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Dissociations in the neural substrates of language and social functioning in autism spectrum disorder

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Abstract

Background—Impairments in social communication (coupled with intact non-social language skills) are common in Autism Spectrum Disorder (ASD). However, the neural correlates of these social communication deficits in adolescents and young adults with ASD are not fully understood.

Methods—The Communication Checklist Self-Report (CC-SR) was administered to adolescents and young adults with ASD (n=52) and typically developing (TD) controls (n=64) to assess Structural-Language, Pragmatic-Language, and Social-Engagement. One high-resolution T1-weighted structural image was obtained from each participant. FreeSurfer was used to quantify cortical thickness.

Results—A main effect of diagnosis, with the ASD group performing worse than the TD group on all three CC-SR scales, and a diagnosis by scale interaction, driven by low Social-Engagement self-ratings in the ASD group, were found. There were also group differences in the relationship between scores on two of the three CC-SR scales and cortical thickness in multiple regions (Pragmatic-Language: left rostral frontal; Social-Engagement: left medial prefrontal). These interactions were driven by poorer self-ratings of language/social skills associated with decreased cortical thickness in the ASD group, while in the TD group worse self-ratings were associated with thicker cortex.

Conclusion—Self-ratings of language/social-communication were lower in the ASD than the TD group. Moreover, language/social-communication self-ratings showed a different relationship with cortical thickness for the ASD and TD groups in the left inferior frontal region for Pragmatic Language ratings and the left medial prefrontal cortex for Social Engagement ratings. These findings suggest thinner cortex is associated with more impaired pragmatic language and social communication abilities in ASD.

Keywords

Autism; Language; Social Communication; Cortical Thickness; Adulthood

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Introduction

Impairments in social communication skills and pragmatic language are classic, pathognomonic signs of Autism Spectrum Disorder (ASD). Due to the heterogeneity of ASD, there is a wide range of symptoms seen in the disorder specifically related to the complexity of basic language skills versus higher order language abilities. Although the DSM-5 no longer requires anomalies in basic components of language structure (e.g., speech, syntax, and grammar) for an ASD diagnosis, they are still considered important components of the ASD phenotype, particularly in the subgroup of ASD individuals that have intellectual impairments and delayed language development early in life (American Psychiatric Association, 2013; Lai et al., 2014). In contrast, higher order language skills, such as pragmatic language, which relies on the ability to use and comprehend social language in interactions with others, has been shown to be central to ASD (Bishop et al., 2003; Whitehouse et al., 2008). Pragmatic language skills include what we say, how we say it, our body language and whether they are appropriate to the given situation. The Children's Communication Checklist (Bishop, 1998) and the subsequent update (CCC-2; Bishop, 2006) are questionnaires that breakdown different aspects of language/communication ability using three subscales (Language Structure, Pragmatic Skills, and Social Engagement). More recently the Communication Checklist-Self-Report (CC-SR) (2009) and Communication Checklist-Adult (CC-A) (2009) were developed as modified forms of the CCC-2 to make them appropriate for adolescents and adults (ages: CC-SR = 10-80, CC-A = 17-80). Previous research with different versions of the CCC consistently showed that both Pragmatic Skills and especially Social Engagement scores were lower in children with ASD compared to same-age Typically Developing (TD) children (Bishop et al., 2003; Geurts et al., 2004; Kuijper et al., 2017; Norbury et al., 2004; Volden & Philips, 2010; Whitehouse et al., 2008), although there have also been reports of impaired Language Structure scores in ASD as well (Bishop, 2003; Mayer & Heaton 2014; Mayer & Heaton 2016; Norbury et al., 2004; Whitehouse et al., 2010). These results broadly show a similar pattern of impairment in both language and communication abilities, but there is some inconsistency about Structural Language impairment in ASD.

There is considerable evidence of abnormal brain structure in regions associated with language and communication in ASD; however, there are discrepancies in the directionality of these structural abnormalities depending on the study (Hadjikhani et al., 2006; Herbert et al., 2004; Knaus et al., 2009; Lai et al., 2014; Richter et al., 2015; Sato et al., 2017; Sharda et al., 2017; Wallace et al., 2010; Zielinski et al., 2014). These inconsistencies in regions and directionality should not be surprising given the varying sample characteristics, such as age, IQ, ASD symptomatology, presence or absence of psychiatric and neurological co-morbidities, and differences in methodological approach such as brain structural metric (e.g., white matter vs. grey matter; volume vs. thickness vs. area, etc.) or analytic technique (e.g., voxel-based vs. surface-based morphometry) utilized in these investigations. Despite these discrepancies there is a convergence of evidence of neuroanatomical differences in regions associated with language including the left inferior frontal gyrus, pars opercularis/pars triangularis and the temporo-parietal junction (Hadjikhani et al., 2006; Herbert et al., 2004; Knaus et al., 2009; Lai et al., 2014; Sharda et al., 2017; Zielinski et al., 2014). These results

are somewhat consistent with functional neuroimaging studies of ASD that have demonstrated altered neural activation in these regions during different types of language related tasks such as language/sentence comprehension and verbal fluency tasks (Herringshaw et al., 2016; Just et al., 2004; Kenworthy et al., 2013; Tesink et al. 2011). However, there is also evidence of increased activation in the right homologue of left hemisphere language regions as well as regions outside of what is considered the language network, possibly showing compensatory mechanisms for individuals with ASD (Eigsti et al., 2016; Herringshaw et al., 2016; Just et al., 2004; Tesink et al., 2009).

Structural differences in language-related brain regions have also been shown to be more robust in ASD individuals with language delays compared to those without language delays (Lai et al., 2014; Lombardo et al., 2015) and correlated with poorer performance on measures of language structure when using standardized assessment tools (Knaus et al., 2009; Sharda et al., 2017). Using the Clinical Evaluation of Language Fundamentals (CELF-3 & CELF-4) as a measure of language structure, both Knaus et al. (2009) and Sharda et al. (2017) found negative correlations with grey matter structure in children and adolescents with ASD, the former in the left pars triangularis using grey matter volume and the latter in the bilateral temporal and left medial frontal regions using cortical thickness. However, there has been virtually no research on the relationship between cortical thickness and multiple aspects of language in adults with ASD. Even for children with ASD, only one study to date (Sharda et al., 2017) has examined how these language skills using a questionnaire (i.e., the CCC-2) correlated with gray matter structure (i.e., cortical thickness). While there were group differences behaviorally based on the omnibus General Communication Composite (GCC) score combining Language Structure, Pragmatic Skill, and Social Engagement from the CCC-2, there were no significant correlations between the GCC and cortical thickness in either group (Sharda et al., 2017). Possibly because the GCC is an aggregate of each subscale, there was no specificity of language function assessed to detect correlations with brain structure. Therefore, using the individual subscales instead of the composite might lead to more fruitful results.

Research into social processing has found a network of cortical regions selectively involved in social processing that collectively are referred to as the ‘social brain’ (for review, see Frith, 2007). These regions include the medial and ventromedial prefrontal cortex, the posterior cingulate/precuneus, the amygdala and anterior hippocampus, the anterior temporal lobes, the posterior superior temporal sulcus (STS), temporo-parietal junction, the lateral portion of the fusiform gyrus, the left inferior frontal gyrus, somatosensory and anterior intraparietal cortices, and the anterior insula (for review, see: Amodio and Frith, 2016; Frith, 2007; Frith & Frith, 2010; Mitchell, 2009). Because social deficits are often considered the most salient symptom of ASD, there has been abundant research on the anatomical differences in the social brain of adults with ASD compared to TD controls showing thinner cortex and decreased grey matter utilizing other metrics (e.g., volume) in areas such as the prefrontal cortex, STS, fusiform, anterior cingulate, medial parietal cortex, supramarginal gyrus, and middle and inferior temporal cortex (e.g., Hadjikhani et al., 2006; Richter et al., 2015; Sato et al., 2017; Wallace et al., 2010; Wallace et al., 2015; Zielinski et al., 2014). However, because of the heterogeneity of deficits seen in ASD, it is still difficult to parse which of these regions are associated with either language or social related deficits or which

regions may be involved with more global dysfunction in ASD. Recently Sato et al. (2017) looked to address this by focusing on ASD adults without language impairments or delay and found decreases in grey matter volume within several regions of the “social brain”, including the bilateral medial prefrontal, left dorsomedial prefrontal cortex, right middle temporal gyrus, left fusiform, bilateral amygdala, and right inferior occipital gyrus. These regions that showed differences between ASD and TD groups were not influenced by language dysfunction often seen in ASD and may point to the neural underpinnings of specifically social related deficits.

Taken as a whole, the literature converges in demonstrating substantial ASD-TD group differences in the neural substrates of language and social cognition, but there has been less research to parse different aspects of language abilities (i.e., Structural Language vs. Pragmatic Language) and social communication in relation to brain structure in adults with ASD. The CC-SR provides a tool to assess diverse aspects of language as well as non-linguistic aspects of social communication. Furthermore, the limited data to date linking brain structure and behavior in ASD has rarely utilized self-report measures that have the advantage of conveying a person’s lived experience as opposed to a proxy reporter’s perceptions. To our knowledge, no investigation to date has examined the neural substrates of multiple aspects of language, as assessed in the CC-SR. Therefore, our goal is to investigate (1) the profile of self-rated language and social communication deficits among adults with ASD as compared to TD controls and (2) shared and distinct neural correlates of language and social communication difficulties associated with ASD as compared to those found in a TD comparison group.

Methods and Materials

Participants

Participants included 64 TD individuals ranging in age from 16-36 years and 52 individuals with ASD ranging in age from 15-31 years that did not differ significantly in age ($t=-1.86$, $p=.066$), sex ratio ($\chi^2=.009$, $p=.925$), or handedness ($\chi^2=.009$, $p=.926$) (see Table 1 for demographic details of participants). All 52 ASD participants met DSM-5 diagnostic criteria for ASD as assessed by an experienced clinician. Forty-four participants with ASD received the Autism Diagnostic Interview (ADI) or ADI-R (Le Couteur et al., 1989; Lord et al., 1994), and all 52 participants with ASD received the Autism Diagnostic Observation Schedule (ADOS) or the Autism Diagnostic Observation Schedule-2 (ADOS-2) (Lord et al., 2000; Lord et al. 2012), by a research-reliable and experienced clinician to confirm diagnoses. Participants with ASD received one of four different versions of the ADOS: ADOS-1 Module 4 ($n=19$), ADOS-2 Module 4 ($n=30$), ADOS-1 Module 3 ($n=2$), or ADOS-2 Module 3 ($n=1$). All ASD participants met diagnostic criteria for ‘broader ASD’ according to criteria established by the National Institute of Child Health and Human Development/National Institute on Deafness and Other Communication Disorders Collaborative Programs for Excellence in Autism (see Lainhart et al., 2006). Exclusion criteria included individuals with a full-scale intelligence quotient (FSIQ) or verbal intelligence quotient (VIQ) below 80 and comorbidities such as Fragile X or other neurogenetic disorders and brain trauma/injury.

Measures

FSIQ scores were obtained for each participant and measured by the Wechsler Abbreviated Scale of Intelligence (ASD: $n=10$, TD: $n=37$), the Wechsler Abbreviated Scale of Intelligence-II (ASD: $n=40$, TD: $n=27$), the Wechsler Intelligence Scale for Children-IV (ASD: $n=1$), and the Wechsler Intelligence Scale for Children-V (ASD: $n=1$). Although the ASD group had significantly lower FSIQ, Performance IQ (PIQ) and Verbal IQ (VIQ) scores, all FSIQ, PIQ, and VIQ scores fell within the average to above average range (see Table 1). Language and social communication ability were assessed using the Communication Checklist Self-Report (Bishop, Whitehouse, & Sharp, 2009). The three subscales used in the CC-SR are Language Structure, Pragmatic Language, and Social Engagement. There was a significant difference between the ASD ($M=221.10$ days, $SD=441.88$) and TD ($M=40.38$, $SD=95.90$) groups in the time between the administration of the CC-SR and acquiring the structural scan ($p<.01$). However, this group difference was driven by eight participants with ASD who completed their structural scan more than one year before CC-SR administration. To confirm that these time differences exerted no undue influence on findings, all analyses were rerun without these eight individuals. After removing these individuals there were no longer significant administration time gap differences between the ASD ($M=62.18$ days, $SD=105.66$) and TD ($M=40.48$, $SD=95.90$) groups ($p=.28$).

Imaging and Cortical thickness calculations

One high-resolution T1-weighted structural image was obtained from each subject with one of two magnetization-prepared rapid gradient-echo (MPRAGE) array spatial sensitivity encoding technique (ASSET) sequences. Thirty-five individuals with ASD and 64 TD individuals had the MPRAGE ASSET sequence (124 slices, 1.2mm slice thickness, 224×224 acquisition matrix, flip angle = 12° , field of view = 24 cm) on a 3T General Electric Signa scanner (Milwaukee, WI) using an 8-channel head coil and 17 ASD individuals had the MPRAGE ASSET sequence (172 slices, 1-mm slice thickness, 256×256 acquisition matrix, flip angle = 7° , field of view = 24 cm) on a 3T General Electric Signa scanner (Milwaukee, WI) using a 32-channel head coil. All neuroimaging analyses were rerun without the 17 ASD individuals with the 32-channel head coil, which resulted in no change in the pattern of results from those found in the full sample. Visual inspections were completed from sagittal views of the T1-weighted images. Ratings ranging from 1-5 were completed for each scan, with 1 being a surface with very little to no motion and 5 being considerable motion, deemed unusable. All scans rated as a 4 or 5 were thrown out prior to analysis. There were no significant differences in motion ratings between the ASD ($M=2.31$, $SD=.78$) and TD ($M=2.12$, $SD=.75$) groups ($t=1.28$, $p=.20$). FreeSurfer image analysis methods have been previously described in detail and were used to view surfaces and generate cortical thickness at each surface vertex (Dale et al., 1999; Fischl et al., 1999, 2004; Fischl & Dale 2000). The semi-automated processing pipeline included visual inspection and scoring of scans for motion artifacts, transformation to Talairach space, intensity normalization for correction of magnetic field inhomogeneities, and removal of non-brain tissues (i.e. skull-stripping). The resulting surface models generated were reviewed for accuracy and manually edited in all cases due to over-inclusion of white matter around the optic nerve. Cortical thickness was calculated as the distance (in mm) from the grey matter-white matter boundary to the pial surface at each vertex (Fischl & Dale 2000). This method

of cortical thickness measurement has been validated against post-mortem brains and histological analysis (Rosas et al., 2002) and hand tracings (Kuperberg et al., 2003; Salat et al., 2004) and has shown good reliability across sites and platforms (Han et al., 2006). Vertex-level cortical thickness values were obtained and mapped onto a normalized cortical surface. These cortical thickness maps were smoothed with a 15mm full width at half maximum kernel.

Data analysis

Ratings of language skills on the CC-SR were examined using a repeated-measures ANOVA with diagnosis (ASD vs. TD) as the between subjects factor and Scale (Structural vs. Pragmatic vs. Social Interaction) as the within subjects factor. Next, we investigated discrepancies in the association between cortical thickness (across the whole brain) and each of the three subscales on the CC-SR for the ASD versus TD group using general linear models within FreeSurfer's Qdec application. To control for multiple comparisons, Monte Carlo simulation with 10,000 iterations (vertex-wise threshold of $p < .05$) was used for cluster correction (Hagler Jr., Saygin, & Sereno 2006). The group discrepancies in CC-SR – cortical thickness associations were examined again entering IQ and age as covariates together, as well as verbal-IQ as a separate covariate to ensure that group differences in IQ and VIQ as well as trending significant difference in age did not account for any findings. When significant group discrepancies in CC-SR – cortical thickness associations were observed, these models were run again entering motion ratings and the complementary CC-SR subscales as covariates to confirm that in-scanner motion artifacts did not cause group difference and to investigate whether these group differences were specific to that CC-SR subscale.

Results

When examining ratings on the CC-SR, main effects of diagnosis [$F=68.07$, $p < .001$] and subscale [$F=17.07$, $p < .001$] emerged which was qualified by a diagnosis by subscale interaction [$F=6.86$, $p < .001$]. The ASD group self-rated lower language/social-communication skills than the TD group on all three subscales [Language-Structure: $t=-5.56$, $p < .001$, Pragmatic-Skill: $t=-5.88$, $p < .001$, Social-Engagement: $t=-8.07$, $p < .001$] (see Figure 1). However, in the context of the CC-SR standardized scores, the ASD group performed within the normal range, on average, on both the Language Structure (z scores: $M=0.08$, $SD=1.07$) and Pragmatic Skill (z scores: $M=-0.13$, $SD=1.18$) subscales, while the Social Engagement (z scores: $M=-0.83$, $SD=1.27$) subscale self-rated almost 1 standard deviation below the mean of the standardization sample of the CC-SR. Moreover, there was no significant difference between the two language scores [$t=-0.95$, $p=.35$] in the ASD group. The diagnosis by subscale interaction was driven by particularly low Social Engagement self-ratings in the ASD group in comparison to the TD group [$t=-8.07$, $p < .001$]. All three of the subscale scores in the TD group were approximately one standard deviation above those from the normative sample (z scores: Language Structure: $M=1.12$, $SD=0.92$, Pragmatic Language: $M=1.04$, $SD=0.91$, Social Engagement: $M=0.91$, $SD=1.00$). Controlling for both IQ and VIQ did not alter the results for the main effects of diagnosis [IQ covariate: $F=66.71$, $p < .001$, VIQ covariate: $F=59.66$, $p < .001$] or the diagnosis by scale

interaction [IQ covariate: $F=7.13$, $p=.001$, VIQ covariate: $F=7.31$, $p=.001$], but the main effect of subscale [IQ covariate: $F=1.24$, $p=.292$, VIQ covariate: $F=1.78$, $p=.171$] was no longer significant. Age was not significantly correlated with any of the CC-SR subscales. However, there were significant positive correlations among all the three subscales on the CC-SR whether examined in the combined full sample or in each of the groups separately ($ps<.05$) (Table 2).

Analyses of the relationship between self-reported language skills/communication skills and cortical thickness revealed significant group differences on two of the three CC-SR subscales (cluster corrected $ps<.05$) (Pragmatic Language: left rostral middle frontal; Social Engagement: left medial orbitofrontal; see Figure 2 and Table 3). These interactions were driven by lower self-ratings of language/social skills on the CC-SR being associated with thinner cortex in the ASD group, unlike the TD group, which largely showed the inverse relationship (i.e., lower self-ratings associated with increased cortical thickness).

These analyses were rerun using IQ and age as covariates together to control for the significant difference in IQ and trending difference in age between the groups. Results demonstrated that group differences in the association between language skills/communication skills and cortical thickness remained significant at both clusters (cluster corrected $ps<.05$) previously seen (Pragmatic Language: left rostral middle frontal; Social Engagement: left medial orbitofrontal; see Figure 3 and Table 4) showing that IQ and age differences did not account for the initial results. Also, this analysis revealed a new significant cluster (cluster corrected $p<.05$) between self-reported language skills and cortical thickness (Pragmatic Language: superiortemporal; see Figure 3 and Table 4). Again, the interaction was driven by lower self-ratings on the CC-SR being associated with thinner cortex in the ASD group and the opposite relationship in the TD group.

Due to group differences between the amount of time between CC-SR administration and structural, the original analyses were rerun without the 8 ASD individuals who had time difference greater than a year between CC-SR and scan. Results showed the same significant clusters as the analysis with IQ and age as covariates. Original analyses were again rerun using in-scanner motion ratings a covariate in order to confirm that motion did not account for results. This analysis also found the same significant clusters as the analysis with IQ and age as covariates. Finally, analysis using the complementary CC-SR subscale as a covariate was completed. This analysis found group differences in the relationship between self-rated pragmatic language skills and cortical thickness with social engagement as a covariate, the significant cluster (Pragmatic Language: left rostral middle frontal; cluster corrected $ps<.05$; see Figure 4 and Table 5) remained; however, the group differences in the relationship between social engagement and cortical thickness after controlling for pragmatic language no longer remained statistically significant.

Discussion

In the present study, we examined the language and communication skills profile and its association with gray matter structure (i.e., cortical thickness) in adolescents and adults with ASD. Consistent with previous research we found the ASD group provided lower self-

ratings than age and sex-matched TD controls on all three subscales (Structural Language, Pragmatic Language, and Social Engagement) of the CC-SR (Bishop, Whitehouse, & Sharp, 2009; Mayer & Heaton 2014; Mayer, Hannent, & Heaton, 2016; Norbury et al., 2004; Whitehouse et al., 2008). However, it is important to note that both language subscale scores in the ASD group were comparable to those found in the CC-SR normative sample while the Social-Engagement score fell one standard deviation below the standardization sample mean. Moreover, these behavioral differences on the CC-SR likely were not driven by group differences in IQ or VIQ given that both IQ and VIQ for the ASD group were, if anything, above average and that group differences and significant interactions were not altered by including either IQ or VIQ as a covariate. Specifically, when examining the language subscales on the CC-SR the findings have been mixed: Bishop et al. (2009) found self-ratings in an ASD group did not differ from the standardization sample scores on Language Structure but that Pragmatic Language was worse than Language Structure within the ASD group. In contrast, Mayer and Heaton (2014) found their ASD group self-reported worse scores on Language Structure and Pragmatic Language compared to a group of age and IQ matched TD controls, but no difference between Language Structure and Pragmatic Language scores in the ASD group. These contradictory findings may be partly due to how pragmatic language is defined in the CC-SR manual. Pragmatic Skills are defined as expressive pragmatic behaviors that include inappropriate initiation, stereotyped language, use of context, and nonverbal communication (Bishop, Whitehouse, & Sharp, 2009). These first three factors that contribute to the pragmatic skills subscale still rely largely on linguistic abilities. This conclusion is also supported by the fact that there is a strong correlation between Language Structure and Pragmatic Language in both the TD and ASD groups.

Interestingly, even though there was a strong correlation between self-ratings of Language Structure and Pragmatic Skills and no significant difference in these scores in the ASD group, only the Pragmatic Language subscale's association with cortical thickness was discrepant between the ASD and TD groups. This interaction was driven by a significant positive correlation between pragmatic language and cortical thickness in the left inferior frontal gyrus and rostral middle frontal gyrus in the ASD group, a region implicated in phonology and semantic processing (for review, see: Costafreda et al., 2006). This finding suggests that pragmatic language may have separate neural substrates from more basic structural language abilities in ASD even though these two components of language are fairly strongly correlated with one another. Crucially, the interaction was mainly driven by strong correlations in the ASD group with poorer scores on the Pragmatic Language subscale related to thinner cortex, while the TD group had a weaker correlation in the opposite direction. This corresponds with other studies that also found that greater reported difficulties on behavioral ratings and performance-based tests correlated with atypical cortical thickness in ASD. Studies in children with ASD found that greater cortical thickness was associated with greater impairments in language ability using the CELF (Knaus et al., 2009; Sharda et al., 2017) and social functioning using the Social Responsiveness Scale (SRS) (Richter et al., 2015), while two studies in adults with ASD found that thinner cortex was correlated with more executive function problems on the Behavior Rating Inventory of Executive Function (BRIEF) and greater ASD social symptom severity using the ADI

(Hadjikhani et al., 2006; Wallace et al., 2015). Importantly, cross-sectional and longitudinal studies have shown increased cortical thinning in ASD during adolescence and young-middle adulthood (Wallace et al., 2010; Wallace et al., 2015; Zielinski et al., 2015), and that this increase in cortical thinning is associated with behavioral difficulties (Wallace et al., 2015). The current study extended these findings to another important characteristic of the ASD phenotype, pragmatic language abilities. More specifically, we showed that thinner left inferior frontal cortex was associated with lower self-ratings of pragmatic language. Additionally, we found that thinner left medial prefrontal cortex was associated with lower self-ratings of social functioning.

Two recent studies by Lombardo et al. (2015) and Lai et al. (2014) provide context for our findings within a sample of individuals with ASD with average range VIQ. The former studied fMRI response to speech in children with ASD (pre-diagnostically) around one year old and made a distinction between children that had good or poor language outcomes later in childhood, while the latter looked at structural differences in adults with ASD who either did or did not have language delay in childhood. Both found that the ASD subgroups with better language outcome/no language delay had very few neural differences compared to the TD group, while the ASD group with poor language outcome/delayed language showed robust differences in brain regions associated with both social cognition and language. In the study by Lombardo et al. (2015) this manifested in decreased activation across left hemisphere temporo-parietal areas including planum temporale, anterior, middle and posterior superior temporal regions, and Heschl's gyrus in children with poor language outcome. Lai et al. (2014) showed increased grey matter volumes for adults with ASD in superior temporal gyrus, medial temporal gyrus, and superior temporal sulci, all of which are associated with both social cognition and language. It is interesting to note vis-à-vis the current study that when analyzing the cortical correlates of Pragmatic Language after controlling for IQ and age we found another significant cluster that extended to portions of the superior and middle temporal gyri, two regions that were highlighted as having altered activation and grey matter volumes in ASD individuals with language deficits (Lai et al., 2014; Lombardo et al., 2015). Given that the current ASD group had average to above average VIQ and provided self-ratings on both language subscales that were not impaired relative to the CC-SR normative sample, our findings may represent, if anything, an underestimate of associations between pragmatic language functioning and gray matter structure in ASD.

Consistent with our findings of associations between gray matter structure in the medial prefrontal cortex and social engagement scores, a large body of research has highlighted the key role played by this region in social cognition (e.g., for review, see Frith and Frith 2010). For example, studies have shown both structural and functional neuroanatomical abnormalities in the medial prefrontal cortex in ASD (Baron-Cohen et al., 1999; Gotts et al., 2012; Hadjikhani et al., 2006; Jiao et al., 2010; Herringshaw et al., 2016; Richter et al., 2015; Sato et al. 2017). As with the Pragmatic Language subscale, thinner cortex is associated with lower ratings of social engagement in the ASD group. This finding corresponds directly with work by Gotts et al. (2012) who found reduced functional connectivity between the left ventromedial prefrontal cortex and a cluster of other regions associated with social processing including the left amygdala and the anterior portion of the

hippocampus, bilateral anterior ventral temporal cortex, right anterior middle temporal gyrus and right anterior medial frontal cortex correlated with greater autistic traits on the SRS in adolescents with ASD. The distinct cortical regions implicated in associations with the Pragmatic Language subscale versus the Social Engagement subscale suggest a possible dissociation in the neural substrates of linguistic and social deficits seen in ASD. This argument is bolstered by finding that the group differences in the association between pragmatic language self-ratings and left inferior frontal cortical thickness remained even after using the Social Engagement subscale scores as a covariate. Although this group difference in the association between Social Engagement self-ratings and left medial prefrontal cortical thickness was no longer statistically significant when controlling for Pragmatic Language scores, results from Sato et al. (2017) strengthen this claim by finding significantly decreased grey matter volume in adults with ASD without language impairments compared to an age-matched TD group in the bilateral medial prefrontal region including the right orbitofrontal cortex and left dorsomedial prefrontal cortex.

The current study has a number of limitations. As with many studies of ASD, the generalizability of the study is limited by the characteristics of the current sample. For example, the present ASD sample did not include individuals with intellectual disability; thus, these findings might not apply to this portion of the broader ASD population. Another limitation is this study's reliance on self-ratings alone without a proxy rater or performance based measure of pragmatic language/social communication. It is important to note that the ASD sample did not self-report structural and pragmatic language scores worse than those found in the standardization sample, even though impaired pragmatic language is a prominent characteristic of ASD. With that said the average range score on Language Structure and below average score on Social Engagement are very similar to what is seen in prior studies of ASD using the CC-SR (Bishop, Whitehouse, & Sharp, 2009). Moreover, given that the ASD group in this study exhibited above average VIQ scores, the intact Pragmatic Language ratings are not wholly surprising. Also, the CC-SR shows good internal consistency ($\alpha=.87, .88, .83$) for the three respective subscales as well as strong convergent validity given moderate to strong correlations with proxy ratings from the CCC-2 ($r=.42, .63, .67$) and the CC-A ($r=.35, .74, .33$). Although utilizing self-rating instruments can present challenges, it also presents unique strengths and potential opportunities. The CC-SR is a well-validated questionnaire designed for both ASD and neurotypical groups and therefore provides insight into how people with ASD view their own language and social abilities. Ideally, a performance-based measure would have been implemented; however, existing measures often struggle to consistently detect pragmatic difficulties, particularly among adolescents and adults with average range language abilities. For example, Volden and Philips (2010) has shown that the CCC-2 may be more sensitive at identifying individuals with pragmatic language impairment compared to the performance based Test of Pragmatic Language (TOPL). More research examining the validity of self-reports of (especially pragmatic) language functioning and their overlap with performance based measures, like the TOPL, is needed.

We identified strong behavioral differences in language and social abilities between ASD and TD groups. Additionally, discrepancies in brain regions associated with pragmatic language and social communication were found for the two groups. Specifically, in the ASD

group greater pragmatic language deficits correlated with thinner left inferior frontal cortex, a region consistently linked with language functioning, while greater social deficits correlated with thinner left ventromedial prefrontal cortex, a region robustly associated with social cognition. In the TD group, we found, if anything, inverse relationships where poor scores on language and social communication were correlated with thicker cortex. These results provide evidence that thinner cortex in adolescents and adults with ASD is associated with worse self-reported functioning in two key components of the ASD phenotype, pragmatic language and social-communication.

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Lay Summary

The present study examines the associations between brain structure and language/social communication ability in adolescents and young adults with autism spectrum disorder (ASD) as compared to neurotypical adolescents and young adults. We utilized thickness of the cerebral cortex as a measure of brain structure, and we found different correlations between language or social communication ability and cortical thickness in distinct regions for the ASD and TD groups. These findings suggest that for regions implicated in language/social communication ability, decreased cortical thickness is associated with more impaired pragmatic language and social communication abilities in ASD.

Figure 1.
Behavioral self-ratings scores of CC-SR subscales between ASD and TD groups

Figure 2. Neural correlates of CC-SR subscales between ASD and TD groups

A: Images were cluster corrected using Monte Carlo simulation at $p = 0.05$ level. Images shows significant interaction between subscale Pragmatic Skill and group in LH rostral middle frontal. The Pearson correlation for pragmatic language in the LH rostral middle frontal cluster was $r = .44$ ($p = .001$) in the ASD group, while it was $r = -.27$ ($p < .05$) for the TD group.

B: Images were cluster corrected using Monte Carlo simulation at $p=0.05$ level. Image shows significant interaction between subscale Social-Engagement and LH medial orbitofrontal. The Pearson correlation for the social engagement in the medial prefrontal cortex cluster was $r=0.32$ ($p<0.05$) in the ASD group, while it was $r=-0.35$ ($p<0.01$) for the TD group.

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Figure 3. Neural correlates of CC-SR subscales between ASD and TD groups with age and IQ as covariates together

A: Images were cluster corrected using Monte Carlo simulation at $p = 0.05$ level. Images shows significant interaction between subscale Pragmatic Skills and group in LH rostral middle frontal with age and IQ as covariates. The Pearson correlation for pragmatic language in the LH rostral middle frontal cluster was $r = .42$ ($p = .002$) in the ASD group, while it was $r = -.25$ ($p < .05$) for the TD group.

B: Images were cluster corrected using Monte Carlo simulation at $p = 0.05$ level. Images show significant interaction between subscale Pragmatic Skill and LH superior temporal with age and IQ as covariates. The Pearson correlation for pragmatic language in the LH rostral middle frontal cluster were $r = 0.48$ ($p < .001$) in the ASD group, while it was $r = -0.26$ ($p < .05$) in the TD group.

C: Images were cluster corrected using Monte Carlo simulation at $p = 0.05$ level. Image shows significant interaction between subscale Social-Engagement and LH medial orbitofrontal with age and IQ as covariates. The Pearson correlation for the social engagement in the medial prefrontal cortex cluster was $r = 0.32$ ($p < .05$) in the ASD group, while it was $r = -0.35$ ($p < .01$) for the TD group.

Figure 4. Neural correlates of Pragmatic Skills between ASD and TD groups with Social Engagement as a covariate

Images were cluster corrected using Monte Carlo simulation at $p = 0.05$ level. Images shows significant interaction between subscale Pragmatic Skills and group in LH rostral middle frontal with Social Engagement CC-SR subscale as covariate. The Pearson correlation for pragmatic language in the LH rostral middle frontal cluster was $r = .46$ ($p = .001$) in the ASD group, while it was $r = -.26$ ($p < .05$) for the TD group.

Table 1

Demographic characteristics and descriptive statistics of ASD diagnostic scores

	Autism Spectrum Disorder (n=52)	Typically Developing (n=64)
Age	20.88 (4.45)	22.35 (3.96)
Sex Ratio (F:M)	11:41	14:50
Handedness Ratio (right:nonright)	45:7	55:9
FSIQ	110.52 (13.26)	119.45 (9.66) *
VIQ	108.60 (14.27)	117.94 (11.85) *
PIQ	110.25 (16.81)	116.80 (9.20) *
ADI social [†]	18.82 (6.28)	
ADI verbal communication [†]	15.66 (5.14)	
ADI restricted and repetitive behaviors [†]	5.43 (2.49)	
ADOS social [‡]	7.37 (2.54)	
ADOS communication [‡]	3.57 (1.69)	
ADOS stereotyped behaviors [‡]	1.80 (1.47)	

ADI = Autism Diagnostic Interview; ADOS = Autism Diagnostic Observation Schedule; FSIQ = full-scale intelligence quotient; VIQ = verbal intelligence quotient. Data are mean (SD).

* = significant difference between Autism Spectrum Disorder and Typically Developing groups

[†]: n = 44

[‡]: n = 51; Note: ADOS-2 Module-3 scores are not reported here due to difference in scoring procedure, n=1

CC-SR correlations between the subscales in both diagnosis groups together and each diagnosis group individually

Table 2

	All Participants		ASD Group		TD Group	
	Lang-Struc	Prag-Skill	Lang-Struc	Prag-Skill	Lang-Struc	Prag-Skill
Prag-Skill	.66**	—	.52**	—	.61**	—
Soc-Eng	.66**	.56**	.45**	.35*	.66**	.43**

Lang-Struc = Language Structure

Prag-Skill = Pragmatic Skill

Soc-Eng = Social Engagement

* = significant correlation $p < .05$

** = significant correlation $p < .01$

Table 3

Cluster statistics for significant group differences in the association between cortical thickness and CC-SR subscale scores.

Subscale	Region	Size (mm ²)	X	Y	Z	p value	No. of vertices
Pragmatic-Skill	Rostral middle frontal	3309.67	-25.4	55.3	-11.3	p<.05	5297
Social-Engagement	Medial orbitofrontal	1618.54	-12.5	45.8	-6.4	p<.05	2397

Cluster statistics for significant group differences in the association between cortical thickness and CC-SR subscale scores, after covarying the effects of FSIQ and age.

Table 4

Subscale	Region	Size (mm ²)	X	Y	Z	Monte Carlo p value	No. of vertices
Pragmatic-Skill	Rostral middle frontal	3716.63	-24.9	54.9	-12.2	$p<.05$	5914
Pragmatic-Skill	Superior temporal	2926.28	-56.8	-30.8	8.1	$p<.05$	5991
Social-Engagement	Medial orbitofrontal	1578.94	-12.3	46.4	-6.2	$p<.05$	2322

Table 5

Cluster statistics for significant group differences in the association between cortical thickness and Pragmatic Skill scores, after covarying the effects of Social Engagement.

Subscale	Region	Size (mm2)	X	Y	Z	Monte Carlo p value	No. of vertices
Pragmatic-Skill	Rostral middle frontal	2725.53	-24.6	55.4	-12.1	$p<.05$	4248