Relationship Between Surface-Based Brain Morphometric Measures and Intelligence in Autism Spectrum Disorders: Influence of History of Language Delay

Joana Bisol Balardin, João Ricardo Sato, Gilson Vieira, Yeu Feng, Eileen Daly, Clodagh Murphy, MRC AIMS Consortium[†], Declan Murphy, and Christine Ecker

Autism spectrum disorders (ASD) are a group of conditions that show abnormalities in the neuroanatomy of multiple brain regions. The variability in the development of intelligence and language among individuals on the autism spectrum has long been acknowledged, but it remains unknown whether these differences impact on the neuropathology of ASD. In this study, we aimed to compare associations between surface-based regional brain measures and general intelligence (IQ) scores in ASD individuals with and without a history of language delay. We included 64 ASD adults of normal intelligence (37 without a history of language delay and 27 with a history of language delay and 80 neurotypicals). Regions with a significant association between verbal and nonverbal IQ and measures of cortical thickness (CT), surface area, and cortical volume were first identified in the combined sample of individuals with ASD and controls. Thicker dorsal frontal and temporal cortices, and thinner lateral orbital frontal and parieto-occipital cortices were associated with greater and lower verbal IQ scores, respectively. Correlations between cortical volume and verbal IQ were observed in similar regions as revealed by the CT analysis. A significant difference between ASD individuals with and without a history of language delay in the association between CT and verbal IQ was evident in the parieto-occipital region. These results indicate that ASD subgroups defined on the basis of differential language trajectories in childhood can have different associations between verbal IQ and brain measures in adulthood despite achieving similar levels of cognitive performance. ***Autism Res*** *2015, 8: 556–566.* © 2015 International Society for Autism Research, Wiley Periodicals, Inc.

Keywords: autism; Asperger syndrome; brain anatomy; intelligence

Introduction

Autism spectrum disorders (ASD) are a group of neurodevelopmental conditions that are highly heterogeneous in terms of their etiology and phenotype [Abrahams & Geschwind, 2010]. Although there is now a consensus that people with ASD have differences in the anatomy of several brain regions in multiple neurocognitive systems [Amaral, Schumann, & Nordahl, 2008; Ecker et al., 2012], the specific neural substrates of these conditions and how these relate to phenotypic variation remain poorly understood.

Research into the identification of biologically meaningful subgroups on the ASD spectrum is currently a dominant theme [Lai, Lombardo, Chakrabarti, Baron-Cohen, 2013]. For example, a considerable amount of research has focused on the examination of similarities and differences between Asperger syndrome (ASP) and high-functioning autism. The differential diagnosis for these subgroups, which encompasses individuals without intellectual impairment (i.e. have an IQ in the normal range or above), was traditionally based on the absence of a history of language/speech delay in ASP at the age of 36 months. There is some evidence showing

[†]The Medical Research Council Autism Imaging Multicentre Study Consortium (MRC AIMS Consortium) is a UK collaboration between the Institute of Psychiatry (IoP) at King's College, London, the Autism Research Centre, University of Cambridge, and the Autism Research Group, University of Oxford. The Consortium members are in alphabetical order: Anthony J. Bailey (Oxford), Simon Baron-Cohen (Cambridge), Patrick F. Bolton (IoP), Edward T. Bullmore (Cambridge), Sarah Carrington (Oxford), Marco Catani (IoP), Bhismadev Chakrabarti (Cambridge), Michael C. Craig (IoP), Eileen M. Daly (IoP), Sean C. L. Deoni (IoP), Christine Ecker (IoP), Francesca Happé (IoP), Julian Henty (Cambridge), Peter Jezzard (Oxford), Patrick Johnston (IoP), Derek K. Jones (IoP), Meng-Chuan Lai (Cambridge), Michael V. Lombardo (Cambridge), Anya Madden (IoP), Diane Mullins (IoP), Clodagh M. Murphy (IoP), Declan G. M. Murphy (IoP), Greg Pasco (Cambridge), Amber N. V. Ruigrok (Cambridge), Susan A. Sadek (Cambridge), Debbie Spain (IoP), Rose Stewart (Oxford), John Suckling (Cambridge), Sally J. Wheelwright (Cambridge), Steven C. Williams (IoP), and C. Ellie Wilson (IoP).

From the Department of Neurology and NIF-LIM44, FMUSP, University of Sao Paulo, Sao Paulo, Brazil (J.B.B., G.V.); Center of Mathematics, Computation and Cognition, Universidade Federal do ABC, Santo Andre, Brazil (J.B.B., J.R.S.); Department of Forensic and Neurodevelopmental Sciences, Institute of Psychiatry, King's College, London, UK (Y.F., E.D., C.M., D.M., C.E.)

Received December 05, 2012; accepted for publication February 04, 2015

Address for correspondence and reprints: Joana Bisol Balardin, Center of Mathematics, Computation, and Cognition, Universidade Federal do ABC, Rua Santa Adélia, 166, Santo André, SP 09210-170, Brazil. E-mail: jbbalardin@gmail.com

Published online 3 March 2015 in Wiley Online Library (wileyonlinelibrary.com)
DOI: 10.1002/aur.1470

that differences in language acquisition are associated with less severe developmental abnormalities and communication problems in Asperger syndrome [Koyama, Tachimori, Osada, Takeda, & Kurita, 2007]. Particularly, different cognitive profiles have been associated with each one of these subgroups [Chiang, Tsai, Cheung, Brown, & Li, 2013]. The cognitive profile is an individual's pattern of performance in cognitive domains, such as the verbal and nonverbal reasoning (or performance) scores on the Wechsler Intelligence Scales. For instance, Asperger syndrome has been associated with a bias toward verbal processing, whereas high-functioning autism has been associated with a less uneven profile or bias toward visuospatial mediation [Ghaziuddin & Mountain-Kimchi, 2004; Sahyoun, Soulières, Belliveau, Mottron, & Mody, 2009]. This discrepancy or split has been described as a potential autism-related phenotype based on findings of its association with genetic variants in children with ASD, one of which is also implicated in speech-language impairment [Chapman et al., 2011]. However, it remains unknown whether these putative cognitive differences between ASD subtypes are also reflected on the neurobiological level.

Evidence from neuroimaging studies suggests that general intelligence might be mediated by the overall connectivity among multimodal association regions in the brain [Jung & Haier, 2007; Narr et al., 2007; Shaw et al., 2006]. The construct of general intelligence (g) is also supported by the observation that verbal and performance IQ scores are tightly correlated between individuals. The shared variance among IQ subtests accounts for 50% of the total variance in individual performance. Although 70% of this shared variance constitutes general intelligence, the other 30% is captured by factors representing domain-specific abilities [Watkins, 2006]. However, the investigation of the neural systems that support intraindividual discrepancies in verbal- and performance-specific abilities remain poorly understood in the general population, as well as in ASD. It has been suggested that these stystems involve brain regions associated with specific aspects of information processing that are relevant to performance on verbal IQ (VIQ) and performance IQ (PIQ) tasks [Margolis et al., 2013]. Giving the suggestions that an uneven IQ profile during development may serve as a potential autism-related phenotype, the examination of brain morphology in relation to differences in domain-specific abilities in general intelligence might help to elucidate the neural correlates of putative ASD subtypes.

To date, few studies have been conducted to examine whether ASD individuals with an atypical trajectory of language development also differ in neuroanatomical measures [Via, Radua, Cardoner, Happé, & Mataix-Cols, 2011; Yu, Cheung, Chua, & McAlonan, 2011]. Differences in gray matter volumes between individuals with Asperger syndrome and high-functioning autism have been described in the body of the cingulate gyrus [Kwon, Ow, Pedatella, Lotspeich, & Reiss, 2004], basal ganglia [McAlonan et al., 2009], posterior cingulate, and precuneous cortices [McAlonan et al., 2008] as well as in classical language regions such as the posterior superior temporal lobe extending into the supramarginal gyrus and inferior parietal lobe [Toal et al., 2010]. These preliminary findings provided first evidence to suggest that ASD individuals with and without language delay may have differences in brain anatomy in regions that underpin variability in cognitive profile.

However, most of these previous studies examined relatively small samples, which also differed in several key respects within and across participant groups (e.g. diagnostic criteria, IQ, and age). Also, these prior magnetic ressonance imaging (MRI) anatomical studies were based on volumetric analyses. Therefore, it would be informative for our biological understanding of the clinical heterogeneity in ASD to determine whether possible differences in gray matter volume between ASD subtypes are driven by differences in cortical thickness (CT) or surface area (SA), or a combination of both. Moreover, previous studies have focused on children, and relatively little is known about adults with ASD. It remains unknown, however, whether the anatomical differences noted in previous studies focusing on children and adolescents with ASD persist (or change) during adulthood in ASD individuals with or without a history of developmental language delay.In this study, we, therefore, investigated differences in brain morphometry in ASD individuals with and without a history of language delay, which have traditionally been referred to as individuals with Asperger syndrome and high-functioning autism. We used a well-characterized sample of ASD individuals and typically developing controls during adulthood [Ecker et al., 2012] to test the hypothesis that putative ASD subgroups have differences in the neuroanatomy of cortical regions subserving verbal processing. For this purpose, we used a spatially unbiased vertex-based approach that provided measures of cortical volume (CV), SA, and CT at several thousand points across the cortical sheet. Also, we investigated differences in brain-IQ relationships between the ASD subgroups. Here, we first identified brain regions that are significantly associated with verbal and performance IQ scores in the combined sample of individuals with ASD and adult controls. In regions, where brain surface measures and IQ scores were significantly correlated, we then tested the subsidiary hypothesis that differences in regional anatomy are differentially associated with variation in IQ, especially

Table 1. Subject Demographics

	ASD ($n = 64$)			*P*-value	
	Without a history of language delay ($n = 37$)	With a history of language delay ($n = 27$)	Control ($n = 80$)	ASD vs. Control	With vs. without a history of language delay
Age, years	27 ± 7	24 ± 6	28 ± 6	0.047	0.068
FSIQ, WASI	114 ± 13	109 ± 10	114 ± 12	0.31	0.14
Verbal IQ, WASI	113 ± 12	107 ± 9	109 ± 13	0.56	0.056
Performance IQ, WASI	112 ± 15	109 ± 12	116 ± 11	0.012	0.52
ADI-R social	17.39 ± 4.81	19.96 ± 5.57	–	–	0.059
ADI-R communication	13.94 ± 3.78	16.24 ± 4.68	–	–	0.04
ADI-R repetitive behavior	4.91 ± 1.97	5.04 ± 2.3	–	–	0.821
ADOS total	9.24 ± 3.97	9.50 ± 5.46	–	–	0.831
AQ	31.03 ± 8.85	30.72 ± 7.58	14.48 ± 6.11	<0.001	0.888
BDI	14.31 ± 11.59	12.12 ± 9.61	5.81 ± 5.75	<0.001	0.441
BAI	13.35 ± 10.91	10.88 ± 8.69	5.25 ± 5.81	<0.001	0.348

Note. Data expressed as mean ± standard deviation.

Abbreviations: ADI-R, Autism Diagnostic Interview-Revised; ADOS, Autism Diagnostic Observation Schedule; AQ, Autism Spectrum Quotient; ASD, autism spectrum disorders; WASI, Wechsler Abbreviated Scale of Intelligence; BDI, Beck Depression Inventory; BAI, Back Anxiety Inventory.

in the verbal domain, between ASD individuals with and without a history of language delay.

Materials and Methods

Participants

Individuals with ASD and controls were recruited for a large multicenter imaging study within the Medical Research Council UK Autism Imaging Multicentre Study (MRC AIMS) Consortium. Previous studies have been recently published on the brain anatomy of these data using different approaches [Christine Ecker et al., 2013; Ecker et al., 2012]. To address the specific purpose of this study (i.e. to examine pattern of brain-behavior correlations in ASD subgroups with different cognitive developmental trajectories but similar intelligence functioning in adulthood), we selected ASD participants with or without language delay. Table 1 summarizes demographic, clinical, and neuropsychological characteristics of the participants. The final sample was composed by 64 male right-handed adults with ASD and 80 matched controls (aged from 18 to 43 years). Exclusion criteria for all participants included a history of major psychiatric disorder, head injury, genetic disorder associated with autism, or any other medical condition affecting brain function. We excluded participants with substance abuse and participants on antipsychotic medication, mood stabilizers or benzodiazepines. Diagnosis of ASD was made by a Consultant Psychiatrist using ICD-10 research diagnostic criteria and confirmed using the Autism Diagnostic Interview-Revised [ADI-R—Lord, Rutter, & Le Couteur, 1994]. All ASD individuals reached ADI-R algorithm cut-offs in the three domains of impaired reciprocal social interaction, communication, and repetitive behaviors and stereotyped patterns. However, failure to reach cut-off in one of the domains by one point was permitted. ASD participants also completed the Autism Diagnostic Observation Schedule [ADOS—Lord et al., 1989]. "History of language delay" was assessed as part of the ADI-R interview [Lord et al., 1994], based on diagnostic algorithm items 9 and 10. The caregiver was asked about the age of participant's "first single words," defined as "words used repeatedly and constantly for the purpose of communication with reference to a particular concept, object, or event," excluding "mommy" and "daddy" (item 9). The caregiver was also asked about the age at which the participant started using phrases (age of first phrases; item 10), defined as two or more words including a verb. In accordance with standard clinical practice that categorically defines language delay in autism, as well as the common research definition [Kwon et al., 2004; Lotspeich et al., 2004; McAlonan et al., 2008, 2009; Toal et al. 2010], a positive history of language delay was defined either as having "first single words" later than 24 months, or an "age of first phrases" later than 33 months, or both (see also Lai et al., in press). The final ASD sample was composed of 27 participants with a history of language delay and 37 individuals with no history of language delay.

The Wechsler Abbreviated Scale of Intelligence [WASI—Wechsler, 1999] was used to assess participants' general intellectual ability. The WASI consists of four subtests, two of each in the verbal and performance domains. VIQ estimates were derived from a combination of scores from the Vocabulary and Similarities subtests. Block Design and Matrix Reasoning subtests contribute to PIQ score. Full-scale IQ (FSIQ) estimates were generated using the results from all four subtests. All participants had a FSIQ >70, which constituted

individuals within the high-functioning range on the autism spectrum. All participants gave informed written consent in accordance with ethics approval by the National Research Ethics Committee, Suffolk, UK. Between-group differences in clinical and demographic data were assessed using *t*-tests for independent samples.

Image Processing

Detailed image acquisition and processing information are described in Ecker et al. [Christine Ecker et al., 2013]. Structural MRI datasets were obtained using 3T scanners with an eight-channel head coil (GE Medical Systems HDx, Department of Radiology, University of Cambridge; GE Medical Systems HDx, Centre for Neuroimaging Sciences, Institute of Psychiatry, Kings College London; and Siemens Medical Systems Trim Trio, FMRIB Centre [Oxford Centre for Functional Magnetic Resonance Imaging of the Brain], University of Oxford). A specialized acquisition protocol using quantitative imaging (driven equilibrium single-pulse estimation of T1) was used to ensure standardization of structural MRI scans across the three-scanner platforms.

After the screening by a radiologist for quality control, each T_1-weighted image was processed using FreeSurfer freeware (http://surfer.nmr.mgh.harvard.edu/) to derive models of the cortical surface [Dale, Fischl, & Sereno, 1999]. In brief, a single filled white-matter volume was generated for each hemisphere after intensity normalization, "skull stripping," and image segmentation using a connected components algorithm [Dale et al., 1999]. Then, a surface tessellation was generated for each white-matter volume by fitting a deformable template. This resulted in a triangular cortical mesh for gray/white-matter surfaces consisting of ~150,000 vertices (i.e. points of triangles) per hemisphere. Measures of CT are the closest distance from the gray/white boundary to the gray/cerebrospinal fluid (CSF) boundary at each vertex on the tessellated surface [Fischl, Sereno, & Dale, 1999]. Vertex-based estimates of SA were obtained by computing the average of the area of the triangles incident to that vertex (i.e. sharing that vertex) in a standardized, spherical atlas-space surface tessellation, when mapped into the individual subject space (also see supplementary material). This provides point-by-point estimates of the relative areal expansion or compression of each location in atlas space [Palaniyappan, Mallikarjun, Joseph, White, & Liddle, 2011]. Here, the local SA was used interchangeably with areal expansion/compression. Estimates of regional CV were derived by multiplying CT measures by their areal expansion/compression at each vertex. These measures are, thus, different from conventional measures of brain volume resulting from the standard FreeSurfer pipeline, and indicated the degree of volumetric expansion/compression at each vertex. To improve the ability to detect population changes, each parameter was smoothed using a 15-mm surface-based smoothing kernel.

Group differences in total brain volume, gray matter volume, mean CT, and SA as estimated by FreeSurfer were assessed using *t*-tests for independent samples.

Data Analysis

Statistical analyses were implemented using SurfStat (http://www.math.mcgill.ca/keith/surfstat/), a statistical toolbox for MATLAB (MathWorks, Natick, MA). The main analyses were performed in two steps. First, parameter estimates for each measure (CV, CT, and SA) and the main effect of group (*Gi*) were estimated by regression of a general linear model at each vertex *i* and subject *j*, with center (*Ci*) as a categorical fixed-effects factor and age, IQ, and a total brain measure (indicated by *Bi*: total brain volume for CV, mean CT for CT, and total SA for SA) as continuous covariates:

$$y_{ij} = \beta_0 + \beta_1 G_j + \beta_2 C_j + \beta_3 \mathrm{Age}_j + \beta_4 \mathrm{IQ}_j + \beta_5 B_j + \varepsilon_{ij},$$

where ε is the residual.

Differences between controls, ASD with a history of language delay and ASD without a history of language delay were estimated from the fixed-effect coefficient β_1.

Second, in the combined sample of patients and controls, parameter estimates for each measure (CV, CT, SA) and the main effect of each IQ subtest separately (verbal IQ_i or performance IQ_i) were estimated by linear regression at each vertex *i* and subject *j*, with centre, C_i, as a categorical fixed-effects factor and age, and a total brain measure, indicated by B_i (total brain volume for CV; mean CT for CT; total SA for SA) as continuous covariates:

$$y_{ij} = \beta_0 + \beta_1 \mathrm{IQsubtest}_j + \beta_2 C_j + \beta_3 \mathrm{Age}_j + \beta_5 B_j + \varepsilon_{ij}$$

Positive and negative correlations between each morphometric measure and IQ subtest score were estimated from the coefficient β_1.

Corrections for multiple comparisons across the whole brain were performed using random-field theory-based (RFT) cluster analysis [Worsley, Andermann, Koulis, MacDonald, & Evans, 1999] for nonisotropic images using a $P < 0.05$ (two-tailed) cluster significance threshold, and a $P < 0.05$ (two-tailed, corrected) threshold applied at each vertex for defining clusters. Next, significant clusters within cortical areas in which a main effect of IQsubtest were detected in the first step analysis were investigated in a region-of-interest approach for the presence of an interaction with diagnosis. The interaction term was investigated separately in the comparison between controls vs. ASD, and ASD with a history of language delay vs. ASD without a history of language

Table 2. Relationships Between Surface-Based Brain Measures and IQsubtests ($P < 0.05$, Cluster Corrected)

Region	Side	BA	*x*	*y*	*z*	*t*	Cluster size	Cluster-corrected *P*-value
Positive CT—VIQ associations								
							4945	Cluster 1 $P < 0.001$
Dorsal superior frontal	L	9	−19.58	9.09	54.51	2.81		
Medial superior frontal	L	6	−7.49	36.50	43.90	2.30		
Precentral gyrus	L	4	−27.91	−11.86	59.09	2.48		
Paracentral	L	4	−6.06	−31.69	55.79	2.46		
							3647	Cluster 2 $P = 0.035$
Caudal middle frontal	R	6	38.97	5.40	45.53	2.42		
Precentral gyrus	R	4	56.97	1.05	21.15	2.50		
							3503	Cluster 3 $P = 0.051$
Superior temporal gyrus	L	22	−51.67	3.60	−15.43	3.55		
Middle temporal gyrus	L	21	−55.84	−6.09	−20.81	2.10		
							6655	Cluster 1 $P < 0.001$
Lateral orbital frontal	R	11	17.77	29.83	−19	−2.32		
Medial superior frontal	R	10	10.87	50.03	4.18	−3.53		
Rostral anterior cingulate	R	9	6.48	32.35	−5.73	−3.12		
							5872	Cluster 2 $P < 0.001$
Isthimuscingulate	R	23	6.97	−50.53	17	−3.11		
Precuneus	R	7	6.39	−55.66	31.61	−2.26		
Lingual gyrus	R	18	4.92	−78.22	2.79	−2.23		
							6608	Cluster 1 $P < 0.001$
Rostral middle frontal	R	9/46	22.71	51.34	15.19	−2.33		
Lateral orbital frontal	R	11	17.20	28.63	−19.90	−19.90		
Medial orbital frontal	R	12	9.36	40.46	−10.54	−2.86		
Rostral anterior cingulate	R	32	6.10	30.60	−6.44	−2.69		
Medial superior frontal	R	10	9.85	53.56	10.64	−2.52		
							5249	Cluster 2 $P < 0.001$
Precuneus	R	7	8.52	−53.47	31	−2.34		
Isthmuscingulate	R	23	7.03	−48.65	16.31	−3.22		
Paracentral	R	4	16.12	−35.34	50.96	−2.52		
							3413	Cluster 1 $P = 0.035$
Middle frontal gyrus	L	46	−22.65	52.56	8.17	2.86		
Lateral orbital frontal	L	10	−11.66	39.49	−19.56	2.79		

delay. At each vertex within a cluster, the proportion of total variance in each brain anatomy measure (CT, SA, CV) accounted for by two linear regression models was compared.

The first did not include an IQsubtest-by-group interaction term:

$$y_{ij} = \beta_0 + \beta_1 \text{IQsubtest}_j + \beta_2 G_j + \beta_3 C_j + \beta_4 \text{Age}_j + \beta_5 B_j + \varepsilon_i,$$

and another including these terms:

$$y_{ij} = \beta_0 + \beta_1 \text{IQsubtest}_j + \beta_2 G_j + \beta_3 C_j + \beta_4 \text{Age}_j + \beta_5 B_j + \beta_6 (\text{IQsubtest}_j * G_j) + \varepsilon_i$$

with group G_j as a categorical fixed-effects factor. This resulted in an *F* ratio map for each cluster showing the degree to which the inclusion of an IQsubtest-by-group term increased the proportion of the morphometric measure variance (CT, SA, CV) that was accounted for. The resulting *P*-values from the *F* maps were corrected for multiple comparisons using a false discovery rate (FDR) threshold of 0.05 [Benjamini & Hochberg, 1995].

Results

Participant Demographics and Global Brain Measures (Table 1)

Controls vs. ASD. No between-group differences were observed in FSIQ ($P = 0.31$) or VIQ ($P = 0.57$). Performance IQ score was significantly higher in the control group ($P = 0.012$). There was also a significant marginal difference on age between groups ($P = 0.047$). On global brain measures comparisons (Table 2), there were no significant group differences in total brain volume (0.60) or mean CT ($P = 0.95$). However, significant higher SA values were observed in ASD participants compared to controls ($P = 0.028$).

ASD with a history of language delay vs. ASD without a history of language delay comparison. û ôThere were marginal differences between ASD subgroups in age ($P = 0.068$), VIQ ($P = 0.056$), ADI-R Social ($P = 0.059$), and ADI-R communication domains ($P = 0.04$), as participants categorized as high-functioning autism (HFA) presented more severe retrospective

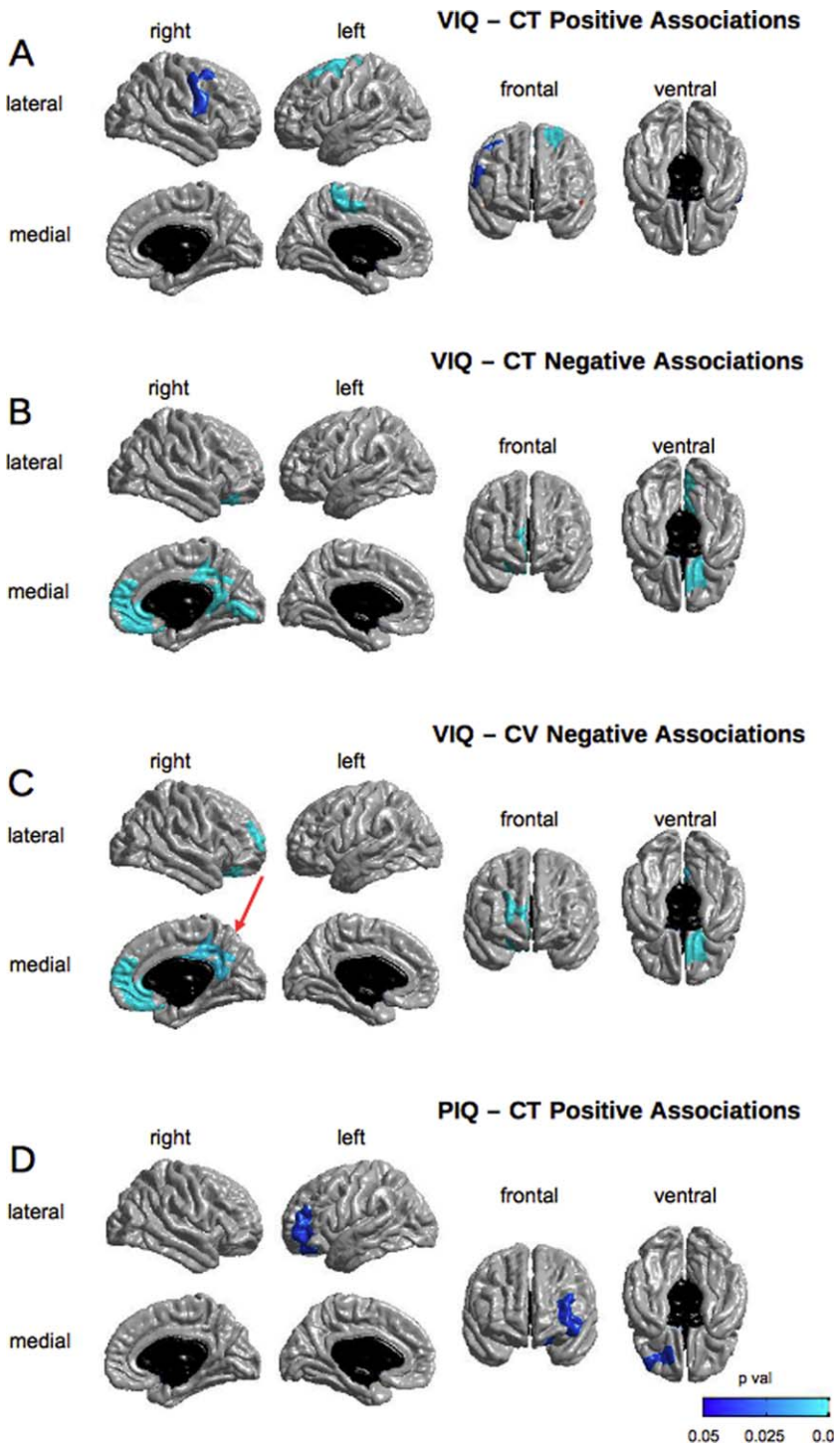

Figure 1. Random-field theory-based cluster-corrected ($P < 0.05$) maps for the relationships between IQ subscores and surface-based brain measures after removing the partial effects of age, centre, and global brain measures (average CT for CT, total SA for SA or total CV for CV) in the combined sample of ASD and controls. Clusters *P*-values are presented in the color bar. A: Thicker cortices whithin the left superior frontal gyrus/precentral gyrus/paracentral cortex and superior and middle temporal gyrus and within right precentral gyrus/caudal middle frontal cortex were associated to better performance on VIQ subtest. B: Thinner cortices were associated with increased verbal intelligence performance in right lateral orbital frontal cortex/superior frontal gyrus and within the isthmuscingulate cortex/precuneous/lingual gyrus. C: Greater cortical volume was associated to diminuish VIQ performance in rostral middle frontal/lateral orbital frontal/medial orbital frontal/superior frontal/rostral anterior cingulate cortices and within precuneous/isthmuscingulate/paracentral cortices. D: Greater middle frontal gyrus/lateral orbital frontal gyrus SA was associate with better PIQ scores. The red arrow points to the cluster located in the isthmuscingulate cortex/precuneous/lingual gyrus in which a group diagnosis (ASD with/without a history of language delay) $\times$ verbal IQ interaction was significant.

language symptoms. No differences were neither observed in FSIQ ($P = 0.14$) nor PIQ ($P = 0.52$). Regarding global brain measures, there were no significant group differences in total brain volume ($P = 0.67$), total SA ($P = 0.69$), or mean CT ($P = 0.27$).

Differences in surface anatomy. Following correction for multiple comparisons across the brain, no significant differences between controls and ASD with a history of language delay or ASD without a history of language delay, neither within ASD subgroups, were observed in vertex-based estimates of CT, SA, or CV.

IQsubscore—related brain regions (Table 2). After After correction for multiple comparisons across the brain, CT was positively associated with VIQ score in a cluster located in the left superior frontal gyrus in its dorsal (BA 9) and medial portions (BA 6), precentral gyrus (BA 4) and paracentral cortex (BA 4; cluster $P = 0.0018$). Positive CT-VIQ correlations were also found in a right cluster located in the right precentral gyrus (BA 4) and in caudal middle frontal cortex (BA 6; cluster $P = 0.035$). A marginal significant positive correlation was found in a cluster in the left superior temporal gyrus (BA 22; cluster $P = 0.051$; Fig. 1A). Thinner cortices were associated with increased verbal intelligence performance in right hemisphere clusters located in the lateral orbital frontal cortex (BA 11) and in the medial portion of the superior frontal syrus (BA 9 and 10; cluster $P < 0.001$) and in a large posterior region including the isthmus-cingulate cortex (BA 23), precuneous (BA 7), and lingual gyrus (BA 18; cluster $P < 0.001$; Fig. 1B). In addition, significant negative associations between CV and VIQ were evident in large right hemisphere clusters in regions such as the rostral middle frontal (BA 9/46), lateral orbital frontal cortex (BA 11), medial orbital frontal (BA 12), rostral anterior cingulate (BA 32), and medial portion of the superior frontal gyrus (BA 10), and in a posterior cluster ($P = 0.007$) located in the precuneus (BA 7), isthmus-cingulate cortex (BA 23), and paracentral cortex (BA 4; Fig. 1C).

Regarding brain—PIQ associations, the only significant finding after correction for multiple comparisons was a positive correlation with CT in a cluster located in the left middle frontal gyrus (BA 46) and lateral orbital frontal (BA 10; cluster $P = 0.0358$; Fig. 1D). No significant relationships between verbal or nonverbal IQ scores and SA survived after correction for multiple comparisons on the cluster level.

IQsubscores x diagnosis interaction. The VIQ by diagnosis (ASD with a history of language delay vs. ASD without a history of language delay) interaction was significant for CT in the right hemisphere cluster including the posterior cingulate cortex, precuneus, and lingual gyrus [$F(1,56) = 6.7952$, $P = 0.011$). Figure 2 shows the regression plot comparing the slopes of verbal IQ-CT relationships between ASD with a history of language delay and ASD without a history of language delay after removing the partial effects of age, centre and whole brain average CT. The correlation between VIQ and CT in this region was significant for ASD with a history of language delay ($r = -0.385$, $P = 0.024$), but not ASD without a history of language delay ($r = -0.184$; $P = 0.137$). This difference in VIQ-CT correlations between groups did not change after adjusting for ADI-R communication or social scores. However, the interaction was significant at a threshold uncorrected for multiple comparisons and should hence be interpreted as a trend.

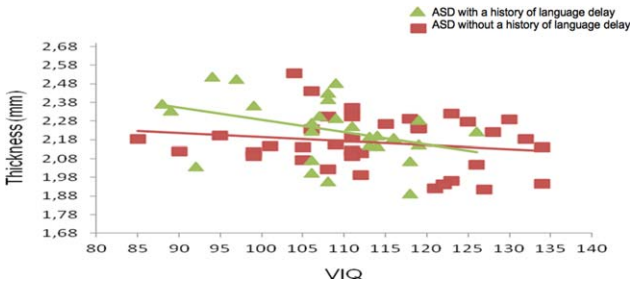

Figure 2. Scatterplot of the diagnosis group × VIQ interaction (ASD without a history of language delay $r = -0.184$; $P = 0.137$; ASD with a history language delay $r = -0.385$, $P = 0.024$) in the right hemisphere posterior cluster located in the precuneus, isthmuscingulate, and lingual gyrus.

In all other clusters in which positive or negative associations between CT or CV and IQ subtests were identified in the first step analysis, the relationships were consistent between the ASD and controls and also between ASP and HFA, as evident from a lack of significant interactions.

Discussion

In this study, we examined regional differences in CV on the basis of its two components, CT and SA, in a large and well-characterized sample of men with ASD categorized as individuals with ASD with a history of language delay vs. ASD individuals without a history of language delay. We found that these ASD subgroups had no significant differences in CT, SA, and CV. We also investigated differences in the pattern of relationships between surface-based regional brain measures and IQ scores between the groups. We have confirmed previous evidence suggesting that localized variations

in CT are related to IQ performance; i.e. thicker dorsal frontal and temporal cortices and thinner lateral orbitofrontal and parieto-occipital cortices were associated with greater and lower VIQ scores, respectively. In addition, we expanded findings to CV and SA measures: i.e. greater CV was associated with reduced VIQ performance in parts of the medial frontal cortex and within the parietal cortex, overlapping with the CT findings. Thicker left medial frontal cortex was also associated with higher PIQ scores. Finally, we have shown that the relationship between CT and VIQ in the parieto-occipital region was atypical in ASD participants with a history of language delay relative to ASD individuals without a history of language delay. The findings described here could be interpreted as preliminary, exploratory evidence about the influence of developmental language delay on brain-intelligence relationships in ASD.

The significant associations between surface-based brain measures and IQ scores in frontal, temporal, parietal, and occipital regions observed in our study are consistent with the distributed correlational patterns reported for IQ measures in previous studies using CT. Positive and negative partial correlations between CT and FSIQ have been reported in frontal, parietal, temporal, and occipital cortices in healthy adolescents and adults [Choi et al., 2008; Karama et al., 2011; Narr et al., 2007]. Our results are also consistent with neural correlates of intelligence established using voxel-based morphometry (VBM) studies. Correlations between local variation in gray matter volume and different measures of intelligence were reported in widely distributed regions throughout the entire brain [for a review see Deary, Penke, & Johnson, 2010; Luders, Narr, Thompson, & Toga, 2009]. These significant correlations have been interpreted in light of cognitive theories of intelligence, such as the parieto-frontal integration theory [Jung & Haier, 2007]. According to Jung et al.'s theory, primary occipital and temporal cortical regions play a role in the recognition, imagery, and elaboration of visual and auditory input, which is then processed in supramarginal, superior parietal, and angular gyri of the parietal lobe resulting in structural symbolism, abstraction and elaboration phenomena. The interaction between parietal, parts of the frontal cortex and anterior cingulate occurs during working memory processing, response engagement, and inhibition.

We also observed that VIQ was negatively associated with CT and CV, but not SA, in medial frontal and parietal regions. CV is a product of CT and SA, and it has been proposed that separate genetic processes determine the development of these two cortical characteristics [Panizzon et al., 2009], with SA being determined earlier in neurodevelopment and being less affected by environmental factors than CT [Habets, Marcelis, Gronenschild, Drukker, & van Os, 2011; Rakic, 1988]. These developmental differences could underlie the greater sensitivity observed in this study in detecting associations between IQ scores and CT—rather SA—thus, extending the previous evidence for socioenvironmental influences on measures of intelligence [Jefferis, Power, & Hertzman, 2002]. Furthermore, a significant proportion of IQ variation might also be attributable to genetic factors [Posthuma et al., 2002].

In most of the brain regions in which verbal or nonverbal IQ scores explained significant variance in regional CT or CV, there were similar pattern of correlations in both neurotypicals and ASD individuals, and between ASD with or without a history of language delay. These findings suggest that at least in adults within the high-functioning range, ASD does not disrupt general brain-behavior associations. However, for the relationship between CT and VIQ in the right posterior cingulate gyrus, precuneus, and lingual gyrus, a significant negative correlation was observed within the ASD group with a history of language delay, but not for ASD individuals without a history of language delay. A similar region was found in children and adolescents with high-functioning autism as compared to children with Asperger syndrome [McAlonan et al., 2008]. Although it is well established that language is processed by a specific subset of brain regions in the brain, the involvement of parietal and more posterior occipital brain regions in verbal intelligence tasks have been proposed to be related to sensory information processing and integration, as well as abstraction [Jung & Haier, 2007]. Consistent with these observations, it is possible that ASD individuals with a history of language delay may rely more heavily on posterior regions, perhaps to compensate for an early age dysfunction in language-related brain regions that may also be involved in verbal intelligence. Moreover, the role of nonfrontal brain regions in verbal intelligence tasks may have been considerably underestimated in previous studies, in which analyses were based on a priori defined regions of interest in exclusively anterior sections of the brain [Konrad, Vucurevic, Musso, & Winterer, 2012]. However, given the exploratory character of our research, these results need further replication.

The observed lack of differences in morphometric measures between ASD subtypes may be due to a variety of reasons. Most of the previously published studies examined differences in gray matter volume between ASP and/or HFA and neurotypicals without controlling for the confounding effects of age. This is particularly important as there is a large body of evidence showing that ASD is accompanied by an atypical developmental trajectory of total gray or white-matter volume [Courchesne, Carper, & Akshoomoff, 2003],

head circumferences [Lainhart et al., 2006], and/or SA [Hazlett et al., 2005]. In the only study that directed compared differences in gray matter volumes between adults with Asperger syndrome and high-functioning autism [Toal et al., 2010], the samples were not matched for IQ, which is another factor mediating gray matter structures in typical development [Narr et al., 2007; Shaw et al., 2006], and in individuals with ASD [Misaki, Wallace, Dankner, Martin, & Bandettini, 2012]. Therefore, the results of this study agrees with evidence suggesting that by adulthood, Asperger syndrome and high-functioning autism are largely indistinguishable clinically or cognitively, given the little support for the hypothesis that different ASD subgroups have distinct neural substrates.

A limitation of this study is the fact that we studied a subpopulation on the autistic spectrum (i.e ASD individuals with or without a history of language delay and normal intelligence levels), and so our findings cannot be generalized to all individuals on the autism spectrum. Although both ASD subgroups were primarily distinguished based on language developmental delay, they might also show differences in other clinical variables, which we cannot rule out as contributing confounds. It is also important to mention that the criteria to categorize ASD individuals with or without a history of language delay adopted in our study was based on the traditionally differential diagnosis of Asperger syndrome and high-functioning autism. However, the latest edition of the Diagnostic and Statistical Manual of Mental Disorders (the DSM-5) collapses high-functioning autism and Asperger syndrome into one ASD category, differentiating between them only with respect to the severity of individual symptoms. Therefore, it is currently unknown whether subgroups of ASD can be dissociated on the basis of other deficits in language development, and also whether these individuals differ on the level of brain anatomy. However, our findings are reinforced by the fact that we studied a specific hypothesis with regards to group differences in brain-behavior correlations using measures of verbal IQ, which is a variable specifically related to diagnostic category. In addition, from our cross-sectional study design, we cannot with certainty infer if (and how) developmental-related changes in general intelligence and language are responsible for the present results. Future longitudinal studies in children are, thus, needed to characterize brain-behavior associations in primary language-related regions in the presence of wider between-group differences in ASD symptoms.

In conclusion, our results show that the correlations between CT in frontal and temporal brain areas and measures of verbal and performance IQ were similar for ASD adults with or without a history of language delay. However, significant diagnostic interactions were found in the right parieto-occipital cortical region for verbal IQ, hence suggesting different relationships between brain structure and function across individuals with ASD. Moreover, we provide the first evidence that the association between brain morphometry and IQ measures should be investigated for individual morphometric features that underlie measures of CV, and that this could be informative to the characterization of the neurobiological correlates of the clinical heterogeneity in ASD.

Acknowledgments

This work was supported (1) by the Medical Research Council UK (G0400061 and G0800298), (2) by the Dr. Mortimer and Theresa Sackler Foundation, (3) by the EU-AIMS project (European Autism Interventions—a Multicentre Study for developing New Medications) receiving support from the Innovative Medicines Initiative Joint Undertaking under grant agreement no. 115300, which includes financial contributions from the EU Seventh Framework Programme (FP7/2007-2013), (4) by the NIHR Biomedical Research Centre for Mental Health at King's College London, Institute of Psychiatry, (5) by the South London & Maudsley NHS Foundation Trust, and (6) by the Sao Paulo Research Foundation—FAPESP (Grants 2009/09924-5 and 2013/10498-6). We are also grateful to those who agreed to be scanned and who gave their time so generously to this study.

References

Abrahams, B.S., & Geschwind, D.H. (2010). Connecting genes to brain in the autism spectrum disorders. Archives of Neurology, 67(4), 395–399.

Amaral, D.G., Schumann, C.M., & Nordahl, C.W. (2008). Neuroanatomy of autism. Trends in Neurosciences, 31, 137–145.

Benjamini, Y., & Hochberg, Y. (1995). Controlling the false discovery rate: A practical and powerful approach to multiple testing. Journal of the Royal Statistical Society: Series B (Methodological), 57, 289–300.

Chapman, N.H., Estes, A., Munson, J., Bernier, R., Webb, S.J., Rothstein, J.H., et al. (2011). Genome-scan for IQ discrepancy in autism: Evidence for loci on chromosomes 10 and 16. Human Genetics, 129(1), 59–70.

Chiang, H.-M., Tsai, L.Y., Cheung, Y.K., Brown, A., & Li, H. (2013). A meta-analysis of differences in IQ profiles between individuals with Asperger's disorder and high-functioning autism. Journal of Autism and Developmental Disorders, 44(7):1577–1596.

Choi, Y.Y., Shamosh, N.A., Cho, S.H., DeYoung, C.G., Lee, M.J., Lee, J.M., et al. (2008). Multiple bases of human intelligence revealed by cortical thickness and neural activation. The Journal of Neuroscience, 28, 10323–10329.

Courchesne, E., Carper, R., & Akshoomoff, N. (2003). Evidence of brain overgrowth in the first year of life in autism.

JAMA: The Journal of the American Medical Association, 290(3), 337–344.

Dale, A.M., Fischl, B., & Sereno, M.I. (1999). Cortical surface-based analysis. I. Segmentation and surface reconstruction. NeuroImage, 9, 179–194.

Deary, I.J., Penke, L., & Johnson, W. (2010). The neuroscience of human intelligence differences. Nature Reviews Neuroscience, 11, 201–211.

Ecker, C., Ginestet, C., Feng, Y., Johnston, P., Lombardo, M.V., Lai, M.-C., et al. (2013). Brain surface anatomy in adults with autism: The relationship between surface area, cortical thickness, and autistic symptoms. JAMA Psychiatry, 70(1), 59–70.

Ecker, C., Suckling, J., Deoni, S.C., Lombardo, M.V., Bullmore, E.T., Baron-Cohen, S., et al. (2012). Brain anatomy and its relationship to behavior in adults with autism spectrum disorder: A multicenter magnetic resonance imaging study. Archives of General Psychiatry, 69, 195–209.

Fischl, B., Sereno, M.I., & Dale, A.M. (1999). Cortical surface-based analysis. II: Inflation, flattening, and a surface-based coordinate system. NeuroImage, 9(2), 195–207.

Ghaziuddin, M., & Mountain-Kimchi, K. (2004). Defining the intellectual profile of Asperger syndrome: Comparison with high-functioning autism. Journal of Autism and Developmental Disorders, 34(3), 279–284.

Habets, P., Marcelis, M., Gronenschild, E., Drukker, M., & van Os, J. (2011). Reduced cortical thickness as an outcome of differential sensitivity to environmental risks in schizophrenia. Biological Psychiatry, 69, 487–494.

Hazlett, H.C., Poe, M., Gerig, G., Smith, R.G., Provenzale, J., Ross, A., et al. (2005). Magnetic resonance imaging and head circumference study of brain size in autism: Birth through age 2 years. Archives of General Psychiatry, 62(12), 1366–1376.

Jefferis, B.J., Power, C., & Hertzman, C. (2002). Birth weight, childhood socioeconomic environment, and cognitive development in the 1958 British birth cohort study. BMJ, 325(7359), 305.

Jung, R.E., & Haier, R.J. (2007). The parieto-frontal integration theory (P-FIT) of intelligence: Converging neuroimaging evidence. Behavioral and Brain Sciences, 30, 135–154; discussion 154–187.

Karama, S., Colom, R., Johnson, W., Deary, I.J., Haier, R., Waber, D.P., et al. (2011). Cortical thickness correlates of specific cognitive performance accounted for by the general factor of intelligence in healthy children aged 6 to 18. NeuroImage, 55, 1443–1453.

Konrad, A., Vucurevic, G., Musso, F., & Winterer, G. (2012). VBM-DTI correlates of verbal intelligence: A potential link to Broca's area. Journal of Cognitive Neuroscience, 24(4), 888–895.

Koyama, T., Tachimori, H., Osada, H., Takeda, T., & Kurita, H. (2007). Cognitive and symptom profiles in Asperger's syndrome and high-functioning autism. Psychiatry Clin Neurosci, 61(1), 99–104.

Kwon, H., Ow, A.W., Pedatella, K.E., Lotspeich, L.J., & Reiss, A.L. (2004). Voxel-based morphometry elucidates structural neuroanatomy of high-functioning autism and Asperger syndrome. Developmental Medicine & Child Neurology, 46(11), 760–764.

Lai, M-C., Lombardo M.V., Chakrabarti, B., & Baron-Cohen, S. (2013). Subgrouping the autism "spectrum": Reflections on DSM-5. Plos Biology, 11(4), e1001544.

Lai, M-C., Lombardo, M.V., Ecker, C., Chakrabarti, B., Suckling, J., Bullmore, E.T., et al. (2014). Neuroanatomy of individual differences in language in adult males with autism. Cerebral Cortex. Sep 23. pii: bhu211.

Lainhart, J.E., Bigler, E.D., Bocian, M., Coon, H., Dinh, E., Dawson, G., et al. (2006). Head circumference and height in autism: A study by the collaborative program of excellence in autism. American Journal of Medical Genetics. Part A, 140(21), 2257–2274.

Lord, C., Rutter, M., Goode, S., Heemsbergen, J., Jordan, H., Mawhood, L., & Schopler, E. (1989). Autism diagnostic observation schedule: A standardized observation of communicative and social behavior. Journal of Autism and Developmental Disorders, 19(2), 185–212.

Lord, C., Rutter, M., & Le Couteur, A. (1994). Autism diagnostic interview-revised: A revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. Journal of Autism and Developmental Disorders, 24(5), 659–685.

Lotspeich, L.J., Kwon, H., Schumann, C.M., Fryer, S.L., Goodlin-Jones, B.L., Buonocore, M.H., Lammers, C.R., Amaral, D.G., & Reiss, A.L. (2004). Investigation of neuroanatomical differences between autism and Asperger syndrome. Archives of General Psychiatry, 61(3), 291–298.

Luders, E., Narr, K.L., Thompson, P.M., & Toga, A.W. (2009). Neuroanatomical correlates of intelligence. Intelligence, 37(2), 156–163.

Margolis, A., Bansal, R., Hao, X., Algermissen, M., Erickson, C., Klahr, K.W., et al. (2013). Using IQ discrepancy scores to examine the neural correlates of specific cognitive abilities. The Journal of Neuroscience: The Official Journal of the Society for Neuroscience, 33(35), 14135–14145.

McAlonan, G.M., Cheung, C., Cheung, V., Wong, N., Suckling, J., & Chua, S.E. (2009). Differential effects on white-matter systems in high-functioning autism and Asperger's syndrome. Psychological Medicine, 39, 1885–1893.

McAlonan, G.M., Suckling, J., Wong, N., Cheung, V., Lienenkaemper, N., Cheung, C., & Chua, S.E. (2008). Distinct patterns of grey matter abnormality in high-functioning autism and Asperger's syndrome. Journal of Child Psychology and Psychiatry, 49, 1287–1295.

Misaki, M., Wallace, G.L., Dankner, N., Martin, A., & Bandettini, P.A. (2012). Characteristic cortical thickness patterns in adolescents with autism spectrum disorders: Interactions with age and intellectual ability revealed by canonical correlation analysis. NeuroImage, 60(3), 1890–1901.

Narr, K.L., Woods, R.P., Thompson, P.M., Szeszko, P., Robinson, D., Dimtcheva, T., et al. (2007). Relationships between IQ and regional cortical gray matter thickness in healthy adults. Cerebral Cortex, 17, 2163–2171.

Palaniyappan, L., Mallikarjun, P., Joseph, V., White, T.P., & Liddle, P.F. (2011). Regional contraction of brain surface area involves three large-scale networks in schizophrenia. Schizophrenia Research, 129(2–3), 163–168.

Panizzon, M.S., Fennema-Notestine, C., Eyler, L.T., Jernigan, T.L., Prom-Wormley, E., Neale, M., et al. (2009). Distinct

genetic influences on cortical surface area and cortical thickness. Cerebral Cortex, 19, 2728–2735.
Posthuma, D., De Geus, E.J., Baare, W.F., Hulshoff Pol, H.E., Kahn, R.S., & Boomsma, D.I. (2002). The association between brain volume and intelligence is of genetic origin. Nature Neuroscience, 5, 83–84.
Rakic, P. (1988). Defects of neuronal migration and the pathogenesis of cortical malformations. Progress in Brain Research, 73, 15–37.
Sahyoun, C.P., Soulières, I., Belliveau, J.W., Mottron, L., & Mody, M. (2009). Cognitive differences in pictorial reasoning between high-functioning autism and Asperger's syndrome. Journal of Autism and Developmental Disorders, 39(7), 1014–1023.
Shaw, P., Greenstein, D., Lerch, J., Clasen, L., Lenroot, R., Gogtay, N., et al. (2006). Intellectual ability and cortical development in children and adolescents. Nature, 440(7084), 676–679.
Toal, F., Daly, E.M., Page, L., Deeley, Q., Hallahan, B., Bloemen, O., et al. (2010). Clinical and anatomical heterogeneity in autistic spectrum disorder: A structural MRI study. Psychological Medicine, 40, 1171–1181.
Via, E., Radua, J., Cardoner, N., Happé, F., & Mataix-Cols, D. (2011). Meta-analysis of gray matter abnormalities in autism spectrum disorder: Should Asperger disorder be subsumed under a broader umbrella of autistic spectrum disorder? Archives of General Psychiatry, 68(4), 409–418.
Watkins, M.W. (2006). Orthogonal higher order structure of the Wechsler Intelligence Scale for children—fourth edition. Psychological Assessment, 18(1), 123–125.
Wechsler, D. (1999). Wechsler Abbreviated Scale of Intelligence (WASI). San Antonio, TX: Harcourt Assessment.
Worsley, K.J., Andermann, M., Koulis, T., MacDonald, D., & Evans, A.C. (1999). Detecting changes in nonisotropic images. Human Brain Mapping, 8, 98–101.
Yu, K.K., Cheung, C., Chua, S.E., & McAlonan, G.M. (2011). Can Asperger syndrome be distinguished from autism? An anatomic likelihood meta-analysis of MRI studies. Journal of Psychiatry & Neuroscience: JPN, 36(6), 412–421.