with the contention that the poorer performance in pronoun use in the Autism group was due to deictic shifting.

fMRI Results

**Activation distribution.** The two groups showed similar cortical activation locations (Table 3). Both groups showed a large activation cluster in posterior cortical regions, extending from the occipital cortex to the posterior parietal lobule, and including the precuneus, inferior parietal lobule, posterior middle temporal gyrus, inferior temporal gyrus, and cerebellum. Although frontal activation in the right hemisphere was similar for both groups, the Autism group exhibited more activation in the left frontal cortex. A direct group comparison indicated that the Autism group exhibited significantly greater activation in the right frontal and parietal areas; however, there was no area which showed greater activation for the Control group than the Autism group. In addition to these whole brain analyses with uncorrected \( p < 0.001 \),
Table 3

Areas of activation for the contrasts of all task conditions minus fixation

**CONTROL**

<table>
<thead>
<tr>
<th>Region</th>
<th>Cluster size</th>
<th>$t$(14)</th>
<th>MNI Coordinates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occipital/Inferior Parietal/Superior Parietal/Inferior Temporal/Middle Temporal/Cerebellum</td>
<td>45755</td>
<td>16.91</td>
<td>-26 -62 42</td>
</tr>
<tr>
<td>R Middle Frontal (BA9)</td>
<td>121</td>
<td>6.08</td>
<td>50 34 36</td>
</tr>
<tr>
<td>Anterior Cingulate (BA32)</td>
<td>162</td>
<td>5.97</td>
<td>12 22 38</td>
</tr>
<tr>
<td>R Insula (BA13)</td>
<td>565</td>
<td>5.91</td>
<td>20 30 6</td>
</tr>
<tr>
<td>R Superior Frontal (BA10)</td>
<td>34</td>
<td>5.38</td>
<td>40 60 -2</td>
</tr>
<tr>
<td>R Middle Frontal/Precentral (BA6)</td>
<td>109</td>
<td>4.98</td>
<td>36 4 62</td>
</tr>
<tr>
<td>R Amygdala</td>
<td>57</td>
<td>4.62</td>
<td>30 0 -12</td>
</tr>
<tr>
<td>R Middle Frontal (BA10)</td>
<td>13</td>
<td>4.62</td>
<td>34 58 26</td>
</tr>
<tr>
<td>R Middle Frontal (BA6)</td>
<td>19</td>
<td>4.44</td>
<td>24 -12 40</td>
</tr>
</tbody>
</table>

**AUTISM**

<table>
<thead>
<tr>
<th>Region</th>
<th>Cluster size</th>
<th>$t$(14)</th>
<th>MNI Coordinates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occipital/Inferior Parietal/Superior Parietal/Inferior Temporal/Middle Temporal/Cerebellum</td>
<td>43906</td>
<td>16.53</td>
<td>-34 -56 -32</td>
</tr>
<tr>
<td>L Middle Frontal/Precentral (BA6/9)</td>
<td>2536</td>
<td>9.26</td>
<td>-34 6 64</td>
</tr>
<tr>
<td>R Middle Frontal/ Precentral (BA6/9)</td>
<td>1282</td>
<td>7.01</td>
<td>34 4 66</td>
</tr>
<tr>
<td>Posterior Cingulate</td>
<td>357</td>
<td>6.14</td>
<td>-2 -36 24</td>
</tr>
<tr>
<td>R Superior Frontal (BA10)</td>
<td>42</td>
<td>5.51</td>
<td>40 60 2</td>
</tr>
<tr>
<td>R Inferior Frontal (BA45)</td>
<td>72</td>
<td>5.19</td>
<td>56 32 28</td>
</tr>
<tr>
<td>L Superior Frontal (BA10)</td>
<td>18</td>
<td>4.75</td>
<td>-20 60 0</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>18</td>
<td>4.37</td>
<td>-54 -26</td>
</tr>
<tr>
<td>R Insula (BA13)</td>
<td>26</td>
<td>4.33</td>
<td>36 26 -4</td>
</tr>
<tr>
<td>R Middle Frontal (BA46)</td>
<td>22</td>
<td>4.32</td>
<td>32 34 24</td>
</tr>
<tr>
<td>R Caudate</td>
<td>13</td>
<td>4.30</td>
<td>14 16 20</td>
</tr>
<tr>
<td>R Middle Frontal (BA10)</td>
<td>13</td>
<td>4.18</td>
<td>34 50 16</td>
</tr>
<tr>
<td>L Caudate</td>
<td>26</td>
<td>4.10</td>
<td>-10 12 24</td>
</tr>
<tr>
<td>L Postcentral</td>
<td>10</td>
<td>3.92</td>
<td>-54 -18 22</td>
</tr>
</tbody>
</table>
Table 3 (continued)

**AUTISM > CONTROL**

<table>
<thead>
<tr>
<th>Region</th>
<th>Cluster size</th>
<th>t(14)</th>
<th>MNI Coordinates</th>
</tr>
</thead>
<tbody>
<tr>
<td>R Middle Frontal/Precentral/Postcentral (BA 6/4/3)</td>
<td>467</td>
<td>4.67</td>
<td>44 -18 60</td>
</tr>
<tr>
<td>R Postcentral (BA 5)</td>
<td>45</td>
<td>4.41</td>
<td>44 -44 60</td>
</tr>
<tr>
<td>R Precuneus (BA 19)</td>
<td>12</td>
<td>4.04</td>
<td>22 -86 38</td>
</tr>
<tr>
<td>Post Cingulate</td>
<td>28</td>
<td>3.97</td>
<td>-6 -36 28</td>
</tr>
<tr>
<td>R Posterior Middle Temporal (BA 21)</td>
<td>11</td>
<td>3.92</td>
<td>58 -48 -8</td>
</tr>
<tr>
<td>R Middle Frontal (BA 6)</td>
<td>64</td>
<td>3.92</td>
<td>38 10 36</td>
</tr>
</tbody>
</table>

*Note.* The threshold for significant activation was $p < 0.001$ for a spatial extent of at least 10 voxels, uncorrected for multiple comparisons. Region labels apply to the entire extent of the cluster. T-values and MNI coordinates are displayed for the peak activated voxel in each cluster. For group comparison, there was no area which showed greater activation for the control group than the autism group.

...in multiple comparisons based on Gaussian random field theory across all voxels $p = 0.01$, only one cluster in each group survives a family-wise error (FWE) correction [Autism: cerebellum $(x=-32, y=-56, z=-32)$; Control: left hippocampus $(x=-24, y=-32, z=-2)$], and none of the clusters survived, even with a more liberal threshold ($p = 0.05$, FWE) for the group comparison. Additionally, no contrasts between experimental conditions showed significant differences in either group at this threshold.

**Signal change in precuneus.** A three-way (Group by Deixis by Target) mixed ANOVA yielded a marginally significant main effect for Target [$F (1,28) = 3.78, p = 0.06$], such that the mean PSC in the precuneus was marginally greater for OTHER (0.38) than for SELF (0.32), and there was a reliable three-way interaction [$F (1,28) = 5.21, p = 0.03$]. However, no significant interaction between Group and Deixis was found [$F (1,28) = 1.21, p = 0.28$] (Figure 3A), indicating that both groups exhibited similar precuneus activation overall for the SHIFT condition relative to the FIXED conditions.

The three-way interaction was explored by examining the simple Group by Target interactions within each Deixis condition (SHIFT and FIXED), and a significant interaction was found only for the SHIFT condition [$F (1,28) = 6.54, p = 0.02$] (Figure 4A). Tests of the main effect of Target within each group showed that the mean PSC in the precuneus reliably increased when the shift was to the other person (SHIFT-TO-OTHER) (0.39), relative to the shift to the self (SHIFT-TO-SELF) (0.26), only in the Control group [$F (1,14)=10.57, p < 0.01$], as shown as in Figure 4A. Whereas the controls showed significantly lower PSC in precuneus for SHIFT-TO-SELF relative to SHIFT-TO-OTHER, there was little difference between SHIFT-TO-SELF and SHIFT-TO-OTHER for the Autism group.

**Signal change in right anterior insula.** A similar three-way mixed ANOVA was conducted for the PSC of the right anterior insula. This analysis yielded a reliable Group by Deixis interaction [$F (1,28) = 4.80, p = 0.04$], and tests of the simple main effect of Deixis condition within each group revealed significantly greater mean PSC in the right anterior insula for SHIFT compared to FIXED only in the Autism group, as seen in Figure 3B [Autism: SHIFT (0.14) > FIXED (0.09), $F (1,14) = 7.27, p = 0.02$; Control: $F (1,14) = 0.15, p = 0.71$]. The simple main effect
Figure 3. FIXED vs. SHIFT. Percent signal change (PSC) in the precuneus (A) and right anterior insula (B). Functional connectivity between the right anterior insula and precuneus (C). The error bars represent the 95% confidence interval for the within-subject effect in each condition. The picture in the middle indicates the location of the ROI (radius= 12 mm) for the precuneus [0, -64, 50] and right anterior insula [32, 26, 6] on the MNI coordinates.
Figure 4. SHIFT-TO-SELF vs. SHIFT-TO-OTHER. Percent signal change (PSC) in the precuneus (A) and right anterior insula (B). Functional connectivity between the right anterior insula and precuneus (C). The error bars represent the 95% confidence interval for the within-subject effect in each condition.
of Group within each Deixis condition yielded a trend of greater PSC in the Autism group than the Control group only for the SHIFT condition \([F (1,28) = 3.09, p = 0.09]\).

Additional tests of the simple Group by Target interaction for each Deixis condition were not significant, and there was only a marginal simple main effect of the Group for the SHIFT condition \([F (1,28) = 3.24, p = 0.09]\) (see Figure 4B). Therefore, these results indicate that the activation in the right anterior insula tended to be greater in autism than in controls for both Targets of the SHIFT condition (SHIFT-TO-SELF and SHIFT-TO-OTHER).

**Functional Connectivity.** As predicted, underconnectivity between the right anterior insula and precuneus in autism was observed for deictic shifting, particularly when answering about oneself. A 2 (Group) by 2 (Deixis) by 2 (Target) mixed ANOVA was conducted on these functional connectivity measures, and the results showed a significant Group by Deixis interaction \([F (1,27) = 4.92, p = 0.04]\). Tests of the simple main effect of Group within each Deixis condition indicated significantly reduced functional connectivity in Autism (0.41), relative to Controls (0.58), for the SHIFT condition \([F (1,27) = 4.27, p = 0.05]\). In addition, the simple effect of Deixis was reliable only in the Control group, with increased functional connectivity for the SHIFT compared to the FIXED condition \([F (1,13) = 5.44, p = 0.04]\) (see Figure 3C).

There was also a reliable three-way interaction for the functional connectivity between the right anterior insula and precuneus \([F (1,27) = 8.18, p < 0.01]\). Tests of the simple effect of Target conditions, when a deictic shift was required, showed reliably lower functional connectivity in the Autism group (0.39) than in the Control group (0.63) only for questions in the SHIFT-TO-SELF conditions (i.e., with the pronoun you) \([F (1,27) = 6.68, p = 0.02]\), and not in the SHIFT-TO-OTHER condition (i.e., with the pronoun I) \([F (1,27) = 1.16, p = 0.29]\). Tests of the simple effect of Target for trials requiring a shift within each group, indicated a trend of increased functional connectivity for the SHIFT-TO-SELF condition compared to the SHIFT-TO-OTHER condition in the Control group \([F (1,13) = 3.35, p = 0.09]\), and no difference between those conditions in the Autism group \([F (1,14) = 0.80, p = 0.39]\). These results, displayed in Figure 4C, suggest that the Autism group failed to exhibit an adaptive increase of functional connectivity between the right anterior insula and precuneus in the SHIFT-TO-SELF condition relative to the SHIFT-TO-OTHER condition.

**Correlation between Functional Connectivity and Verbal IQ.** Among the participants with autism, the functional connectivity between the right anterior insula and precuneus during the SHIFT-TO-SELF (What can you see now?) condition was positively correlated with VIQ \((r = 0.66, t(14) = 3.17, p < 0.01)\), as shown in Figure 5, whereas the correlation was not significant in the Control group \((r = 0.31, t(13) = 1.18, p = 0.26)\). Although both groups exhibited a positive correlation that did not differ statistically \((z = 1.13, p = 0.26)\), inspection of the data indicated that the positive relationship among controls was due to one participant with low VIQ and a negative functional connectivity score. When this outlier was removed from the Control group, the moderate positive correlation disappeared \((r = -0.04, t(12) = -0.13, p = 0.45)\), and there was a significant difference between correlations of the two groups \((z = 1.95, p = 0.05)\). Thus, the significant correlation in the Autism group indicates that the participants with autism who exhibit greater functional connectivity between the right anterior insula and precuneus, when the task required deictic shifting to refer to oneself, tended to have higher language skill (indicated by high VIQ scores). Other psychometric measures (FSIQ, PIQ, and ADOS scores) did not show a significant correlation with the functional connectivity for either group.

**Correlation between Functional Connectivity and Reaction Time.** Among the participants with autism, the functional connectivity between the right anterior insula and precuneus during the SHIFT-TO-SELF (What can you see now?) condition showed a significant correlation with reaction time \((r = -0.51, t(14) = -2.14, p = 0.03)\), as shown in Figure 6, whereas the correlation was not significant in the Control
Figure 5. Scatterplot showing that for the autism group, Verbal IQ (VIQ) increased as the functional connectivity between the right anterior insula and precuneus increased.
Figure 6. Scatterplot showing that for the autism group, reaction time for the SHIFT-TO-SELF condition (What can you see now?) decreased as the functional connectivity between the right anterior insula and precuneus increased.
group \( (r = 0.18, t(13) = 0.63, p = 0.27) \), (and there was a significant difference between correlations of the two groups \( z = 1.78, p = 0.04 \)). Thus, the correlation in the Autism group indicates that the participants with autism who had lower functional connectivity between the right anterior insula and precuneus tended to show a slower response when the task required deictic shifting to refer to oneself.

**Discussion**

The aim of the study was to evaluate behavioral performance and compare neural activity between adults with high-functioning autism and neurotypical adults during deictic shifting (updating the relationship of generated and referred agents) in a perspective-taking task. The primary finding was diminished functional connectivity between the right anterior insula and precuneus in autism when the task required deictic shifting. Although the functional connectivity between two neural nodes was lower during a deictic shift in autism, the activation of the frontal node of the network, the right anterior insula, was increased relative to when the task used fixed labels of people (i.e., proper names). Another contribution of the present study was that the functional connectivity of the same neural network was particularly low when recognizing *you* as referring to the self in autism. Activations of the posterior neural node, the precuneus, in autism, were similar for both directions of deictic shifting (transforming *you* to *I* for referencing one’s self, and *I* to *you* for referencing the other person), although the control participants’ activations were greater for the referencing to self relative to the other person. These findings extend the previously postulated frontal-posterior underconnectivity theory in autism (Just *et al.*, 2007) by providing evidence for the near-absence of the relevant functional network, with an atypical reliance on a local neural resource in autism, possibly indicating compensatory processing.

**Frontal-Posterior Network for Deictic Shifting**

The present study focused on a cortical network involving the right anterior insula and the precuneus for several reasons. First, the posterior node, the precuneus, comprises part of the dorsal visual stream and plays a critical role in spatial information processing (Haxby *et al.*, 1991), and Culham and colleagues (1998) reported activation in the precuneus for mental navigation of a moving object, indicating an involvement of the area for tracking/shifting spatial attention. Further investigations have revealed that the attention shift function of the precuneus is not limited to spatial information (Nagahama *et al.*, 1999), and is modality-independent (Cavanna & Trimble, 2006; Shomstein & Yantis, 2006). The precuneus may contribute to deictic shifting processes by updating the anchor of a speech act from self-to-other and from other-to-self.

Second, emerging evidence suggests that the right anterior insula is involved in self-awareness and self-consciousness (Craig, 2009). The anterior insula is also believed to mediate integration of internally-oriented information and externally-derived processing (Sridharan *et al.*, 2008). Uddin and Menon (2009) proposed that there is dysfunctional connectivity of the anterior insula in autism, lowering its ability to play the role of a network hub. For deictic shifting in the perspective-taking task, the right anterior insula may provide an axis on which to position oneself on a representational map of self-and-other relationships by being involved in internally-oriented information processing. The observed lower functional connectivity between those two neural nodes in the autism group, therefore, may result in disturbed perspective-taking processes in shifting a center of reference between self and other (Tager-Flusberg, 1990, 1994), based on an understanding of where one stands in a given moment or situation. Elevated activation of the right anterior insula during deictic shifting in the autism group (Figure 3) suggests that this process was more effortful (showing more activation) in autism.

On the other hand, when deictic shifting was not required (i.e., when both the depicted person and the participant were directly referred to by proper name), underconnectivity of the network in autism was not observed. Atypical overreliance on a particular noun expression, as reflected by diminished employment of personal pronouns, has
been reported in autism (Lee, Hobson, & Chiat, 1994; Cole et al., 2009). The present study employed a paradigm similar to that of Lee, Hobson, and Chiat (1994), and in addition to providing congruent behavioral results, it also suggests that diminished frontal-posterior network bandwidth may restrict deictic shifting processes, resulting in an inappropriate preference of proper names (a fixed label referring to a person regardless of who generated the speech).

**Egocentrism and Autism: Mapping Self onto the Pronoun ‘I’**

Another important finding of the present study was the atypical neural activity for transforming the pronoun you to I (SHIFT-TO-SELF: What can you see now?) in autism, relative to I to you (SHIFT-TO-OTHER: What can I see now?). For the transformation of you to I, the autism group showed atypically elevated activation of the precuneus (Figure 4A) and diminished functional collaboration with the right anterior insula (Figure 4C). On the other hand, there was no group difference in precuneus activation and its functional connectivity with the right anterior insula when reversing in the other direction (i.e., I to you, as in What can I see now?). In order to answer this question, the participant could determine that the pronoun I referred to the experimenter independently from one’s own representational position. These findings indicate that the critical disturbance in the successful operation of deictic shifting in autism may be dysfunctional processing when recognizing the self as a referent of you, and shifting to map self onto the pronoun I. An observed positive correlation between functional connectivity and verbal IQ (Figure 5), and a negative correlation between functional connectivity and reaction time in autism (Figure 6), may also indicate that diminished interregional synchronization between the right anterior insula and precuneus restricts the neural communication underlying the shift of a deictic center from another person to oneself. Furthermore, the present study did not require participants to utter their responses, but pronoun reversals in autism may entail the same underlying basis and reflect a consequence of unsuccessful reversal, resulting in producing an overt utterance of you (e.g., saying “You can see the carrot” when expressing that the participant him/herself is able to see the carrot).

The recent fMRI studies of self- and other-representation in autism provide complementary evidence: a greater group difference in brain activity has been found for self-related processing relative to other-related (Chiu et al., 2008; Lombardo et al., 2009). Therefore, as suggested by Frith and de Vignemont (2005), idiosyncratic egocentrism in autism may be characterized as dysfunction of representing the external world on the basis of understanding its relation to oneself. Pronoun reversals in autism may reflect a disturbed processing of understanding of self and other in the reciprocal relationship, rather than a semantic error to adjust pronominal forms.

**Limitations**

The reported underconnectivity in autism in the present study was derived from measures of synchronization of activation between the right anterior insula and precuneus, but did not include measures of white matter tissues that provide anatomical connectivity (which can be measured by Diffusion Tensor Imaging [DTI]). DTI studies in autism have previously reported reduced white matter integrity (Barnea-Goraly, et al., 2004; Keller, Kana, & Just, 2007). Further investigation of the white matter tracts connecting the right anterior insula and precuneus may enhance our understanding of the perspective-taking issues in autism.

**Conclusion and Future Directions**

Over six decades ago, Kanner (1946) documented unique referential expressions with personal pronouns, referred to as pronoun reversals, among young individuals with autism. The current state of the art tool, fMRI, allowed us to assess the underlying neural basis of deictic shifting as a critical component of pronoun reversals, and found an elevated level of neural activity with lower coordination of relevant brain centers. Pronoun reversals are described as idiosyncratic language impairment in autism, but the findings suggest that they may also characterize an atypical
understanding of the social world because deictic shifting is embedded in understanding the self- and other- relationship, which requires the recognition of the self-stance relative to the other’s existence. MacWhinney (2005) advocates this view by emphasizing the significance of the ability to flexibly shift the viewpoint in social communication in stating that “perspective-taking is at the very core of language structure and higher-cognition” (p.198). If the system of perceiving an external world were rooted in the understanding of self-stance, dysfunction of the system would affect not only interpersonal interactions but also intrapersonal cognitive states, such as memory, temporal and spatial mental navigation, and Theory of Mind, all possibly sharing a common neural basis (Spreng et al., 2009). Although our findings may be limited to the disturbed fundamental understanding of self and other among individuals in autism, such disturbances are apparent in many different tasks, such as difficulty with motor mirroring between self and other that may result from mirror neuron system dysfunction (Dapretto et al., 2005; Williams et al., 2008), as well as problems with more abstract cognitive self- and other- representations, possibly resulting from atypical cingulate activation that is associated with an altered default-mode system (Chiu et al., 2008; Lombardo, 2009). In particular, the frontal portion of the system, including medial prefrontal and anterior cingulate cortex, has shown activation for both self- and other-processing in the neurotypical population across different domains (Gillhan & Farah, 2005). An investigation of a potential differential involvement and an interaction of the medial frontal regions and insula for self-related processing and social cognition in autism, could enhance our understanding of this neurodevelopmental disorder. Furthermore, it may be useful for future investigations to examine the neural bases of various coordinate systems within which the various aspects of the world are mentally represented in autism and control groups. These coordinate systems include space (here/there), time (now/then), memory (semantic/episodic), referential frame (egocentrism/allocentrism), and meta-representation or ToM (self/other).

Acknowledgements

This research was supported by the Pre-Doctoral Fellowship 4868 from the Autism Speaks Foundation awarded to Akiko Mizuno, and the Autism Center of Excellence Grant HD055748 from the National Institute of Child Health and Human Development.

We would like to express our sincere appreciation to the individuals and families who generously gave their time and courage to participate in this research. We also appreciate the assistance of the members of the Center of Cognitive Brain Imaging, particularly Kara Cohen and Jennifer Moore for editorial comments on the manuscript.

Correspondence concerning this article should be addressed to Akiko Mizuno, Center for Cognitive Brain Imaging, Department of Psychology, Carnegie Mellon University, Pittsburgh, PA 15213 or e-mail: amizuno@andrew.cmu.edu

References


Hollingshead AA. Four-factor index of social status. Unpublished manuscript. Yale University, New Haven, CT. 1957.


Kana RK, Keller TA, Minshew NJ, Just MA. Inhibitory control in high-functioning autism: Decreased activation and underconnectivity in inhibition networks. Biol Psychiatry 2007;
In Press, Brain

Marshall JC, Fink GR. Spatial cognition: where we were and where we are. Neuroimage 2001; 14(1):S2-7.
Tager-Flusberg H. Dissociations in form and function in the acquisition of language by


