J Autism Dev Disord (2013) 43:1106–1118
DOI 10.1007/s10803-012-1653-2

Autism Traits in Individuals with Agenesis of the Corpus Callosum

Yolanda C. Lau · Leighton B. N. Hinkley · Polina Bukshpun · Zoe A. Strominger · Mari L. J. Wakahiro · Simon Baron-Cohen · Carrie Allison · Bonnie Auyeung · Rita J. Jeremy · Srikantan S. Nagarajan · Elliott H. Sherr · Elysa J. Marco

Published online: 5 October 2012

Abstract Autism spectrum disorders (ASD) have numerous etiologies, including structural brain malformations such as agenesis of the corpus callosum (AgCC). We sought to directly measure the occurrence of autism traits in a cohort of individuals with AgCC and to investigate the neural underpinnings of this association. We screened a large AgCC cohort (n = 106) with the Autism Spectrum Quotient (AQ) and found that 45 % of children, 35 % of adolescents, and 18 % of adults exceeded the predetermined autism-screening cut-off. Interestingly, performance on the AQ's imagination domain was inversely correlated with magnetoencephalography measures of resting-state functional connectivity in the right superior temporal gyrus. Individuals with AgCC should be screened for ASD and disorders of the corpus callosum should be considered in autism diagnostic evaluations as well.

Keywords Agenesis of the corpus callosum · Autism spectrum disorders · Autism Spectrum Quotient · Functional connectivity · Magnetoencephalography · Superior temporal gyrus

Introduction

Autism spectrum disorders (ASD) are clinically defined by a constellation of deficits in communication, social skills, and repetitive interests and behaviors (American Psychiatric Association 2000). There are a myriad of causes, including metabolic-genetic conditions (e.g. Fragile X syndrome, Tuberous Sclerosis, phenylketonuria, and adenylosuccinase deficiency) and in utero toxic exposures (e.g. alcohol and valproic acid). Toxic metabolites from genetic disorders, infection, and maternal exposure all affect early brain development, leading to atypical neural maturation and connection through loss of trophic guidance mediated neurogenesis and synaptic formation (Lukose et al. 2011; Vingan et al. 1986). Interestingly, many of the genetic and

Y. C. Lau
School of Medicine, University of California, San Francisco, 513 Parnassus Avenue, San Francisco, CA 94143, USA

L. B. N. Hinkley · S. S. Nagarajan
Department of Radiology and Biomedical Imaging, University of California, San Francisco, 521 Parnassus Avenue, San Francisco, CA 94143, USA

P. Bukshpun · M. L. J. Wakahiro · E. H. Sherr (✉) · E. J. Marco (✉)
Department of Neurology, University of California, San Francisco, 350 Parnassus Avenue, Ste 609, Box 0137, San Francisco, CA 94143, USA
e-mail: SherrE@neuropeds.ucsf.edu

E. J. Marco
e-mail: marcoe@neuropeds.ucsf.edu

Z. A. Strominger
School of Nursing, University of California, San Francisco, San Francisco, CA, USA

S. Baron-Cohen · C. Allison · B. Auyeung
Department of Psychiatry, Autism Research Centre, University of Cambridge, Douglas House, 18b Trumpington Road, Cambridge, UK

R. J. Jeremy
Pediatric Clinical Research Center, Clinical and Translational Science Institute, University of California, San Francisco, 505 Parnassus Avenue, Box 0105, San Francisco, CA 94143-0105, USA

toxin mediated conditions linked to autism show structural abnormalities of the corpus callosum—the largest white matter structure in the brain and the principal interhemispheric conduit of information transfer (Paul 2011).

There is a growing consensus regarding the disconnection theory of autism, which posits dysfunction in the long-range structural and functional neural networks that subserve language, social, and executive function skills (Williams and Minshew 2007). As the most significant white matter tract connecting the left and right hemispheres of the brain, the corpus callosum has been widely investigated using functional connectivity, diffusion tensor imaging, and volumetric analysis (Shukla et al. 2010, 2011; Alexander et al. 2007; Frazier and Hardan 2009). In autism, the corpus callosum has been found to be consistently smaller, and has lower fractional anisotropy (FA) (Frazier and Hardan 2009; Hardan et al. 2009; Keary et al. 2009). In an attempt to connect these radiographic findings with the underlying neuropathology, Casanova et al. (2009) suggest that a reduced gyral window in autism, a measure of the space for cortical afferent/efferent fibers, may constrain the total number of afferent and efferent cortical projection fibers that constitute the corpus callosum (Casanova et al. 2009). The atypical developmental trajectory of the corpus callosum and other white matter tracts in children with ASD is starting to be investigated with the study of high-risk infant siblings of autistic children. In a longitudinal diffusion tensor imaging study, the authors reports that at 6 months of age, the FA of the corpus callosum and other white matter tracts appeared higher in the infants who developed ASD relative to those who did not (Wolff et al. 2012). Subsequently, the corpus callosum failed to show the expected increase in FA in the ASD group, resulting in the ASD group displaying lower average FA values at 24 months in the corpus callosum and other tracts. Upon close examination, this study also highlights the tremendous variability in measures of white matter integrity among individual children who meet ASD criteria in a well-characterized cohort. Thus, cortical connectivity in autism and other related neurodevelopmental disorders, such as AgCC, must be conceptualized within a prenatal and post-natal developmental framework. Early changes in brain development will have secondary effects on maturational processes in postnatal brain development. Consequently, understanding the role of the corpus callosum in the development of language and social skills over time is an important topic of investigation, and individuals with congenital agenesis of the corpus callosum (AgCC) can provide a model for understanding the primacy of hemispheric connectivity in autism and related neurodevelopmental disorders (Paul et al. 2007).

While the prevalence of ASD for individuals with AgCC is unknown, there is a growing literature documenting social and linguistic deficits in the AgCC cohort (Paul et al. 2003, 2004; Symington et al. 2010). In a study of individuals with a community diagnosis of AgCC (n = 733), 9.5 % of parent respondents indicated a co-morbid diagnosis of ASD (Schilmoeller et al. 2004). These cases were not confirmed by radiographic review and the autism traits were not systematically characterized. In a follow-up study using the Child Behavior Checklist, Badaruddin et al. (2007) evaluated a subset of high-functioning children, ages six to 11 years, from the same database and found that 39 % exceeded clinical cut-offs for social problems and 48 % exceeded clinical cut-offs for difficulties of attention (Badaruddin et al. 2007). In high-functioning individuals with complete AgCC, Symington et al. (2010) report deficits in emotion recognition, understanding sarcasm, and interpreting textual cues. This extends previous findings documenting impaired verbal identification of negative emotions in stories, with evidence of emotional arousal as measured by skin conductance (Paul et al. 2006; Turk et al. 2010).

Anomalies of the corpus callosum appear to play a role in language impairments in autism, however other structural cortical abnormalities can also affect communication and social skills. Gray matter differences have often been noted in the superior temporal gyrus, inferior parietal lobe, inferior frontal gyrus, and the inferior frontal cortex—all areas implicated in social cognition and communication (Hadjikhani et al. 2006; Hyde et al. 2010; Redcay 2008). As suggested by Friauf and Lohmann (1999), similar mechanisms of injury which can lead to corpus callosum abnormalities (e.g. anoxic and toxic exposures) can also affect other neuronal networks such as those subserving central auditory processing and language production (Friauf and Lohmann 1999). In their magnetoencephalography (MEG) studies which explore central auditory processing in children on the autism spectrum, Roberts et al. (2010, 2011) suggest an auditory processing delay, involving the superior temporal gyrus, that is correlated with the degree of language impairment (Roberts et al. 2010, 2011). While differences are recognized in the latency of the cortex response, the dysfunction, in some cases, may originate in the brainstem nuclei or subcortical neurons and be later propagated by the cortico-cortico connections. Just et al. (2004), however, showed increased activation in Wernicke's area but decreased activation in Broca's area, with an overall reduced functional connectivity in the autism group (Just et al. 2007). Belmonte et al. (2004) consequently proposed that autism may be a manifestation of increased local activity with decreased long-range connections (Belmonte et al. 2004). Individuals with AgCC, like those with autism, may exhibit reduced functional connectivity in neural networks critical to communication and social function, a question we explore using functional

connectivity magnetoencephalography (fcMEG) in this study.

The current study is a prospective cross-sectional analysis from a convenience sample, evaluating the risk of autism in a collection of radiologically diagnosed individuals with complete and partial AgCC (cAgCC and pAgCC, respectively). We chose a well established parent- and self-report screening tool, the Autism Spectrum Quotient (AQ), which can be used to quantify autistic traits for a wide age range (Baron-Cohen et al. 2001, 2006; Auyeung et al. 2008). Our primary hypothesis is that a higher percentage of individuals with AgCC will exceed the autism-screening cut-off relative to controls, with specific difficulties in the domains of social skills and communication, and that AQ scores will correlate with resting-state oscillatory coherence using fcMEG. In post hoc analysis, we explore a direct comparison between our AgCC cohort and a previously described autism cohort, investigate the possible differences in the self-report versus parent-report AQ scores in the adult AgCC cohort, and analyze whether parent self-ratings correlate with their children's AQ scores.

Methods

Participants

Age-appropriate AQ questionnaires were sent to all individuals with AgCC (n = 231) in the Brain Development Research Program (BDRP) database at University of California, San Francisco (UCSF). BDRP participants have generally become aware of our program via online search, through the national disorders of the corpus callosum family group, or by physician referral. In our cohort, AgCC has been identified via routine fetal neuroimaging or neuroimaging as a result of epilepsy, developmental delay or head injury. A diagnosis of AgCC was confirmed by a consensus review of MRI brain imaging by two pediatric neuroradiologists and one pediatric neurologist at UCSF. Images were evaluated for the presence and size of the corpus callosum, the anterior commissure, the hippocampal commissure, cortical malformations (e.g. polymicrogyria, periventricular and subcortical heterotopia), Probst bundles, white matter abnormalities, and dysgenesis of the posterior fossa. Individuals with Aicardi syndrome or other primary brain malformations (such as lissencephaly) were excluded. For more information on the analysis of MRI data, see (Hetts et al. 2006). A subset of the AgCC cohort, with IQ > 70 and age >16 years (n = 18), has participated in a functional neuroimaging and cognitive project at UCSF and our collaborating sites. AgCC participants were assessed in accordance with IRB approval and all AgCC individuals gave consent or assent with guardian consent.

The child AQ was sent to the parents of children aged four to 11 years; 68 out of 128 (53 %) were returned. The adolescent AQ was sent to parents of adolescents aged 12–15 years; 24 out of 33 (73 %) were returned. Individuals in the adult cohort, ages 16 years and older, received the self-report adult AQ and their parents or spouses received the parent-report version (Baron-Cohen et al. 2001); 45 out of 70 (64 %) were returned. We compared the responders (n = 137) to the non-responders (n = 94) on the following variables: age, IQ, and presence of epilepsy. There were similar age profiles in the responders (43 % child, 21 % adolescent, 36 % adult) as compared to the non-responders (56 % child, 11 % adolescent, 33 % adult). There was a lower rate of epilepsy and cognitive impairment in the responders (25 and 23 % respectively) relative to non-responders (39 and 85 % respectively) in those with available data.

Of the 137 returned questionnaires, 106 (77 %) were included in the final analysis (child version n = 47, adolescent version n = 20, and adult version n = 39). AQ data were included if all statements were completed. In one child AQ, a single question was omitted that did not alter his cut-off classification; this participant was included. We obtained IQ data from school and clinic-based assessments on 86 (63 %) of our 137 participants. Of the included participants with IQ data (n = 75), 77 % had an IQ equal to or above 70 while 23 % had an IQ below 70. For the excluded participants, all had an IQ below 70 (n = 11) or were reported to be non-verbal. No significant differences were found between the percentage of males and females across the three age groups (χ^2 (2) = 0.03, $p = 0.98$). There was no statistically significant difference in the relationship between the structural anomaly (pAgCC versus cAgCC) and age category (Fisher's exact, $p = 0.5$). We analyzed 39 parent-report adult AQs and 164 adult self-report AQs that parents completed about themselves (78 fathers, 86 mothers). Refer to Table 1 for further demographic information.

The control and the autism comparison cohorts were derived from the published AQ validation studies. The child and adolescent control cohorts consisted of British school children without autism whose parents completed questionnaires distributed by teachers in mainstream classes. The adult control cohort consisted of respondents to the AQ questionnaire received in the mail. We then compare the AgCC cohort to the autism cohort, which consists of children, adolescents, and adults with Asperger's syndrome/high functioning autism (AS/HFA) were recruited via several sources, including the National Autistic Society (UK), autism specialist clinics, and media advertisements. All AS/HFA individuals received a diagnosis by psychiatrists using established criteria for autism or AS, attended mainstream classes, and had an IQ in the average range.

Table 1 Demographics of the AgCC cohort by AQ age group

	Child (n = 47)	Adolescent (n = 20)	Adult (n = 39)	Total
Age				
Mean (SD, range)	8.0 (2.4, 4–11)	13.6 (0.9, 12–15)	28.2 (13.4, 16–74)	
Sex				
Males	31	13	25	69
Females	16	7	14	37
AgCC type				
Complete	33	15	24	72
Partial	14	5	15	34

Autism Spectrum Quotient (AQ)

The AQ is a standardized questionnaire designed to assess for autism traits in high-functioning individuals. The questionnaire serves as a screening tool for autism in research and is stratified for children, adolescents, and adults. The child and adolescent AQs was completed by parents, and the adult AQ was completed by the affected individual and by their parents. In addition, the parents filled out an AQ self-report. Each version of the AQ has a cut-off score indicating a greater likelihood for the presence of ASD.

The child AQ consists of 50 statements pertinent to cognitive and behavioral aspects of an individual. Three of these statements are eliminated from the total because they were found to be unreliable in young children. Each statement has a four-point scale from zero to three, in which a higher score represents a greater degree of autistic traits. The total child AQ is scored out of 141, with a cut-off score of 76. The questionnaire is further divided into four domains: social skills (45 points), attention to detail (27 points), imagination (21 points), and mind-reading (48 points).

The adolescent and adult AQs consist of 50 statements as well. Each item receives a score of one if the respondent reports the abnormal behavior to be either mild or strong, and a zero score for non-autistic behavior. Both tests are divided into five domains (10 points each)—social skills, attention to detail, imagination, communication, and attention switching—for a total score of 50. The cut-off score for the adolescent and adult AQs are 30 and 32, respectively. For the adult group, in addition to the self-report AQ, there is a parent-report version with 40 statements; 10 statements were eliminated by the AQ authors because they can only be answered subjectively by the individual. No cut-off score was generated for the parent-report version. In this study, for purposes of comparison, the same 10 statements from the adult self-report AQ are eliminated only when used for comparison with the parent-report AQ; the standard 50-question adult self-report AQ is used for all other purposes.

MRI and MEG Data

MRI scans were used for radiologic confirmation of AgCC, the identification of additional anatomic findings, as well as for generation of MEG functional connectivity maps. MEG, a non-invasive imaging technique that records the magnetic fields arising from the electrical activity of the brain, was conducted for a subset of AgCC individuals.

We estimated functional connectivity from MEG data collected during an eyes-closed resting state acquisition (Guggisberg et al. 2008). Functional connectivity was quantified using imaginary coherence (IC), a technique that can be used to estimate the degree to which the neurons in two voxels are firing in synchrony or with a similar oscillatory pattern. From this estimation, we can calculate a global coherence (GC) value for each voxel which represents the degree to which any voxel of interest is firing in coherence or synchrony will ALL other voxels in the brain. For this study, we focused specifically on neuronal firing in the alpha band oscillatory range (8–12 Hz) as this range is dominant during wakeful rest.

MRI Acquisition

Structural (T1-weighted) anatomical images were acquired for source space reconstruction, data visualization and second-level group analyses. Scanning was performed using a 3.0T GE Signa EXCITE scanner installed at Surbeck Lab for Advanced Imaging at the UCSF China Basin campus. For each participant, a 3D-FSPGR high-resolution MRI was acquired (160 1 mm thick slices; matrix = 256 × 256, TE = 2.2 ms, TR = 7 ms, flip angle = 15°).

MEG Acquisition

Data were collected from patients and controls using a 275-channel whole-head biomagnetometer (MEG International Services, Coquitlam, BC, Canada), using a sampling rate of 1,200 Hz. Coils were placed at the nasion and 1 cm rostral to the left and right preauricular points angled toward the nasion in order to localize the position of the head relative to the sensor array. These points were later co-registered to the structural MRI through a spherical single-shell head model. Scan sessions where head movement exceeded 0.5 cm within a run were discarded and repeated. Participants were lying in a supine position and instructed to remain awake with their eyes closed during a 4-min continuous recording session.

Data Reconstruction

From the 4-min recording session, a single, contiguous 60-s period free of significant artifacts (e.g. eyeblinks, EMG noise) was selected for analysis. Previous fcMEG investigations in individuals with brain lesions and schizophrenia have determined that this window provides reliable, consistent measurement of power for reconstruction of brain activity from the resting-state MEG data (Guggisberg et al. 2008; Hinkley et al. 2011). Source-space reconstructions and functional connectivity metrics were computed using NUTMEG (Neurodynamic Utility Toolbox for Magneto-encephalo- and Electroencephalo-Graphy) software suite which is an MEG/EEG analysis toolbox for reconstructing the spatiotemporal dynamics of neural activations and overlaying them onto structural MR images (http://nutmeg.berkeley.edu). In each subject, alpha frequency bins (8–12 Hz range) were selected that showed the greatest power density during the 60-s epoch, selected from a broad 1–20 Hz band with a frequency resolution of 1.17 Hz. A peak in the alpha band was easily identifiable from this amount of data in AgCC patients and controls.

Global Connectivity Analysis

Source estimates were derived using an adaptive spatial filtering technique (Dalal et al. 2008). Functional connectivity between these sources was estimated using imaginary coherence (IC), a metric that overcomes estimation biases in MEG source data by isolating non-zero, time-lagged interactions (Nolte et al. 2004; Guggisberg et al. 2008). Global connectivity (GC) at each location was derived by averaging across all Fisher's Z-transformed IC values between that voxel and all remaining elements (voxels) in the reconstruction. For a second-level group analysis, anatomical T1-weighted MRIs were spatially normalized to the MNI template (a standard adult brain template created by using a large series of MRI scans on normal controls) using SPM2. SPM2 is a statistical parametric mapping program, designed for the analysis of brain imaging data in which an individual's brain images are realigned, spatially normalized into a standard space, and smoothed so that they can be directly compared to other individuals on a voxel by voxel basis (www.fil.ion.ucl.ac.uk/spm/software/spm2). The transformation matrix from the normalization was then applied to each individual subject's GC map.

Statistical Analysis

Statistical analysis of behavioral data was performed using STATA (version 11.0, College Station, TX, USA). Participant demographics were compared using Chi squared analyses and two-sided Fisher's exact tests. To explore our primary hypothesis that the percentage of individuals with AgCC who exceed the autism-screening cut-off will differ from controls, we conducted a Chi-squared analysis for each age cohort and adjusted for the three age cohort comparisons using a Bonferroni correction ($p < 0.017$). If there was a statistically significant difference at this level, we compared AQ domain comparisons within each age group. These comparisons were performed using two-tailed T tests, Bonferroni adjustment based on the number of comparisons: the child AQ has four comparisons ($p = 0.013$), and the adolescent and adult AQs each have five comparisons ($p = 0.01$).

To explore the relationship between resting-state functional connectivity and autism traits, we computed a voxel-wise Pearson's r correlation between GC maps and the AQ domain scores. Statistically significant correlations were corrected for multiple comparisons for these voxel-wise tests using a statistically stringent 5 % False Discovery Rate threshold (5 % FDR).

Results

Autism Trait Occurrence in AgCC

To address our primary hypothesis, we compared AQ scores between the AgCC and control cohort. We found that in all age groups, a greater proportion of individuals with AgCC exceeded the autism-screening AQ cut-off relative to controls. In children, 45 % of the AgCC cohort scored in the autism range versus 4.3 % of the published control cohort (χ^2 (1) = 134.5, $p < 0.001$). In adolescents, 35 % of the AgCC cohort exceeded the cut-off compared to none of the adolescent controls (Fisher's exact, $p < 0.001$). In adults, 18 % of the AgCC individuals exceeded the cut-off compared to 2.3 % of the adult controls (Fisher's exact, $p = 0.001$).

There was no statistically significant relationship between sex and those exceeding cut-off in any of the age groups (χ^2 (2) = 0.032, $p = 0.51$; Adolescent: Fisher's exact, $p = 1.00$; Adult: Fisher's exact, $p = 0.08$). Similarly, there was no statistically significant relationship between the categorical callosal morphology (pAgCC vs. cAgCC) and those exceeding cut-off in any of the ages groups (Fisher's exact, Child: $p = 0.11$; Adolescent: $p = 0.29$; Adult: $p = 0.36$). There was also no statistical difference in the percentage of individuals with high and low IQs (IQ $\geq$ 70 and <70) who scored above the AQ cut-off (χ^2 (1) = 0.38, $p = 0.5$).

Given that all age cohorts show significant differences from controls based on the total AQ measure, we conducted a domain-specific analysis. For the child AQ, the

AgCC group showed greater deficits in three of four domains: social skills, imagination, and mind-reading (Table 2). Similarly, in adolescents and adults, the AgCC group showed impairment relative to controls in four out of five domains: social skills, imagination, communication, and attention switching. We did not find differences in attention to detail for any of the groups. Refer to Table 2 for means, standard deviations, and significance levels for each domain. Figure 1 shows distribution patterns of AQ scores.

Across all ages, a greater proportion of individuals with AgCC screened positive for autistic traits relative to controls. Individuals with AgCC shared deficits in social skills, imagination, mind-reading, communication, and attention switching. Individuals with AgCC did not show enhanced attention to detail.

Autism Trait Correlation with Resting-State Brain Connectivity

To explore the neural mechanisms that contribute to autism traits in individuals with AgCC, we examined resting-state functional connectivity using MEG and the AQ continuous domain scores. We computed a linear correlation between global resting-state functional connectivity measures and behavioral variables for each of the five parent-report domains in the adult AgCC cohort. Global connectivity (GC) of one region in the right superior temporal gyrus (R-STG; $x = 45$, $y = 5$, $z = -15$; Fig. 2) showed a strong negative correlation with the imagination measure on the parent-report adult AQ ($r = -0.74$, $p < 0.0005$, 5 % FDR correction). The other AQ domain scores did not significantly correlate with the voxel-based GC.

Post Hoc Analyses

Individuals with AgCC Compared to Individuals with Autism

After determining that individuals with AgCC differed from controls on the AQ, we sought to investigate how this AgCC cohort compared with a group of high-functioning individuals with autism. In all age cohorts, fewer individuals with AgCC exceeded the AQ cut-off and fewer deficits were seen in each AQ domains relative to individuals with autism (Table 2). The only exception was in the adult cohort, in which the individuals in the AgCC group did not statistically differ from the autism cohort on the attention to detail domain after correction for multiple comparisons. In general, the distribution of AQ scores for individuals with AgCC appeared intermediate between controls and individuals with autism across all domains with the exception of attention to detail, which is more similar to controls.

Adult Cohort: Self-Report AQ Scores Compared to Parent-Report AQ Scores

Clinical and investigative evidence suggests that AgCC individuals lack insight into their behavioral and cognitive impairments (Badaruddin et al. 2007; Brown and Paul 2000; Stickles et al. 2002). We therefore investigated

Table 2 AQ scores summary for AgCC cohort, control cohort and autism cohort

Child	Social	Detail	Imagination	Mind-read	Above cut-off (%)
AgCC (n = 47)	20.6 (8.3)	11.1 (5.6)	10.7 (5.1)	29.3 (9.0)	45
Controls (n = 1,225)	10.8 (7.4)**	11.6 (5.7)	4.0 (3.7)**	15.3 (7.9)**	4.3
Autism (n = 192)	32.7 (7.2)$^{++}$	16.7 (5.5)$^{++}$	15.4 (4.2)$^{++}$	38.1 (5.9)$^{++}$	95.2

Adolescent	Social	Detail	Imagination	Communication	Switching	Above cut-off (%)
AgCC (n = 20)	4.6 (2.2)	4.3 (2.7)	5.1 (2.2)	6.0 (2.2)	6.8 (1.7)	35
Controls (n = 50)	2.0 (1.9)**	5.3 (2.4)	3.2 (2.3)*	2.7 (1.7)**	4.5 (2.0)**	0
Autism (n = 79)	8.0 (1.9)$^{++}$	6.5 (2.1)$^{++}$	7.6 (2.0)$^{++}$	8.0 (1.5)$^{++}$	8.3 (1.6)$^{++}$	88.6

Adult	Social	Detail	Imagination	Communication	Switching	Above cut-off (%)
Self-report AgCC ~ 50 (n = 39)	3.7 (2.8)	5.7 (2.3)	3.4 (1.7)	4.3 (2.6)	5.4 (2.2)	18
Controls (n = 174)	2.6 (2.3)*	5.3 (2.3)	2.3 (1.7)**	2.4 (1.9)**	3.9 (1.9)**	2.3
Autism (n = 58)	7.5 (1.9)$^{++}$	6.7 (2.3)	6.4 (2.1)$^{++}$	7.2 (2.0)$^{++}$	8.0 (1.8)$^{++}$	79.3

Social social skills, *detail* attention to details, *Switching* attention switching. Below each domain is listed the mean value, followed by the standard deviation with the significance for the comparison as denoted below to either the control cohort or the autism cohort. Control and autism cohort scores are from original published AQ data: Auyeung et al. 2008; Baron-Cohen et al. 2001, 2006; AgCC versus controls: * significant at $p < 0.01$; ** significant at $p < 0.0005$; AgCC versus autism: $^{++}$ significant at $p < 0.0005$

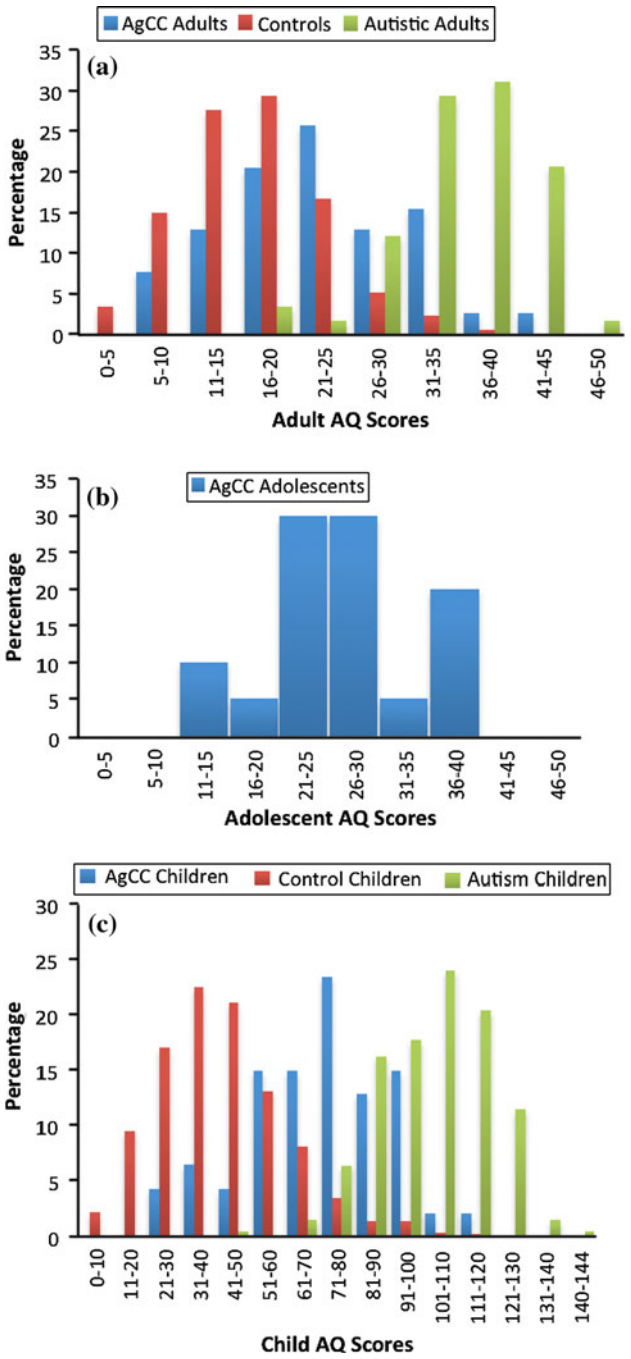

Fig. 1 Distribution of AQ scores in the AgCC, control, and autism cohorts by age. **a** Distribution of AQ scores in children, total possible score = 141, cut off for autism 76. **b** Distribution of AQ scores in adolescents, total possible score = 50, cut off for autism 30. Data for the autism and control adolescents was not available. **c** Distribution of self-report AQ scores in adults, total possible score = 50, cut off for autism 32

whether parents and their children with AgCC have a similar perception of their child's degree of disability, expecting that AgCC individuals would score themselves less affected relative to parental ratings. We tested this hypothesis in the adult cohort, as only the adult AQ allows for both a self and parental assessment. Using a paired *t* test, we compared self-report adult AQ scores to parent-report AQ scores and found that parental scores were significantly higher than the self-reported scores ($p = 0.001$). Therefore, parents rate their adult children as more affected than individuals rate themselves.

Individuals with AgCC Compared to Their Parents

Both genetic and environmental factors are clearly important contributors to ASD as evidenced by twin studies as well as large genetic studies (Hallmayer et al. 2011; Weiss et al. 2008). Previous research suggests that autism traits exist on a continuum. Some, but not all, first-degree relatives of autistic individuals display higher autistic traits than the general population. This finding is commonly referred to as "the broader autism phenotype" (Constantino and Todd 2005; Pickles et al. 2000; Piven et al. 1997; Wheelwright et al. 2010). By contrast, AgCC has a very low rate of multiply affected members in a family (Moes et al. 2009) and de novo genetic events likely play a more significant role (Sherr et al. 2005; Glass et al. 2008). Consequently, we assessed autism traits in parents of individuals with AgCC. We administered the adult self-report AQ to parents and found that only two parents (1 %) exceeded the cut-off score with no significant differences compared to adult controls (Fisher's exact, $p = 0.686$). We also performed a Pearson's correlation comparing the AQ total between parents' self-report score and their child's AQ score. We found no significant correlation. Therefore, within our AgCC cohort, autistic traits do not appear to be shared by their parents.

Discussion

This study explored the extent of autism traits in a large cohort of individuals with AgCC. We found that on average 33 % of individuals with AgCC exceeded the autism-screening cut-off. Interestingly, as a whole, the AgCC cohort appeared to have deficits in the same domains as the autism cohort, with the notable exception of enhanced attention to detail. Furthermore, our functional imaging analysis showed a correlation between a domain of the AQ and the right superior temporal gyrus (R-STG), a brain region implicated in language perception and social processing (Akiyama et al. 2006; Cheng et al. 2010). These findings suggest the need for autism trait assessment in individuals with disorders of the corpus callosum, but also a need for a higher level for surveillance of structural brain anomolies in children with autism.

Screening for autism is recommended by the American Academy of Pediatrics and the American Academy of

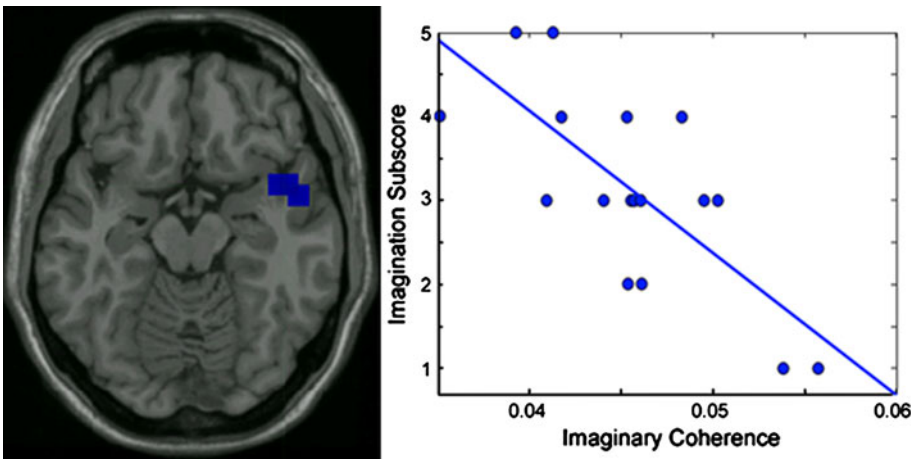

Fig. 2 Results of a correlation analysis between resting-state MEG functional connectivity values (imaginary coherence) and AQ scores (imagination subscore) for the AgCC cohort. A significant negative correlation ($p < 0.0005$) is seen between functional connectivity of the superior temporal gyrus (*left column*, green crosshairs) and AQ imagination scores. The correlation map is overlaid on a canonical T1-weighted MNI template brain

Neurology for all children failing routine developmental surveillance (Johnson and Myers 2007; Filipek et al. 2000). Many screening tools are used in current practice, including: the Modified Checklist for Autism in Toddlers and the Social Communication Questionnaire (Robins et al. 2001; Rutter et al. 2003). However, given the accumulating clinical evidence of autism traits in the AgCC population, we wished to screen for autism in AgCC individuals of all ages and chose the AQ because it has been validated across all age groups (Doherty et al. 2006; Badaruddin et al. 2007). The AQ is a robust instrument, with high sensitivity and specificity of 95 % for autism and Asperger syndrome in the child AQ (Auyeung et al. 2008). In this study, 33 % of AgCC individuals, averaged across all age domains, exceeded the initially defined screening threshold for ASD. In a recent publication, the authors of the AQ suggest that a less stringent criteria may be useful in considering behavioral variables to reflect their continuous natures. The Broader Autism Phenotype (BAP) corresponds to a total AQ score between one and two standard deviations above the mean, while a Medium Autism Phenotype (MAP) corresponds to an AQ score between two and three standard deviations from the control mean. In addition to the BAP and MAP, the narrow autism phenotype (NAP) is greater than three standard deviations from the mean (Wheelwright et al. 2010). Using this parcellated scoring system, we find that in children with AgCC, 34 % meet BAP criteria, 32 % meet MAP criteria, and 4 % meet NAP criteria. For adolescents with AgCC, 40 % meet BAP criteria, 15 % meet MAP criteria, and 20 % meet NAP criteria. Finally, for adults with AgCC, 23 % meet BAP criteria, 18 % meet MAP criteria, and 5 % meet NAP criteria. Clearly, individuals with disorders of the corpus callosum are also beset by symptoms characteristic of autism. In comparison, other genetic disorders associated with autism, such as Fragile X and Tuberous sclerosis, are reported to have ASD prevalence (more broadly defined) between 21 and 33 % (Bailey et al. 2001; Hatton et al. 2006; Hunt and Shepherd 1993). Therefore, similar to other disorders, AgCC has a high prevalence of autism traits and as a result, disorders of the corpus callosum should be considered an important contributor to ASD.

Beyond assessing autism traits as a whole, the AQ domains relate to specific core deficits of autism as defined by the DSM-IV TR: (1) social interaction, (2) communication, and (3) repetitive and restricted behaviors and interests. In general, the social skills and mind-reading domains are most similar to the social interaction criterion; communication and imagination domains are most similar to the communication criterion; and attention switching and attention to detail domains relate to the repetitive and restricted behaviors criterion. While our AgCC cohort shows impairment across all core deficits, Badaruddin et al. (2007) suggested that children with AgCC are more affected in two out of three criteria, with less impairment in repetitive and restricted behaviors and interests. We found significant impairment in attention switching, but not in attention to detail. For instance, on the AQ attention switching domain, participants displayed a more autistic phenotype by endorsing a strict adherence to routines and persistent preoccupation with limited interests. In contrast, AgCC individuals report more typical attention to detail, with the preserved ability to appreciate the whole rather than a preoccupation with patterns or parts.

In an attempt to understand the difference between attention switching and attention to detail, we highlight a theory proposed by Rubenstein and Merzenich (2003). They suggest an imbalance of excitatory and inhibitory inputs at the level of primary sensory cortices, which may account for symptoms observed in autistic individuals, including poor early auditory processing and seizures (Roberts et al. 2010; Spence and Schneider 2009). It is unclear whether individuals with AgCC, on the whole, share this increased early cortical excitation which has also

been suggested to lead to a "local bias" or attention to parts rather than the whole (Mottron et al. 2000). If the individuals with AgCC show decreased long range connectivity but not increased local excitation, then we would expect a divergence in the attention switching score. Attention switching relies heavily on frontal-parietal connections while attention to detail is thought to be more heavily reliant on localized primary sensory cortex activation. However, there are common biological pathways reported in autistic individuals with and without AgCC which result in both disrupted connectivity and neuronal excitation, namely mutations in the ARX gene (Sherr 2003). In this case, inactivation of this transcription factor can affect the birth of inhibitory interneurons and development of commissural projection neurons. It is not known, for example, whether all individuals with ARX mutations show increased attention to detail but as we move toward a deeper understanding of autism etiology and neural mechanisms, we will able to relate etiologies to phenotypes and use this information to provide more targeted treatments. AgCC, as more homogenous anatomic model than idiopathic autism, provides an excellent system for exploring how disruption in long-range connectivity beginning in utero affects cognition and behavior.

Neuroanatomy and neuroimaging autism research are converging to suggest that a combination of abnormalities in local cortical activity and long-range connections may contribute to an autism phenotype (Just et al. 2007; Thomas et al. 2010). While much of the autism neuroimaging literature has addressed the connectivity question from the starting point of an autism diagnosis, this study asks the question with a starting point of the neuroanatomy. When beginning from the autism diagnosis, it is unclear whether the observed diminutive corpus callosum and reduced long range connectivity is a primary finding or a secondary effect of abnormal earlier sensory processing. However, when beginning with a model system that is created in utero without all or part of the corpus callosum, we can interrogate the role of this long-range connectivity and its relationship to autism symptoms more directly. This study allows us to state that, in addition to ongoing developmental effects, interrupted interhemispheric information transfer, served by the corpus callosum, is a primary contributor to the core autism traits as measured by the AQ. The MEG-I data allows us to speculate further regarding the neural mechanisms underlying some of the deficits.

Previous research suggests that some individuals with autism and AgCC rely more heavily on the right hemisphere for language processing (Leighton et al., in review). For example, individuals with autism were shown to have increased right temporal activation for reading passages that required inferences based on intentions, emotional states, or physical causality. The functional connectivity of the evoked theory of mind network was positively correlated with the size of the anterior portion of the corpus callosum as well (Mason et al. 2008). Here, we observe that the degree of connectivity to the right superior temporal gyrus in adults with AgCC predicts the AQ imagination domain score (Fig. 2). The imagination domain measures an individual's interest and ability to engage in imaginative play and creative thinking with language and mental imagery components. Questions contributing to this score include: he/she finds making up stories easy, he/she used to enjoy playing games involving pretending with other children, and he/she would rather go to a theatre than a museum. Our finding is consistent with previous imaging work probing the neurophysiological bases of imagination, including both imagined motor behavior and imagined melodic perception (la Fougere et al. 2010; Halpern and Zatorre 1999). Moreover, in previous autism studies the R-STG has been reported to be atypical when using structural imaging and functional activation studies of language, emotion, and social intelligence (Baron-Cohen et al. 1999; Casanova et al. 2002; Jou et al. 2010; Wicker et al. 2003). The increased reliance on R-STG connectivity might reflect a compensatory, but less effective, recruitment of a right hemisphere region for a traditionally left hemisphere function or may reflect a continuous behavioral trait that exists across the general population (Kleinhans et al. 2008). Taken together, the autism screening and functional imaging data suggest that the long-range communication mediated by the corpus callosum plays a primary role in the development of autism traits and that, in particular, the connectivity of the right superior temporal cortex may underlie some of the communication differences. Given the dynamic nature of brain connectivity maturation, a longitudinal study of brain coherence from infancy through early childhood would be of tremendous value to further delineate the general network connectivity in AgCC and idiopathic autism.

In our post hoc analysis, we explored whether AgCC individuals lack insight into their cognitive and behavior difficulties similar to what has been reported for adults with autism (Kanner 1971; Adolphs et al. 2001). Parents of individuals with AgCC frequently describe poor social competence, superficial relationships, inability to understand another's perspective, and failure to appreciate language pragmatics (Badaruddin et al. 2007; Brown and Paul 2000; Stickles et al. 2002). Anecdotally we observed that parents did in fact view their adult child as having a greater level of impairment than was perceived by their adult child. Thus, we performed a post hoc adjustment to equalize the self-report and parental scores (by adding the total AQ score + (mean item score × 10). Using this approach, which was also performed by the authors of the child AQ, the parental scores show that 38 % (15 out of 39) of the

AgCC adults exceeded the autism cut-off, whereas only 18 % reached threshold in the self-reported scoring. This new estimate is similar to the results found in our child and adolescent cohorts.

In the last part of our post hoc analysis, we explore whether or not the parents of AgCC individuals might show a higher rate of autistic traits similar to their children. The heredity of autism has been well studied and previous studies show that some first-degree relatives or parents will score in an intermediate range on autism scales, in line with a continuously distributed trait (Virkud et al. 2009). However, in individuals with AgCC, we observe that their structural abnormalities are often associated with de novo chromosomal mutations and that the recurrence risk for families is quite low, suggesting that the behavioral phenotypes may also be discontinuous (Sherr et al. 2005). In this study, AQ scores of parents did not differ from the control cohort and thus the parents did not show traits consistent with an autism phenotype. Therefore, we hypothesize that the autistic traits in individuals with AgCC are related to their structural anomalies as opposed to other shared genetic or environmental factors. In an ongoing parallel study, we have shown that AgCC individuals are more likely to share large genomic copy number variants with autistic individuals as compared to controls (E. H. Sherr, personal communication). This suggests that there is not only a shared behavioral similarity between AgCC and autism, but that there are shared genetic etiologies as well.

A few limitations and issues in this study should be highlighted. First, there is a referral bias based on our cohort recruitment and the tool that we are using. While some individuals are identified through routine fetal screening, most are identified due to neuroimaging prompted by seizures or developmental delay. Caution must be exercised when generalizing these occurrence rates to a prevalence for autism traits in the AgCC population at large. In addition, the AQ is not designed to assess non-verbal individuals; as such, our study cannot address this segment of the AgCC population. It is possible that by using a screening tool, we may observe a higher rate of autism by selecting for lower functioning patients. However, the majority of our included participants have IQs above 70, and there was no difference between the IQ in those who did and did not exceed the AQ cut-off. Therefore, IQ did not appear to bias this finding towards overestimation.

Second, there is an assessment limitation. It is important to consider that a parent-report questionnaire does not definitively constitute a diagnosis of autism. Based on best practice recommendations, a diagnosis must be determined by the combination of a parent interview and direct observation of the individual by an experienced clinician. Therefore, the positive screens in this study are an estimate and not a diagnostic measurement of the occurrence of autism in our AgCC cohort.

Third, we have limited risk factor and phenotype data on our participants as this is a national sample collected through the mail, phone calls, and online information gathering. A comprehensive research medical history, neuroimaging, and cognitive/autism assessment is essential, particularly given the suggestive nature of these results.

Fourth, our adolescent sample has a small sample size and we had a 59 % response rate of the mailed questionnaires. The percentage of individuals exceeding cut-off in the adolescent cohort is consistent with the child group and the adjusted parent-report adult estimate, suggesting that we had an adequate sample for establishing occurrence rates in this age category. As addressed in the participant section, the non-responder group has roughly similar representation in the three age categories with lower rates of epilepsy but higher levels of cognitive impairment.

Finally, we have a cultural bias in that the published control and autism participants for the AQ are primarily from the UK and online sources. The AQ has been utilized by studies conducted in the United States, Japan and the Netherlands with adult control and autism cohorts (Bishop and Seltzer 2012; Ketelaars et al. 2008; Kurita et al. 2005). The US, Japanese and Netherland studies suggest a lower mean AQ score for the ASD cohort relative to the original UK sample even when controlling for IQ variation. This may reflect a cultural variation in self-reflection that would be most salient in the self-report adult version of the assessment. In our sample, we also note that parents rate their adult offspring as more affected than the offspring rate themselves. This cultural bias would suggest that our findings would underestimate the true occurrence of autism traits in this US based cohort. A prospective, longitudinal, population-based direct assessment of individuals, with and without AgCC, using IQ-and culturally appropriate diagnostic tools is needed to discover a more accurate estimate of autism spectrum conditions in the AgCC population.

In summary, a high percentage of individuals with AgCC display many traits characteristic of individuals diagnosed with autism spectrum conditions. We suggest that all individuals with AgCC should be clinically assessed for deficits in communication, social skills, and repetitive interests and behavior. Also, given these findings, structural causes such as AgCC should be considered in the etiologic investigation of autism spectrum conditions. Imaging of autistic children may prove to be valuable especially if patients present with other features such as motor delay, epilepsy, and/or macrocephaly.

Acknowledgments This work was supported in part by NIH grants R01 DC004855, DC006435, DC010145, NS067962, NS64060, and by NSF grant BCS-0926196 to S.S.N, NIH grant K23 MH083890 to E.J.M., K02 NS052192 to E.H.S., KL2 RR024130 to E.J.M, E.H.S.), the Sandler Program for Breakthrough Biomedical Research (E.H.S.), the Simons Foundation (L.K.P), NARSAD (L.K.P.) and the Dystonia Medical Research Foundation (L.B.N.H.). This project was supported by NIH/NCRR UCSF-CTSI Grant Number UL1 RR024131. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH. This project is made possible primarily through the efforts of our participants and their families.

References

Adolphs, R., Sears, L., & Piven, J. (2001). Abnormal processing of social information from faces in autism. *Journal of Cognitive Neuroscience, 13*(2), 232–240.

Akiyama, T., Kato, M., Muramatsu, T., Saito, F., Nakachi, R., & Kashima, H. (2006). A deficit in discriminating gaze direction in a case with right superior temporal gyrus lesion. *Neuropsychologia, 44*(2), 161–170. doi:10.1016/j.neuropsychologia.2005.05.018.

Alexander, A. L., Lee, J. E., Lazar, M., Boudos, R., DuBray, M. B., Oakes, T. R., et al. (2007). Diffusion tensor imaging of the corpus callosum in autism. *Neuroimage, 34*(1), 61–73. doi:10.1016/j.neuroimage.2006.08.032.

American Psychiatric Association. (2000). *Diagnostic criteria from DSM-IV-TR*. Washington, DC: American Psychiatric Association.

Auyeung, B., Baron-Cohen, S., Wheelwright, S., & Allison, C. (2008). The Autism Spectrum Quotient: Children's Version (AQ-Child). *Journal of Autism and Developmental Disorders, 38*(7), 1230–1240. doi:10.1007/s10803-007-0504-z.

Badaruddin, D. H., Andrews, G. L., Bolte, S., Schilmoeller, K. J., Schilmoeller, G., Paul, L. K., et al. (2007). Social and behavioral problems of children with agenesis of the corpus callosum. *Child Psychiatry and Human Development, 38*(4), 287–302. doi:10.1007/s10578-007-0065-6.

Bailey, D. B., Jr., Hatton, D. D., Skinner, M., & Mesibov, G. (2001). Autistic behavior, FMR1 protein, and developmental trajectories in young males with fragile X syndrome. *Journal of Autism and Developmental Disorders, 31*(2), 165–174.

Baron-Cohen, S., Hoekstra, R. A., Knickmeyer, R., & Wheelwright, S. (2006). The Autism-Spectrum Quotient (AQ)—Adolescent version. *Journal of Autism and Developmental Disorders, 36*(3), 343–350. doi:10.1007/s10803-006-0073-6.

Baron-Cohen, S., Scahill, V. L., Izaguirre, J., Hornsey, H., & Robertson, M. M. (1999). The prevalence of Gilles de la Tourette syndrome in children and adolescents with autism: A large scale study. *Psychological Medicine, 29*(5), 1151–1159.

Baron-Cohen, S., Wheelwright, S., Skinner, R., Martin, J., & Clubley, E. (2001). The autism-spectrum quotient (AQ): Evidence from Asperger syndrome/high-functioning autism, males and females, scientists and mathematicians. *Journal of Autism and Developmental Disorders, 31*(1), 5–17.

Belmonte, M. K., Allen, G., Beckel-Mitchener, A., Boulanger, L. M., Carper, R. A., & Webb, S. J. (2004). Autism and abnormal development of brain connectivity. *Journal of Neuroscience, 24*(42), 9228–9231. doi:10.1523/JNEUROSCI.3340-04.2004.

Bishop, S. L., & Seltzer, M. M. (2012). Self-reported autism symptoms in adults with autism spectrum disorders. *Journal of Autism and Developmental Disorders,*. doi:10.1007/s10803-012-1483-2.

Brown, W. S., & Paul, L. K. (2000). Cognitive and psychosocial deficits in agenesis of the corpus callosum with normal intelligence. *Cognitive Neuropsychiatry, 5*(2), 135–157.

Casanova, M. F., Buxhoeveden, D. P., & Brown, C. (2002). Clinical and macroscopic correlates of minicolumnar pathology in autism. *Journal of Child Neurology, 17*(9), 692–695.

Casanova, M. F., El-Baz, A., Mott, M., Mannheim, G., Hassan, H., Fahmi, R., et al. (2009). Reduced gyral window and corpus callosum size in autism: possible macroscopic correlates of a minicolumnopathy. *Journal of Autism and Developmental Disorders, 39*(5), 751–764. doi:10.1007/s10803-008-0681-4.

Cheng, Y., Chou, K. H., Chen, I. Y., Fan, Y. T., Decety, J., & Lin, C. P. (2010). Atypical development of white matter microstructure in adolescents with autism spectrum disorders. *Neuroimage, 50*(3), 873–882. doi:10.1016/j.neuroimage.2010.01.011.

Constantino, J. N., & Todd, R. D. (2005). Intergenerational transmission of subthreshold autistic traits in the general population. *Biological Psychiatry, 57*(6), 655–660. doi:10.1016/j.biopsych.2004.12.014.

Dalal, S. S., Guggisberg, A. G., Edwards, E., Sekihara, K., Findlay, A. M., Canolty, R. T., et al. (2008). Five-dimensional neuroimaging: localization of the time–frequency dynamics of cortical activity. *Neuroimage, 40*(4), 1686–1700. doi:10.1016/j.neuroimage.2008.01.023.

Doherty, D., Tu, S., Schilmoeller, K., & Schilmoeller, G. (2006). Health-related issues in individuals with agenesis of the corpus callosum. *Child: Care, Health and Development, 32*(3), 333–342. doi:10.1111/j.1365-2214.2006.00602.x.

Filipek, P. A., Accardo, P. J., Ashwal, S., Baranek, G. T., Cook, E. H., Jr., Dawson, G., et al. (2000). Practice parameter: Screening and diagnosis of autism: Report of the Quality Standards Subcommittee of the American Academy of Neurology and the Child Neurology Society. *Neurology, 55*(4), 468–479.

Frazier, T. W., & Hardan, A. Y. (2009). A meta-analysis of the corpus callosum in autism. *Biological Psychiatry, 66*(10), 935–941. doi:10.1016/j.biopsych.2009.07.022.

Friauf, E., & Lohmann, C. (1999). Development of auditory brainstem circuitry. Activity-dependent and activity-independent processes. *Cell and Tissue Research, 297*(2), 187–195.

Glass, H. C., Shaw, G. M., Ma, C., & Sherr, E. H. (2008). Agenesis of the corpus callosum in California 1983–2003: A population-based study. *American Journal of Medical Genetics. Part A, 146A*(19), 2495–2500. doi:10.1002/ajmg.a.32418.

Guggisberg, A. G., Honma, S. M., Findlay, A. M., Dalal, S. S., Kirsch, H. E., Berger, M. S., et al. (2008). Mapping functional connectivity in patients with brain lesions. *Annals of Neurology, 63*(2), 193–203. doi:10.1002/ana.21224.

Hadjikhani, N., Joseph, R. M., Snyder, J., & Tager-Flusberg, H. (2006). Anatomical differences in the mirror neuron system and social cognition network in autism. *Cerebral Cortex, 16*(9), 1276–1282. doi:10.1093/cercor/bhj069.

Hallmayer, J., Cleveland, S., Torres, A., Phillips, J., Cohen, B., Torigoe, T., et al. (2011). Genetic heritability and shared environmental factors among twin pairs with autism. *Archives of General Psychiatry, 68*(11), 1095–1102. doi:10.1001/archgenpsychiatry.2011.76.

Halpern, A. R., & Zatorre, R. J. (1999). When that tune runs through your head: A PET investigation of auditory imagery for familiar melodies. *Cerebral Cortex, 9*(7), 697–704.

Hardan, A. Y., Pabalan, M., Gupta, N., Bansal, R., Melhem, N. M., Fedorov, S., et al. (2009). Corpus callosum volume in children with autism. *Psychiatry Research, 174*(1), 57–61. doi:10.1016/j.pscychresns.2009.03.005.

Hatton, D. D., Sideris, J., Skinner, M., Mankowski, J., Bailey, D. B., Jr., Roberts, J., et al. (2006). Autistic behavior in children with fragile X syndrome: prevalence, stability, and the impact of

FMRP. *American Journal of Medical Genetics. Part A, 140A*(17), 1804–1813. doi:10.1002/ajmg.a.31286.

Hetts, S. W., Sherr, E. H., Chao, S., Gobuty, S., & Barkovich, A. J. (2006). Anomalies of the corpus callosum: An MR analysis of the phenotypic spectrum of associated malformations. *AJR. American Journal of Roentgenology, 187*(5), 1343–1348. doi:10.2214/AJR.05.0146.

Hinkley, L. B., Vinogradov, S., Guggisberg, A. G., Fisher, M., Findlay, A. M., & Nagarajan, S. S. (2011). Clinical symptoms and alpha band resting-state functional connectivity imaging in patients with schizophrenia: implications for novel approaches to treatment. *Biological Psychiatry, 70*(12), 1134–1142. doi:10.1016/j.biopsych.2011.06.029.

Hunt, A., & Shepherd, C. (1993). A prevalence study of autism in tuberous sclerosis. *Journal of Autism and Developmental Disorders, 23*(2), 323–339.

Hyde, K. L., Samson, F., Evans, A. C., & Mottron, L. (2010). Neuroanatomical differences in brain areas implicated in perceptual and other core features of autism revealed by cortical thickness analysis and voxel-based morphometry. *Human Brain Mapping, 31*(4), 556–566. doi:10.1002/hbm.20887.

Johnson, C. P., & Myers, S. M. (2007). Identification and evaluation of children with autism spectrum disorders. *Pediatrics, 120*(5), 1183–1215. doi:10.1542/peds.2007-2361.

Jou, R. J., Minshew, N. J., Keshavan, M. S., Vitale, M. P., & Hardan, A. Y. (2010). Enlarged right superior temporal gyrus in children and adolescents with autism. *Brain Research, 1360*, 205–212. doi:10.1016/j.brainres.2010.09.005.

Just, M. A., Cherkassky, V. L., Keller, T. A., & Minshew, N. J. (2004). Cortical activation and synchronization during sentence comprehension in high-functioning autism: Evidence of underconnectivity. *Brain, 127*(Pt 8), 1811–1821.

Just, M. A., Cherkassky, V. L., Keller, T. A., Kana, R. K., & Minshew, N. J. (2007). Functional and anatomical cortical underconnectivity in autism: evidence from an FMRI study of an executive function task and corpus callosum morphometry. *Cerebral Cortex, 17*(4), 951–961. doi:10.1093/cercor/bhl006.

Kanner, L. (1971). Follow-up study of eleven autistic children originally reported in 1943. *Journal of Autism and Childhood Schizophrenia, 1*(2), 119–145.

Keary, C. J., Minshew, N. J., Bansal, R., Goradia, D., Fedorov, S., Keshavan, M. S., et al. (2009). Corpus callosum volume and neurocognition in autism. *Journal of Autism and Developmental Disorders, 39*(6), 834–841. doi:10.1007/s10803-009-0689-4.

Ketelaars, C., Horwitz, E., Sytema, S., Bos, J., Wiersma, D., Minderaa, R., et al. (2008). Brief report: adults with mild autism spectrum disorders (ASD): Scores on the autism spectrum quotient (AQ) and comorbid psychopathology. *Journal of Autism and Developmental Disorders, 38*(1), 176–180. doi:10.1007/s10803-007-0358-4.

Kleinhans, N. M., Muller, R. A., Cohen, D. N., & Courchesne, E. (2008). Atypical functional lateralization of language in autism spectrum disorders. *Brain Research, 1221*, 115–125. doi:10.1016/j.brainres.2008.04.080.

Kurita, H., Koyama, T., & Osada, H. (2005). Autism-Spectrum Quotient—Japanese version and its short forms for screening normally intelligent persons with pervasive developmental disorders. *Psychiatry and Clinical Neurosciences, 59*(4), 490–496. doi:10.1111/j.1440-1819.2005.01403.x.

la Fougere, C., Zwergal, A., Rominger, A., Forster, S., Fesl, G., Dieterich, M., et al. (2010). Real versus imagined locomotion: A [18F]-FDG PET-fMRI comparison. *Neuroimage, 50*(4), 1589–1598. doi:10.1016/j.neuroimage.2009.12.060.

Lukose, R., Schmidt, E., Wolski, T. P., Jr., Murawski, N. J., & Kulesza, R. J., Jr. (2011). Malformation of the superior olivary complex in an animal model of autism. *Brain Research, 1398*, 102–112. doi:10.1016/j.brainres.2011.05.013.

Mason, R. A., Williams, D. L., Kana, R. K., Minshew, N., & Just, M. A. (2008). Theory of mind disruption and recruitment of the right hemisphere during narrative comprehension in autism. *Neuropsychologia, 46*(1), 269–280. doi:10.1016/j.neuropsychologia.2007.07.018.

Moes, P., Schilmoeller, K., & Schilmoeller, G. (2009). Physical, motor, sensory and developmental features associated with agenesis of the corpus callosum. *Child: Care, Health and Development, 35*(5), 656–672. doi:10.1111/j.1365-2214.2009.00942.x.

Mottron, L., Peretz, I., & Menard, E. (2000). Local and global processing of music in high-functioning persons with autism: Beyond central coherence? *Journal of Child Psychology and Psychiatry, 41*(8), 1057–1065.

Nolte, G., Bai, O., Wheaton, L., Mari, Z., Vorbach, S., & Hallett, M. (2004). Identifying true brain interaction from EEG data using the imaginary part of coherency. *Clinical Neurophysiology, 115*(10), 2292–2307. doi:10.1016/j.clinph.2004.04.029.

Paul, L. K. (2011). Developmental malformation of the corpus callosum: A review of typical callosal development and examples of developmental disorders with callosal involvement. *Journal of Neurodevelopmental Disorders, 3*(1), 3–27. doi:10.1007/s11689-010-9059-y.

Paul, L. K., Brown, W. S., Adolphs, R., Tyszka, J. M., Richards, L. J., Mukherjee, P., et al. (2007). Agenesis of the corpus callosum: Genetic, developmental and functional aspects of connectivity. *Nature Reviews Neuroscience, 8*(4), 287–299. doi:10.1038/nrn2107.

Paul, L. K., Lautzenhiser, A., Brown, W. S., Hart, A., Neumann, D., Spezio, M., et al. (2006). Emotional arousal in agenesis of the corpus callosum. *International Journal of Psychophysiology, 61*(1), 47–56. doi:10.1016/j.ijpsycho.2005.10.017.

Paul, L. K., Schieffer, B., & Brown, W. S. (2004). Social processing deficits in agenesis of the corpus callosum: Narratives from the Thematic Appreciation Test. *Archives of Clinical Neuropsychology, 19*(2), 215–225. doi:10.1016/S0887-6177(03)00024-6.

Paul, L. K., Van Lancker-Sidtis, D., Schieffer, B., Dietrich, R., & Brown, W. S. (2003). Communicative deficits in agenesis of the corpus callosum: Nonliteral language and affective prosody. *Brain and Language, 85*(2), 313–324.

Pickles, A., Starr, E., Kazak, S., Bolton, P., Papanikolaou, K., Bailey, A., et al. (2000). Variable expression of the autism broader phenotype: Findings from extended pedigrees. *Journal of Child Psychology and Psychiatry, 41*(4), 491–502.

Piven, J., Palmer, P., Jacobi, D., Childress, D., & Arndt, S. (1997). Broader autism phenotype: Evidence from a family history study of multiple-incidence autism families. *American Journal of Psychiatry, 154*(2), 185–190.

Redcay, E. (2008). The superior temporal sulcus performs a common function for social and speech perception: Implications for the emergence of autism. *Neuroscience and Biobehavioral Reviews, 32*(1), 123–142. doi:10.1016/j.neubiorev.2007.06.004.

Roberts, T. P., Cannon, K. M., Tavabi, K., Blaskey, L., Khan, S. Y., Monroe, J. F., et al. (2011). Auditory magnetic mismatch field latency: A biomarker for language impairment in autism. *Biological Psychiatry, 70*(3), 263–269. doi:10.1016/j.biopsych.2011.01.015.

Roberts, T. P., Khan, S. Y., Rey, M., Monroe, J. F., Cannon, K., Blaskey, L., et al. (2010). MEG detection of delayed auditory evoked responses in autism spectrum disorders: Towards an imaging biomarker for autism. *Autism Research, 3*(1), 8–18. doi:10.1002/aur.111.

Robins, D. L., Fein, D., Barton, M. L., & Green, J. A. (2001). The Modified Checklist for Autism in Toddlers: An initial study investigating the early detection of autism and pervasive

developmental disorders. *Journal of Autism and Developmental Disorders, 31*(2), 131–144.

Rubenstein, J. L., & Merzenich, M. M. (2003). Model of autism: Increased ratio of excitation/inhibition in key neural systems. *Genes, Brain, and Behavior, 2*(5), 255–267.

Rutter, M., Bailey, A., & Lord, C. (2003). *Social Communication Questionnaire manual*. Los Angeles: Western Psychological Services.

Schilmoeller, G., Schilmoeller, K., & Doherty, D. (2004). *Social interaction in individuals with and without a corpus callosum.* Paper presented at the Journal of International Neuropsychology Society, Baltimore, MD.

Sherr, E. H. (2003). The ARX story (epilepsy, mental retardation, autism, and cerebral malformations): One gene leads to many phenotypes. *Current Opinion in Pediatrics, 15*(6), 567–571.

Sherr, E. H., Owen, R., Albertson, D. G., Pinkel, D., Cotter, P. D., Slavotinek, A. M., et al. (2005). Genomic microarray analysis identifies candidate loci in patients with corpus callosum anomalies. *Neurology, 65*(9), 1496–1498. doi:10.1212/01.wnl.0000183066.09239.b6.

Shukla, D. K., Keehn, B., Lincoln, A. J., & Muller, R. A. (2010). White matter compromise of callosal and subcortical fiber tracts in children with autism spectrum disorder: a diffusion tensor imaging study. *Journal of the American Academy of Child and Adolescent Psychiatry, 49*(12), 1269–1278, 1278.e1–2. doi:10.1016/j.jaac.2010.08.018.

Shukla, D. K., Keehn, B., & Muller, R. A. (2011). Tract-specific analyses of diffusion tensor imaging show widespread white matter compromise in autism spectrum disorder. *Journal of Child Psychology and Psychiatry, 52*(3), 286–295. doi:10.1111/j.1469-7610.2010.02342.x.

Spence, S. J., & Schneider, M. T. (2009). The role of epilepsy and epileptiform EEGs in autism spectrum disorders. *Pediatric Research, 65*(6), 599–606. doi:10.1203/01.pdr.0000352115.41382.65.

Stickles, J. L., Schilmoeller, G. L., & Kathyrn, J. (2002). A 23-year review of communication development in an individual with agenesis of the corpus callosum. *International Journal of Disability, Development, and Education, 49*(4), 367–383.

Symington, S. H., Paul, L. K., Symington, M. F., Ono, M., & Brown, W. S. (2010). Social cognition in individuals with agenesis of the corpus callosum. *Social Neuroscience, 5*(3), 296–308. doi:10.1080/17470910903462419.

Thomas, C., Humphreys, K., Jung, K. J., Minshew, N., & Behrmann, M. (2010). The anatomy of the callosal and visual-association pathways in high-functioning autism: A DTI tractography study. *Cortex, 47*(7), 863–873. doi:10.1016/j.cortex.2010.07.006.

Turk, A. A., Brown, W. S., Symington, M., & Paul, L. K. (2010). Social narratives in agenesis of the corpus callosum: linguistic analysis of the Thematic Apperception Test. *Neuropsychologia, 48*(1), 43–50. doi:10.1016/j.neuropsychologia.2009.08.009.

Vingan, R. D., Dow-Edwards, D. L., & Riley, E. P. (1986). Cerebral metabolic alterations in rats following prenatal alcohol exposure: A deoxyglucose study. *Alcoholism, Clinical and Experimental Research, 10*(1), 22–26.

Virkud, Y. V., Todd, R. D., Abbacchi, A. M., Zhang, Y., & Constantino, J. N. (2009). Familial aggregation of quantitative autistic traits in multiplex versus simplex autism. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics, 150B*(3), 328–334. doi:10.1002/ajmg.b.30810.

Weiss, L. A., Shen, Y., Korn, J. M., Arking, D. E., Miller, D. T., Fossdal, R., et al. (2008). Association between microdeletion and microduplication at 16p11.2 and autism. *New England Journal of Medicine, 358*(7), 667–675. doi:10.1056/NEJMoa075974.

Wheelwright, S., Auyeung, B., Allison, C., & Baron-Cohen, S. (2010). Defining the broader, medium and narrow autism phenotype among parents using the Autism Spectrum Quotient (AQ). *Molecular Autism, 1*(1), 10. doi:10.1186/2040-2392-1-10.

Wicker, B., Perrett, D. I., Baron-Cohen, S., & Decety, J. (2003). Being the target of another's emotion: A PET study. *Neuropsychologia, 41*(2), 139–146.

Williams, D. L., & Minshew, N. J. (2007). Understanding autism and related disorders: What has imaging taught us? *Neuroimaging Clinics of North America, 17*(4), 495–509. doi:10.1016/j.nic.2007.07.007.

Wolff, J. J., Gu, H., Gerig, G., Elison, J. T., Styner, M., Gouttard, S., et al. (2012). Differences in white matter fiber tract development present from 6 to 24 months in infants with autism. *American Journal of Psychiatry,*. doi:10.1176/appi.ajp.2011.11091447.