Specialization of right temporo-parietal junction for mentalizing and its relation to social impairments in autism

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A hallmark of autism spectrum conditions (ASC) are marked impairments in reciprocal social interaction. At the cognitive level, one theory that can help explain such difficulties is the "mindblindness" theory of autism (Baron-Cohen, 1995; Frith, 2001). Mindblindness makes three predictions about the mechanisms involved in social-communication difficulties in autism spectrum conditions (ASC). In this study, we show that one of the neural systems responsible for mindblindness in ASC and its relation to social impairments is the right temporo-parietal junction (RTPJ). Twenty-nine adults with ASC and 33 age and IQ-matched Controls were scanned with fMRI while making reflective mentalizing or physical judgments about themselves or another person. Regions of interest within mentalizing circuitry were examined for between-group differences inactivation during mentalizing about self and other and correlations with social symptom severity. RTPJ was the only mentalizing region that responded atypically in ASC. Understanding the contribution of RTPJ in conjunction with other neural systems responsible for other component processes involved in social cognition will be illuminating in fully explaining the hallmark social-communication difficulties of autism.

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judging whether the experimenter was being helpful or unhelpful (Gilbert et al., 2009), judging trustworthy from faces (Pinkham et al., 2008), and making introspective emotion judgments versus judging the color of pictures (Silani et al., 2008). This wide variability may account for some of the lack of consistency across studies. The most replicable result appears to be hypoactivation of the dorsomedial prefrontal cortex (dMPFC) (Castelli et al., 2002; Happé et al., 1996; Kana et al., 2009; Kennedy and Courchesne, 2008; Silani et al., 2008; Wang et al., 2007). However, because of the marked variability amongst tasks it is hard to explain why other studies did not observe the same effect (Baron-Cohen et al., 1999; Gilbert et al., 2009; Mason et al., 2008; Pinkham et al., 2008; Tesink et al., 2009; Wang et al., 2006). Finally, with respect to tasks, it is not always apparent that the task used in any individual study can elicit engagement of all regions within the standard mentalizing circuit; that is, medial prefrontal cortex (MPFC), posterior cingulate cortex/precuneus (PCC), and bilateral temporo-parietal junction (RTPJ, LTPJ) (e.g., Amodio and Frith, 2006; Frith and Frith, 2003; Jenkins and Mitchell, 2010; Saxe and Powell, 2006; Saxe et al., 2009)). This point is particularly important, because without a task that can elicit engagement of various regions within the mentalizing circuit in the comparison group, it is hard to tell whether these areas would have been sensitive to any real impairments if given a sensitive enough task. It is also particularly noteworthy that sample sizes of existing studies tend to be relatively low (range=5–24; mean Control n=14.72; mean ASC n=14.63) and that not all studies directly investigate whether atypical neural systems involved in mentalizing relate to variation on clinical measures of social impairment.

Acknowledging these difficulties is an important first step if we are to attempt to gain a clearer understanding of which neural systems are specifically implicated in “mindblindness” in ASC. It is important that we do this because there are likely to be many component processes affecting the phenotypic variability in autistic social impairment (e.g., mindblindness, self-referential processes, face-processing, emotion, etc.) (Lombardo and Baron-Cohen, 2011, 2010; Lombardo et al., 2011). By identifying specific neural systems that can account for these component processes (mindblindness being one of these component processes) we are in a better position to shed insight into the mechanisms that lead to autism (Happé et al., 2006; Lombardo et al., 2011).

In this study we directly address the main three predictions of mindblindness in ASC; that is, which neural systems are responsible for the domain-specific impairments in representing mental state information, whether deficits are observed across both self and other, and how (if at all) does the atypical functioning of these neural systems relate to variation on clinical measures of social impairment? We employ a mentalizing task known to elicit robust activation of the mentalizing circuit across both self and other in the general population (Lombardo et al., 2010b) and which is constrained to being selective to the demands of representing mental state information while holding constant semantic and social judgment demands and controlling for the target for which the judgment is about (self or other). Furthermore, our sample size is double that of the average sample size observed in existing studies, thus increasing statistical power to detect more subtle effects. Finally, we directly investigate whether any atypical neural systems involved in mentalizing are related variation on clinical measures of social impairment.

We predict that areas known to be involved in mentalizing, such as bilateral TPJ, PCC, and MPFC (Mitchell et al., 2005; Saxe and Kanwisher, 2003; Saxe and Powell, 2006; Saxe et al., 2009), would be less selective for representing mental state information in ASC. Furthermore, this decreased specialization for mentalizing should be a main effect of mentalizing and generalize across self and other, rather than being target-specific. Finally, decreased specialization for mentalizing should be associated with variation on clinical measures of reciprocal social impairment.

### Materials and methods

#### Participants

Thirty-three typical adult males (mean age 27.97 years±6.10 SD, range 18–42) and 33 male adults with ASC (mean age 26.59 years±7.04 SD, range 18–41) participated in this study. Both groups were matched on age and all subscales of the Wechsler Abbreviated Scales of Intelligence (Weschler, 1999) (see Table 1). ASC participants were all clinically diagnosed by ICD-10 criteria as Asperger syndrome (ICD-10, 1994). The Toronto Alexithymia Scale (Bagby et al., 1994), Autism Spectrum Quotient (AQ) (Baron-Cohen et al., 2001), Autism Diagnostic Interview-Revised (ADI-R) (Lord et al., 1994), and module 4 of the Autism Diagnostic Observation Schedule (ADOS) (Lord et al., 2000) were administered to participants before the fMRI session. Diagnosis was confirmed for 30/33 participants on the ADI-R. The remaining three participants who were subthreshold on the ADI-R were 1 point below the cut-off on the Repetitive Behavior domain. However, these participants were included since they met ADOS criteria, scored above the cut-off of 26 on the Autism Spectrum Quotient (AQ) (Woodbury-Smith et al., 2005), and were diagnosed by experienced clinicians. Due to movement artifact (3 ASC participants) and stimulus delivery equipment malfunction (1 ASC participant), data for 4 ASC participants were excluded, and the remaining 29 ASC participants were reported in all subsequent analyses. See Table 1 for participant characteristics. Informed consent was obtained for all participants in accordance with procedures approved by the Suffolk Local Research Ethics Committee. All participants were native English speakers with normal or corrected vision and were right-handed. Activation analyses from this cohort have been previously reported elsewhere (Lombardo et al., 2010b). However, the specific comparisons reported in this paper regarding between-group differences in mentalizing contrasts and relationships with social impairments have not been reported previously.

#### Task design

The study design was a 2×2 within-subjects factorial block design where participants were asked to make either reflective “Mentalizing” or “Physical” judgments about two target individuals; the “Self” or a familiar non-close “Other” (the British Queen). For Self-Mentalizing blocks (SM), participants judged on a scale from 1 to 4 (where 1=not at all likely and 4=very likely) how likely they themselves would agree with opinion questions that focused on mental characteristics (e.g., “How likely are you to think that keeping a diary is important”). On Other-Mentalizing blocks (OM), the same mentalizing judgments were made, except this time it was in reference to how the British Queen would agree with the opinion questions (e.g., “How

### Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>Controls</th>
<th>ASC</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>33</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>18–42</td>
<td>18–41</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>116.12</td>
<td>116.14</td>
<td>0.55</td>
</tr>
<tr>
<td>Mean</td>
<td>110.79</td>
<td>112.93</td>
<td>0.54</td>
</tr>
<tr>
<td>PIQ</td>
<td>118.52</td>
<td>112.31</td>
<td>0.09</td>
</tr>
<tr>
<td>FIQ</td>
<td>116.27</td>
<td>114.14</td>
<td>0.55</td>
</tr>
<tr>
<td>ADI-R</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Social Communication</td>
<td>N/A</td>
<td>18.07</td>
<td>0.57</td>
</tr>
<tr>
<td>Repetitive Judgments</td>
<td>N/A</td>
<td>15.17</td>
<td>0.24</td>
</tr>
<tr>
<td>AQ</td>
<td>15.24</td>
<td>32.59</td>
<td>8.19×10^-13</td>
</tr>
<tr>
<td>TAS</td>
<td>42.88</td>
<td>59.28</td>
<td>4.44×10^-4</td>
</tr>
</tbody>
</table>

Abbreviations: ASC, autism spectrum condition; VQ, verbal IQ; PIQ, performance IQ; FIQ, full-scale IQ; ADI-R, Autism Diagnostic Interview-Revised; AQ, Autism Spectrum Quotient; TAS, Toronto Alexithymia Scale.
likely is the Queen to think that keeping a diary is important”). During Self-Physical blocks (SP), participants judged how likely they would agree to opinion questions about their own physical characteristics (e.g., “How likely are you to have bony elbows?”). Conversely, the same physical judgments were made during Other-Physical blocks (OP), except that participants rated these questions with the Queen as the target person (e.g., “How likely is the Queen to have bony elbows”). All opinion questions were acquired from Jason Mitchell’s lab and have been used in previous studies on reflective mentalizing judgments of the self and others that reliably elicit robust and consistent activity in mentalizing neural circuits (Jenkins et al., 2008; Mitchell et al., 2006). Stimuli did not differ per condition in the number of characters, syllables, frequency, or valence.

All participants completed one scanning session with one functional imaging run. Within this run there were 20 trials within each condition and 5 blocks per condition. Each trial type was presented in blocks of 4 trials and the trial-duration was 4 seconds each (16 seconds per block). After each block there was a rest period of 16 seconds where participants fixated on a cross in the middle of the screen and were instructed to relax. All trials within blocks and all blocks throughout the functional run were presented in pseudorandom order. Stimulus presentation was implemented with DMDX software and the stimulus presentation computer was synchronized with the onset of the functional run to ensure accuracy of event timing.

fMRI acquisition

Imaging was performed on a 3T GE Signa Scanner (General Electric Medical Systems, Milwaukee, WI) at the Cambridge Magnetic Resonance Imaging and Spectroscopy Unit (MRIS Unit). Our functional imaging run consisted of 325 whole-brain functional T2*-weighted echoplanar images (EPI) (slice thickness, 3 mm; 0.8 mm skip; 33 axial slices; repetition time (TR), 2000 ms; echo time (TE), 30 ms; flip angle 90°; matrix, 64 x 64; field of view (FOV), 240 mm; serial slice acquisition). The first 5 timepoints of the run were discarded to allow for T2 stabilization effects. In addition, a high-resolution 3-D spoiled gradient (SPGR) anatomical image was acquired for each subject for registration purposes.

Data analysis

Behavioral and ROI data were analyzed in SPSS 16 (http://www.spss.com). fMRI data preprocessing and first-level statistics were implemented in SPM5 (Wellcome Trust Centre for Neuroimaging, http://www.fil.ion.ucl.ac.uk/spm). The preprocessing steps were identical to those in previous reports (Lombardo et al., 2010a,b): slice-timing correction, realignment to the mean functional image, coregistration of the functional data with a high-resolution SPGR, segmentation of the SPGR, normalization into standard anatomical space (MNI) by applying the transformations estimated from the segmentation step, and spatial smoothing with an 8 mm full width half maximum (FWHM) Gaussian kernel.

First-level analyses were performed using the general linear model in SPM5. Each trial was convolved with the canonical hemodynamic response function. High-pass temporal filtering with a cut-off of 128 seconds was applied to remove low frequency drift in the time-series and global changes were removed by proportional linear scaling. Serial autocorrelations were estimated with a restricted maximum likelihood algorithm with an autoregressive model of order 1. Parameter estimate images for each condition as well as contrast images were output from this first-level analysis.

In second-level group analyses, between-group differences in mentalizing activity were assessed within independently selected regions of interests (ROI) in VMPFC, dMPFC, RTPJ, LTPJ, and PCC. ROIs were constructed from quantitative meta-analytic maps generated from the coordinates of 41 functional neuroimaging studies of mentalizing or theory of mind that employ verbal stimuli (e.g., reading sentences, vignettes/stories). See Supplementary Materials for more details on the meta-analysis. Local percent signal change (PSC) was computed for each ROI within each subject in the following fashion: Local PSC = Beta(Task) x 100/Beta(Const); where Beta(Task) is the mean parameter estimate within the ROI from the condition of interest (e.g., SM) and Beta(Const) is the mean beta value within the ROI from the constant term within the GLM.

A repeated-measures ANOVA was examined for a 4-way interaction between Region (5 levels), Group (2 levels), Target (2 levels), and Judgment (2 levels) and 3-way interactions between Region x Group x Judgment, Region x Target x Judgment, and Group x Judgment x Target. If there were any interactions with Region, separate follow-up ANOVAs for each region were done to discern the nature of the interaction. These follow-up tests were repeated-measures ANOVAs examining a 3-way interaction of Group x Target x Judgment, 2-way interaction of Group x Judgment, 2-way interaction of Target x Judgment, or main-effects of Group or Judgment. The Group x Target interaction and main-effect of Target are not reported as they have already been assessed and reported in a previous paper on the same dataset and are not relevant for the purposes of the present analysis (Lombardo et al., 2010a). If interaction effects were significant, follow-up tests within each group were used to characterize the nature of the interaction.

Finally, to characterize the relationships between neural response to mentalizing about self and other and individual differences in social impairments, regression analyses were implemented using ADI-R and ADOS social subscore as independent variables. These regressions were done independently on the orthogonal contrasts of SM-SP and OM-OP in order to check the consistency of any correlations across the target of the mental state. The meta-analytic ROIs were again used for these analyses. However, because the ROIs were optimized for testing questions about group-differences instead of correlations with social impairment in ASC, we used the ROIs to constrain the search space for voxel-wise correlations rather than averaging within the ROI and then computing the correlation. Correlations were significant if they passed correction for multiple comparisons using small-volume correction at p < 0.05 FWE (Friston, 1997; Worsley et al., 1996).

Results

Behavioral data

Behavioral data for task performance on the fMRI paradigm has been reported elsewhere (Lombardo et al., 2010a). Briefly reiterating these results for the specific comparisons of interest in this study (mentalizing vs. physical judgments), there was no significant interaction effect of Group x Judgment type (relevance rating, p = 0.40; reaction-time, p = 0.95), thus demonstrating that groups responded similarly while making mentalizing and physical judgments.

fMRI data

Our primary analysis was a repeated-measures ANOVA among 4 factors: Region (5 levels), Group (2 levels), Target (2 levels), and Judgment (2 levels). The 4-way Region x Group x Target x Judgment interaction was not significant (Wilks’ Lambda = 0.936, F(4,57) = 0.940, p = 0.448). Also not significant were the 3-way interactions of Region x Target x Judgment (Wilks’ Lambda = 0.858, F(4,57) = 2.356, p = 0.064) and Group x Judgment x Target (Wilks’ Lambda = 0.999, F(4,57) = 0.039, p = 0.844). However, the Region x Group x Judgment interaction was significant (Wilks’ Lambda = 0.827, F(4,57) = 2.989, p = 0.026). This signals that there is some regional specificity in group-differences in mentalizing. In order to discern the nature of this interaction, follow-up ANOVAs were done separately for each region.
Table 2
Descriptive statistics for ROIs analyses.

<table>
<thead>
<tr>
<th>Region</th>
<th>Controls SM</th>
<th>Controls SP</th>
<th>Controls OM</th>
<th>Controls OP</th>
<th>ASC SM</th>
<th>ASC SP</th>
<th>ASC OM</th>
<th>ASC OP</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTPJ</td>
<td>−0.303 (0.168)</td>
<td>−0.356 (0.141)</td>
<td>−0.239 (0.179)</td>
<td>−0.292 (0.180)</td>
<td>−0.284 (0.218)</td>
<td>−0.313 (0.222)</td>
<td>−0.245 (0.215)</td>
<td>−0.219 (0.175)</td>
</tr>
<tr>
<td>LTPJ</td>
<td>−0.195 (0.223)</td>
<td>−0.203 (0.246)</td>
<td>−0.157 (0.242)</td>
<td>−0.172 (0.245)</td>
<td>−0.126 (0.287)</td>
<td>−0.191 (0.255)</td>
<td>−0.153 (0.225)</td>
<td>−0.199 (0.205)</td>
</tr>
<tr>
<td>PCC</td>
<td>−0.238 (0.164)</td>
<td>−0.338 (0.125)</td>
<td>−0.201 (0.151)</td>
<td>−0.266 (0.155)</td>
<td>−0.238 (0.234)</td>
<td>−0.339 (0.248)</td>
<td>−0.236 (0.192)</td>
<td>−0.287 (0.261)</td>
</tr>
<tr>
<td>vMPFC</td>
<td>−0.153 (0.307)</td>
<td>−0.305 (0.248)</td>
<td>−0.206 (0.263)</td>
<td>−0.349 (0.309)</td>
<td>−0.070 (0.578)</td>
<td>−0.286 (0.566)</td>
<td>−0.159 (0.652)</td>
<td>−0.326 (0.547)</td>
</tr>
<tr>
<td>dMPFC</td>
<td>−0.014 (0.290)</td>
<td>−0.058 (0.248)</td>
<td>−0.025 (0.251)</td>
<td>−0.049 (0.250)</td>
<td>−0.058 (0.313)</td>
<td>−0.120 (0.268)</td>
<td>−0.320 (0.293)</td>
<td>−0.187 (0.247)</td>
</tr>
</tbody>
</table>

Values are mean percentage signal change with standard deviations in parentheses. Abbreviations: ASC, autism spectrum condition; SM, self-mentalizing; SP, self-physical; OM, other-mentalizing; OP, other-physical; RTPJ, right temporo-parietal junction; LTPJ, left temporo-parietal junction; PCC, posterior cingulate cortex/precuneus; vMPFC, ventromedial prefrontal cortex; dMPFC, dorsomedial prefrontal cortex.

Table 3
ANOVA statistics for each ROI.

<table>
<thead>
<tr>
<th>Region</th>
<th>Group × Target × Judgment</th>
<th>Target × Judgment</th>
<th>Group × Judgment</th>
<th>Judgment (Main Effect)</th>
<th>Group (Main Effect)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTPJ</td>
<td>F(1,60) = 0.987, p = 0.324</td>
<td>F(1,60) = 1.051, p = 0.309</td>
<td>F(1,60) = 3.99, p = 0.05</td>
<td>F(1,60) = 4.275, p = 0.043</td>
<td>F(1,60) = 0.604, p = 0.440</td>
</tr>
<tr>
<td>LTPJ</td>
<td>F(1,60) = 0.024, p = 0.878</td>
<td>F(1,60) = 0.704, p = 0.405</td>
<td>F(1,60) = 0.723, p = 0.399</td>
<td>F(1,60) = 7.671, p = 0.007</td>
<td>F(1,60) = 0.011, p = 0.918</td>
</tr>
<tr>
<td>PCC</td>
<td>F(1,60) = 0.998, p = 0.755</td>
<td>F(1,60) = 3.090, p = 0.034</td>
<td>F(1,60) = 0.054, p = 0.817</td>
<td>F(1,60) = 31.041, p = 6.36 × 10−6</td>
<td>F(1,60) = 0.105, p = 0.747</td>
</tr>
<tr>
<td>vMPFC</td>
<td>F(1,60) = 0.024, p = 0.623</td>
<td>F(1,60) = 0.292, p = 0.591</td>
<td>F(1,60) = 0.584, p = 0.448</td>
<td>F(1,60) = 42.176, p = 1.81 × 10−6</td>
<td>F(1,60) = 0.919, p = 0.341</td>
</tr>
<tr>
<td>dMPFC</td>
<td>F(1,60) = 0.020, p = 0.434</td>
<td>F(1,60) = 2.455, p = 0.122</td>
<td>F(1,60) = 1.290, p = 0.261</td>
<td>F(1,60) = 14.485, p = 3.34 × 10−4</td>
<td>F(1,60) = 1.709, p = 0.196</td>
</tr>
</tbody>
</table>

Abbreviations: RTPJ, right temporo-parietal junction; LTPJ, left temporo-parietal junction; PCC, posterior cingulate cortex/precuneus; vMPFC, ventromedial prefrontal cortex; dMPFC, dorsomedial prefrontal cortex.

Among all 5 regions, there were no Group × Target × Judgment interactions (all p > 0.32), Target × Judgment interactions (all p > 0.08), or main effects of Group (all p > 0.19) (see Table 2 for descriptive statistics and Table 3 for full reporting of follow-up ANOVA statistics for each ROI). There were also no Group × Judgment interactions in vMPFC, dMPFC, LTPJ, and PCC. However, RTPJ exhibited a significant Group × Judgment interaction (F(1,60) = 3.99, p = 0.05). Follow-up tests within each group confirmed that this interaction was driven by a significant main effect of Judgment (e.g., Mentalizing > Physical) in Controls (F(1,32) = 13.853, p = 0.001), and a non-significant effect in ASC (e.g., Mentalizing = Physical) (F(1,28) = 0.002, p = 0.969). Broken down into the simple effects (for self and other) within each group, it is apparent that RTPJ is selective to mental state information in Controls for both self (SM > SP: t(32) = 2.161, p = 0.038) and other (OM > OP: t(32) = 2.661, p = 0.012), but not in ASC (SM > SP: t(28) = 1.042, p = 0.306; OM > OP: t(28) = −0.770, p = 0.447) (see Fig. 1A). Finally, corroborating the general fact that the task elicits strong recruitment of all mentalizing ROIs, we found a significant main effect of Judgment in all ROIs in the direction of Mentalizing > Physical (all p < 0.05, see Table 3).

Given that the nature of an ROI analysis is based on assuming a location and then estimating the effect size from that assumed location, we followed these analyses with whole-brain random-effects analyses that do not assume a location, in order to establish correspondence between the two types of analyses. The whole-brain analysis consisted of testing for a between-group difference in the main effect contrast of Mentalizing > Physical in a 2nd level random-effects analysis and was thresholded in SPM8 at a topological FDR cluster-corrected level of q < 0.05 (Chumbley et al., 2010). A largely right-lateralized cluster was observed as hypoactive in ASC compared to Controls (i.e., Controls > ASC). This cluster covered much of the ventral portion of the RTPJ meta-analytic ROI (see Fig. 1B), as well as a good majority of the mid/posterior superior temporal gyrus and sulcus, posterior middle temporal gyrus, inferior and

Fig. 1. Decreased RTPJ specialization for mentalizing in ASC. A) Bar graph plotting results from an ROI analysis of RTPJ. Percent signal change is plotted on the y-axis for Self (red) or Other (blue). Error bars depict ±1 standard error of the mean (SEM). Mentalizing judgments are depicted in solid bars while Physical judgments are shown as outlined bars. RTPJ in Controls is more active for mentalizing than physical judgments across both self and other. This specialization for responding more to mentalizing is absent in ASC. B) Results from a whole-brain random-effects analysis of group-differences during the main effect contrast of Mentalizing > Physical. All areas shown in orange are hypoactive in ASC compared to Controls (i.e., Controls > ASC). The independently selected ROI in RTPJ used for the ROI analysis (white voxels) is overlaid on the whole-brain group-difference map in order to show the correspondence between these two types of analyses.
superior parietal lobule, precuneus, pre- and postcentral gyrus, posterior middle frontal gyrus, and posterior/mid-insula.

Correlations with social impairment

Among the independently selected mentalizing ROIs, only voxels in RTPJ were significantly correlated with social symptom severity on the ADI-R at the level of small-volume correction \( |P_{SVC-FWE}| < 0.05 \) for each individual analysis and at an overall Bonferroni-corrected threshold of \( p < 0.0025 \) for each peak \( p \)-value for all 20 ROI-symptom-severity comparisons (e.g., 5 regions \( \times \) 2 contrasts \( \times \) 2 symptom measures). This correlation was observed for both SM\( \rightarrow \)SP (MNI \( x = 52, y = -62, z = 28; t = 3.64, P_{SVC-FWE} = 0.041, P_{\text{peak voxel}} = 0.001 \)) and OM\( \rightarrow \)OP (MNI \( x = 54, y = -58, z = 24; t = 3.74, P_{SVC-FWE} = 0.031, P_{\text{peak voxel}} = 0.0004 \)) [see Fig. 2]. Individuals with ASC who were most socially impaired had RTPJ responses that were least selective for mental state information, while those who were least socially impaired had RTPJ responses that were relatively more selective for mental state information. No ROIs were correlated with ADOS social symptom severity across SM\( \rightarrow \)SP or OM\( \rightarrow \)OP.

Discussion

This study assessed three fundamentally important questions relevant to the mindblindness theory of autism. First, we wanted to know which neural systems are responsible for the domain-specific difficulties in representing mental state information in autism. Second, we assessed whether such atypical neural systems for mentalizing are atypical both when the target of mentalizing is self or other. Third, we investigated how (if at all) such atypical neural mentalizing systems relate to variation on clinical measures of social impairment. We found that RTPJ functions atypically in ASC and this atypical functioning correlates with reciprocal social impairment. In Controls, RTPJ was functionally specialized for judgments that require representation of mental state information. This specialization for mental state information also generalized across the cases of whether the target is self or other. In ASC, this functional specialization was completely absent. RTPJ responded similarly to both mentalizing or physical judgments and this lack of specialization for mentalizing correlated with degree of social impairment.

These results are particularly striking in light of the fact that RTPJ is one of the primary candidate regions involved specifically in representing mental state information. In adulthood RTPJ typically exhibits a marked domain-specific functional tuning for representing mental state information (Aichhorn et al., 2009; Mitchell et al., 2005; Perrner et al., 2006; Saxe and Kanwisher, 2003; Saxe and Powell, 2006) and is functionally and spatially dissociable from nearby dorsal clusters which respond to attentional reorienting (Decety and Lamm, 2007; Scholz et al., 2009; Young et al., 2010) or ventral clusters in posterior superior temporal sulcus (pSTS) that are more responsible for aspects such as processing animacy, biological motion, and eye gaze (Castelli et al., 2002; Nummenmaa and Calder, 2009; Pelphrey et al., 2003, 2005, 2004; Puce and Perrett, 2003; Saxe et al., 2009). Development also plays an important role in RTPJ specialization for representing mental state information. Like its protracted pattern of structural development (Shaw et al., 2008), RTPJ functional specialization for mentalizing is still developing into late childhood/early adolescence (Saxe et al., 2009). Thus, one way of looking at the lack of “mentalizing specialization” of RTPJ in ASC, is to view it as indicative of delayed neurodevelopment. This idea is intriguing as it mirrors the idea that mentalizing ability in ASC follows a delayed trajectory of development. In a meta-analysis of behavioral mentalizing studies in autism, Happé found that rather than never acquiring the ability to mentalize, some individuals with ASC do develop some rudimentary mentalizing ability, albeit at a very delayed rate (Happé, 1995). These results suggest that a possible neural system linked to delayed mentalizing development in ASC is the delayed development of RTPJ for specializing in representing mental state information.

Unlike prior work, which observed hypoactivation of dMPFC during mentalizing in ASC (Castelli et al., 2002; Happé et al., 1996; Kana et al., 2009; Kennedy and Courchesne, 2008; Silani et al., 2008; Wang et al., 2007), we did not observe any group-difference in this region. However, the lack of an effect here does not mean that dMPFC is not of importance in mindblindness in ASC. Rather, there are more complex considerations to take into account. Whereas RTPJ typically develops increasing specialization for mentalizing from adolescence to adulthood (Saxe et al., 2009), dMPFC decreases in functional specialization for mentalizing during this period (Blakemore, 2008; Blakemore et al., 2007; Burnett et al., 2009; Pfeifer et al., 2007, 2009). Related to ideas about the development of circuits involved in mentalizing, we may also need to consider the fact that with age, advanced mentalizing ability is still developing in the general population throughout adolescence and adulthood. Because such advanced mentalizing is still developing later in life, it may be important to consider the role that increasing levels of metarepresentation may play. Although dMPFC has long been known to play a role in mentalizing (Fletcher et al., 1995; Goel et al., 1995) recent work on the underlying computations of dMPFC suggests that it may play a specific role in the metarepresentational component of mentalizing. Several studies now show that dMPFC is increasingly engaged with increasing demands for higher levels of metarepresentation in the social domain (Coricelli and Nagel, 2009; Hampton et al., 2008; Yoshida et al., 2010). Given the pattern of decreasing recruitment of dMPFC with age, it is interesting that this pattern mirrors the decreasing level of difficulty that individuals have with mentalizing as they mature through adolescence and into adulthood (Choudhury et al., 2006; Dumonthiell et al., 2010). Thus, one explanation behind why some studies find atypical recruitment of dMPFC is that they either catch individuals at a more optimal time point earlier in development when a group-difference may be most pronounced (Kana et al., 2009; Kennedy and Courchesne, 2008; Wang et al., 2007), or the effect pops out more when the task sufficiently taxes metarepresentational ability (Silani et al., 2008). While speculative, these considerations may be important for interpreting the lack of a group difference in dMPFC in the current study. They may also suggest that future research looking into the
development of dMPFC in ASC as well as its role in the metarepresentational component of mindreading may be an intriguing way forward in understanding other components of mindblindness in ASC.

Another important observation of this study is that other mentalizing regions in the autistic brain appear relatively intact. Regions such as vMPFC, PCC, and LTPJ were equally sensitive to mental state information in the autistic compared to the neurotypical brain. This observation is important since it demonstrates some degree of regional specificity within mentalizing circuitry that may be responsible for the component processes that contribute to mindblindness and social-communication deficits in autism. RTPJ is a candidate region involved in mindblindness within this study and as several studies across the literature show, dMPFC may be another. However, an area such as vMPFC does not appear to be responsible for the domain-specific impairments in representing mental states per se. Instead, vMPFC is integral in another component process regarding the coding of self-relevant information and making a self-other distinction. We previously reported within this same dataset that vMPFC in ASC does not distinguish between self and other and the magnitude of this lack of a self-other distinction in the mentalizing domain is associated with variation in social impairments (Lombardo et al., 2010a). The contributions of both RTPJ for representing mental state information and vMPFC for highlighting what information is self-relevant are very interesting, given that the initial observations of theory of mind deficits in autism (Baron-Cohen et al., 1985) hinge critically on these two component processes. In order for young children to pass the false belief test, children need to be able to represent and attribute mental state information to self and other as well as determine what information a naïve other possesses about the situation independently of what “privileged” information oneself knows about the situation. Thus, in conjunction with our previous report on atypical neural self-representation in autism, the current observations demonstrate that isolating specific neural systems responsible for multiple component processes involved in social cognition will be important for shedding insight into the social-communication difficulties in autism as well as informing future research on their specific underlying genetic mechanisms (Happé et al., 2006; Lombardo and Baron-Cohen, 2011).

In conclusion, the current data lend support to the idea that RTPJ is a specific neural system involved in mindblindness and its relationship to social impairments in ASC. RTPJ is known to show a degree of functional specialization for coding mental state information (Mitchell et al., 2005; Saxe and Kanwisher, 2003; Saxe and Powell, 2006) and this specialization increases over a protracted period of development (Saxe et al., 2009). In adults with ASC, we have shown that the RTPJ lacks functional specialization for representing mental state information. This lack of functional specialization mirrors a developmentally prior pattern of RTPJ development in the general population (Saxe et al., 2009) as well as mimicking the generally delayed development of mentalizing ability in ASC (Happé, 1995). In addition to the lack of specialization for representing mental state information, the magnitude of this functional specialization is associated with the variation on clinical measures of social impairment. Individuals who are more socially impaired have an RTPJ that is less specialized for representing mental states. Overall, these observations provide support for the mindblindness theory of autism (Baron-Cohen, 1995; Frith, 2001), and adds to the growing literature supporting the idea that there is specificity in the underlying neural systems involved in multiple component processes that contribute to phenotypic variability in ASC (Happé et al., 2006; Lombardo and Baron-Cohen, 2011; Lombardo et al., 2011).

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Appendix A. Supplementary data

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References
