Brain Imaging and Behavior
DOI 10.1007/s11682-016-9534-5

ORIGINAL RESEARCH

Brain structure in autism: a voxel-based morphometry analysis of the Autism Brain Imaging Database Exchange (ABIDE)

Kaitlin Riddle[1] · **Carissa J. Cascio**[1] · **Neil D. Woodward**[1,2]

Abstract Increased brain volume is a consistent finding in young children with autism spectrum disorders (ASD); however, the regional specificity and developmental course of abnormal brain structure are less clear. Small sample sizes, particularly among voxel-based morphometry (VBM) investigations, likely contribute to this difficulty. Recently established large-scale neuroimaging data repositories have helped clarify the neuroanatomy of neuropsychiatric disorders such as schizophrenia and may prove useful in ASD. Structural brain images from the Autism Brain Imaging Database Exchange (ABIDE), which contains over 1100 participants, were analyzing using DARTEL VBM to investigate total brain and tissue volumes, and regional brain structure abnormalities in ASD. Two, overlapping cohorts were analyzed; an 'All Subjects' cohort ($n = 833$) that included all individuals with usable MRI data, and a 'Matched Samples' cohort ($n = 600$) comprised of ASD and TD individuals matched, within each site, on age and sex. Total brain and grey matter volumes were enlarged by approximately 1–2 % in ASD; however, the effect reached statistical significance in only the All Subjects cohort. Within the All Subjects cohort, VBM analysis revealed enlargement of the left anterior superior temporal gyrus in ASD. No significant regional changes were detected in the Matched Samples cohort. There was a non-significant reduction in the correlation between IQ and TBV in ASD compared to TD. Brain structure abnormalities in ASD individuals age 6 and older consists of a subtle increase in total brain volume due to enlargement of grey matter with little evidence of regionally specific effects.

Keywords Autism · Neuroimaging · Voxel-based morphometry · TBV

Introduction

Autism spectrum disorder (ASD) is characterized by a core of symptoms that include diminished reciprocal social communication and interaction, as well as repetitive and stereotyped behaviors. There is broad consensus that ASD is a neurodevelopmental brain disorder; however, the underlying neuroanatomy of ASD is unclear. One prominent theory posits that ASD involves enlargement of total brain volume (TBV) due to accelerated postnatal brain growth (Courchesne et al. 2001; Piven et al. 1995). This theory is supported by consistent reports of increased head circumference (HC) and TBV (Campbell et al. 1982; Hazlett et al. 2005; Piven et al. 1995). However, there are critical knowledge gaps in our understanding of the trajectory and magnitude of abnormal brain growth in ASD. TBV and HC enlargement have been consistently reported in young children (Courchesne et al. 2003; Hazlett et al. 2005), particularly between the ages of 2 and 4, with some studies reporting approximately 10 % increase in TBV (Courchesne et al. 2007; Redcay and Courchesne 2005; Sparks et al. 2002). This is consistent with the rapid expansion of intracranial and brain volumes that occur in the first few

Kaitlin Riddle and Neil D. Woodward contributed equally to this work.

Electronic supplementary material The online version of this article (doi:10.1007/s11682-016-9534-5) contains supplementary material, which is available to authorized users.

✉ Neil D. Woodward
neil.woodward@vanderbilt.edu

[1] Department of Psychiatry, Vanderbilt University School of Medicine, Nashville, TN, USA

[2] Center for Cognitive Medicine & Psychotic Disorders Program, Vanderbilt Psychiatric Hospital, Suite 3057, 1601 23rd Ave. S., Nashville, TN 37212, USA

Published online: 03 March 2016

years of life (Courchesne et al. 2000; Kamdar et al. 2009; Lenroot et al. 2007). The picture in later childhood through adolescence and adulthood is murkier. Consistent with the idea of early brain overgrowth and subsequent normalization, Aylward at et al. (Aylward et al. 2002) found that TBV is enlarged by approximately 5 % in children under 12, but not adolescents or adults. In contrast, several studies reported marked TBV enlargement, on the order of 5–7 %, in adolescents (Herbert et al. 2003; Palmen et al. 2005; Piven et al. 1995).

The regional specificity of brain structure abnormalities in ASD is also poorly understood. Studies using region of interest (ROI) approaches have found that Increased TBV may be due to an overall increase in grey matter involving all lobes (Palmen et al. 2005), relatively greater enlargement of specific regions, such as the temporal lobe (Courchesne et al. 2007; Hardan et al. 2006), or a combination of localized increases in some areas and volume reduction in others (Duerden et al. 2012). There are also reports of increased white matter volume (Herbert et al. 2003); although other studies found no differences (Palmen et al. 2005) or even reduced white matter volume (Jou et al. 2011). Voxel-based morphometry studies, which, unlike ROI investigations, are capable of examining brain structure changes at the millimeter range throughout the whole brain, have also produced variable findings.

The inconsistent findings are undoubtedly due, at least in part, to small sample sizes. For example, over half of the neuroimaging studies included in a recent meta-analysis of TBV included fewer than 25 individuals with ASD (Stanfield et al. 2008). The situation is more acute for studies examining regional changes in grey matter. Just 2 out of 19 investigations included in an anatomical likelihood estimation (ALE) meta-analysis of VBM studies included more than 25 individuals with ASD (Duerden et al. 2012). A more recent meta-analysis of VBM studies in high functioning ASD found that just 6 out of 21 studies includes more than 25 subjects with ASD, only 1 of which included more than 50 individuals with ASD (DeRamus and Kana 2015). Sample size limitations are especially problematic for voxel-based methods, such as VBM, as they require correction for multiple comparisons which dramatically reduces statistical power. Consequently, the small number of subjects included in many VBM studies raises serious concerns about the replicability of findings, reporting bias, and Type I errors. Indeed, a recent review of VBM studies concluded that the number of affected brain regions implicated in neurological and psychiatric disorders is inflated in studies with small sample sizes, which is consistent with reporting bias (Fusar-Poli et al. 2014).

A large number of neuroimaging data-sharing initiatives have emerged over the past several years and have proven extremely useful for clarifying normal brain function and the neuroanatomy of neuropsychiatric disorders. They include coordinated efforts, such as the Alzheimer's Disease Neuroimaging Initiative (ADNI) and Human Connectome Project (HCP), and grass-roots efforts, such the 1000 Functional Connectomes Project (Biswal et al. 2010; Mueller et al. 2005; Van Essen et al. 2013). Typically, the grass-roots lead initiatives consist of data collected on patient populations and healthy controls at several, often dozens, of different sites which are then deposited into online repositories. Despite the heterogeneity associated with multi-site data, these databases have been instrumental in clarifying the neuroanatomy of neuropsychiatric disorders. For example, grass-roots led data sharing initiatives helped clarify the pattern and magnitude of cortical and sub-cortical abnormalities in schizophrenia (Gupta et al. 2015; van Erp et al. 2015). Large scale, multi-site datasets have even proven sensitive enough to detect the subtle effects of allelic variation in common polymorphisms on brain structure (Stein et al. 2012).

The recently created Autism Brain Imaging Database Exchange (ABIDE), which contains imaging data on over 1100 individuals, is an excellent resource for examining brain structure abnormalities in ASD. Recently, using the ABIDE, Haar and colleagues examined volumetric, thickness, and surface area measurements of over 180 anatomically defined ROIs (Haar et al. 2014). In terms of overall brain volumes, they found that ASD was associated with very slight increases in intracranial and ventricular volumes. With respect to cortical and subcortical areas, individuals with ASD had thicker cortex in left STG and sulcus, bilateral occipital lobe, and midline parietal ROIs. In the present study, we sought to complement these findings by using VBM to characterize brain structure changes at the voxel-wise level, particularly throughout development from mid-childhood to adulthood. As mentioned earlier, the capability of VBM to examine brain structure changes throughout the brain at the millimeter range makes it an excellent complement to ROI approaches and the large size of the ABIDE provides excellent statistical power compared to prior VBM investigations. To put the size of the ABIDE in context, recent meta-analyses of VBM studies by Duerden et al. (2012) and Nickl-Jockschat et al. (2012) included a total of 692 and 584 subjects, respectively.

Methods and materials

Subjects

All data included in this investigation came from the ABIDE which is described in detail in Di Martino et al. (2014). Briefly, the ABIDE is a publically available repository of structural MRI and resting-state fMRI data acquired on individuals with ASD and typically-developing (TD) individuals from 17 independent sites. ABIDE includes 1112 datasets comprised of 539 individuals with ASD and 573 TD individuals. The original studies included in ABIDE received approval from each site's Institutional Review Board (IRB). With

respect to diagnostic procedures, most sites used the Autism Diagnostic Interview-Revised (Lord et al. 1994) or the Autism Diagnostic Observation Schedule (Lord et al. 2000). In addition to diagnostic classification, each site provided basic phenotypic data on each subject, including age and sex. Most sites also included a measure of intellectual functioning.

All subjects and matched samples cohorts

In an effort to maximize statistical power, while also limiting the impact of potential confounds associated with multi-site investigations, two sets of analysis were performed on overlapping samples extracted from the ABIDE. The first sample, the "All Subjects" cohort, included 833 subjects with structural MRI scans that met our quality control criteria described below. From the sample of 833 subjects, we extracted a "Matched Samples" cohort in which ASD and TD subjects were matched within each site on age (±2 years) and sex. Critically, it has been shown that balancing the number of cases to controls within each site effectively mitigates site effects in between groups contrasts, whereas unbalanced numbers of cases to controls has the opposite effect (Takao et al. 2014). Matching was performed objectively using the Case–control Matching feature in the Statistical Package for the Social Sciences (SPSS). The "Matched Samples" cohort consisted of 600 subjects (i.e. 300 case–control pairs). Demographic data for the "All Subjects" and "Matched Samples" cohorts are presented in Table 1.

Structural neuroimaging data Pre-processing and quality control

A whole-brain T1-weighted volumetric Magnetization Prepared Rapid Gradient Echo (MPRAGE) structural MRI was acquired on every subject in the ABIDE (the parameters used at each site can be found at http://fcon_1000.projects.nitrc.org/indi/abide/). Each subject's structural scan was segmented into gray matter, white matter, and cerebral-spinal fluid (CSF) tissue classes using the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm/) for SPM8 (http://www.fil.ion.ucl.ac.uk/spm). Total grey matter, white matter, and total brain volume (TBV = GM + WM) was calculated for each subject from the native space segmented images. These variables served as the primary dependent variables in the total tissue volumes analyses. Following segmentation, the grey matter tissue class images were normalized to a template image included with the VBM8 toolbox, comprised of 550 subjects, using the high dimensional DARTEL normalization method (Ashburner 2007). Images were modulated by the non-linear component only during normalization since the goal of the voxel-wise analysis was to identify regional differences in grey matter volume after adjusting for total brain volume (i.e. linear components). The images were interpolated to voxel dimensions of 1.5 mm isotropic resolution during DARTEL normalization and smoothed with a 6 mm kernel prior to statistical analysis.

Quality control was performed at multiple points in the data preprocessing. First, every structural scan was visually inspected, blind to diagnosis. Scans containing obvious artifacts (e.g., ghosting or blurring due to head motion) were excluded. Second, the accuracy of the spatial normalization step was visually inspected. Third, the segmentation accuracy was assessed by overlaying the segmented images on the original native space T1 structural scan and inspecting for segmentation errors (e.g. missing/misclassified tissue, failed skull stripping). Again, this step was done blind to diagnostic status. Scans with segmentation errors were excluded from further analysis. Finally, the "Check Sample Homogeneity using Covariance" function in VBM8 was used to identify outlier scans. Grey matter segmented images with mean values greater than two standard deviations from the sample mean were again visually inspected to ensure they did not contain artifacts. 279 subjects were excluded due to missing T1 image or obvious imaging artifacts ($n = 133$), and segmentation/normalization failure ($n = 146$). Examples of poor quality scans and segmentation failures are presented in Supplemental Figure 1.

Statistical analysis

Group differences in total brain volumes and regional grey matter volume

Group differences in TBV were analyzed using univariate ANOVA. To identify selective differences in tissue volumes, a multivariate ANOVA (MANOVA) with tissue type (i.e. grey, white, CSF) entered as the dependent variables and diagnosis as a group factor was performed. In cases where there was a main effect of group, post-hoc univariate ANOVAs were carried out to determine which dependent variable(s) differed between groups. All analyses included age, sex, and site as covariates. TBV and total tissue volume analyses were followed up with VBM analysis to identify group differences in grey matter volume at the voxel-wise level. Specifically, within SPM8, the non-linear modulated grey matter tissue class images were entered into an independent groups *t*-test comparing ASD to TD individuals. VBM analyses included age, sex, and site as covariates and the contrast comparing ASD and TD groups was thresholded at the whole-brain, cluster-level Family-wise error corrected $p = .05$ for voxel-wise p-value = .001.

Age effects

Given speculation that abnormalities in brain structure in ASD vary by developmental stage, we also examined group differences as a function of age. Most studies in the ABIDE

Table 1 Demographics for all subjects and matched samples cohorts

Site	All Subjects cohort ($n = 833$)												Matched Samples Cohort ($n = 600$)									
	n		Sex					Age					n		Sex				Age				
	TD	ASD	TD		ASD		p	TD		ASD		p	TD	ASD	TD		ASD		TD		ASD		p
			M	F	M	F		Mean	SD	Mean	SD				M	F	M	F	Mean	SD	Mean	SD	
Caltech	17	18	13	4	14	4	.927	27.6	9.6	27.7	10.5	.971	12	12	9	3	9	3	24.6	8.5	24.9	8.3	.937
CMU	13	14	10	3	11	3	.918	26.8	5.7	26.4	5.8	.828	12	12	10	2	12	2	26.2	6.0	26.3	6.1	.867
KKI	11	7	8	3	6	1	.518	10.5	1.7	9.6	1.6	.303	7	7	6	1	6	1	10.2	1.6	9.6	1.6	.502
Leuven 1	12	14	12	0	14	0	–	23.8	2.8	21.9	4.1	.192	9	9	9	0	9	0	22.7	2.2	22.1	3.1	.666
Leuven 2	15	8	11	4	5	3	.591	14.6	1.6	14.3	0.8	.555	8	8	5	3	5	3	14.2	1.5	14.3	0.8	.968
Max Munich	33	22	29	4	19	3	.869	26.2	9.8	27.7	14.5	.645	18	18	15	3	15	3	24.5	11.8	24.8	11.6	.944
NYU	85	46	62	23	37	9	.341	17.0	6.3	17.3	7.7	.817	43	43	36	7	36	7	15.6	6.3	16.1	6.2	.733
OSHU	15	13	15	0	13	0	–	10.1	1.1	11.7	2.2	.021	9	9	9	0	9	0	10.4	1.1	10.6	1.7	.809
Olin	14	11	12	2	8	3	.420	17.2	3.8	17.8	3.3	.681	9	9	7	2	7	2	17.6	3.0	17.1	2.9	.753
Pitt	23	24	20	3	20	4	.727	19.9	6.7	18.6	7.6	.564	18	18	17	1	17	1	19.2	7.2	19.3	7.7	.991
SBL	13	14	13	0	14	0	–	33.2	7.0	32.9	6.9	.911	7	7	7	0	7	0	32.0	7.8	32.6	7.4	.891
SDSU	18	11	13	5	11	0	.055	14.2	2.0	15.0	1.7	.281	11	11	11	0	11	0	14.5	1.5	15.0	1.7	.436
Standford	6	10	3	3	6	4	.696	10.2	1.9	9.9	1.6	.796	5	5	2	3	2	3	10.1	2.1	10.3	1.5	.909
Trinity	24	23	24	0	23	0	–	17.3	3.7	17.5	3.5	.855	22	22	22	0	22	0	17.6	3.7	17.4	3.6	.856
UCLA 1	23	33	19	4	29	4	.307	13.8	2.0	13.4	2.5	.532	22	22	19	3	19	3	13.9	2.1	13.5	2.5	.573
UCLA 2	8	12	6	2	12	0	.068	12.5	0.7	12.8	1.9	.665	6	6	6	0	6	0	12.4	0.8	12.9	1.5	.498
UM 1	47	25	31	16	21	4	.104	14.2	3.2	13.4	2.6	.264	25	25	21	4	21	4	13.5	3.0	13.4	2.6	.880
UM 2	14	11	13	1	10	1	.859	16.3	3.4	15.0	1.6	.278	9	9	9	0	9	0	15.5	1.7	14.9	1.7	.491
USM	39	56	39	0	56	0	–	21.9	7.8	22.9	7.8	.554	35	35	35	0	35	0	22.5	6.7	22.3	6.6	.897
Yale	13	18	9	4	12	6	.880	12.9	2.7	13.1	3.1	.903	13	13	9	4	9	4	12.9	2.7	12.7	3.1	.829
Total	**443**	**390**	**362**	**81**	**341**	**49**	**.025**	**18.3**	**7.8**	**18.6**	**8.7**	**.560**	**300**	**300**	**264**	**36**	**264**	**36**	**17.8**	**7.4**	**17.8**	**7.4**	**.965**

included either children or adolescents/adults, but not both. Thus, age and site were not independent; there was a significant site by age interaction ($x^2(57) = 636.20$, $p < .001$). This is problematic from a statistical perspective as colinearity between covariates and independent variables is a potential confound when interpreting interactions. To avoid this confound, age was treated as a dichotomous rather than continuous variable and differences between ASD and TD were examined within specific age bands. Subjects were divided into four age bands based on quartiles of age distribution for the entire sample of subjects included in the ABIDE. The four age ranges were labelled as 'Children' (age 6–12.6 years), 'Young Adolescents' (age 12.7–16.1 years), 'Older Adolescents' (age 16.2–22 years), and 'Adults' (age > 22 years). The TBV, total tissue volumes, and VBM analyses described above were repeated within each age band. Demographic variables for each diagnostic group broken down by age band are presented in Supplemental Table 1.

IQ Effects

We also investigated what effect, if any, IQ has on differences in brain structure between ASD and TD, and the relationship between brain volumes and IQ. Many sites reported a full-scale intelligence quotient (IQ) along with verbal and performance IQ (VIQ and PIQ, respectively). A small number of sites reported VIQ and PIQ, but not IQ. In these cases, VIQ and PIQ were averaged to create an IQ score. To determine if group differences in TBV were related to IQ differences, we repeated the primary analysis of TBV and tissue volumes, and the voxelwise analysis including IQ as an additional covariate. The relationship between TBV and IQ was evaluated using a linear regression analysis with TBV entered as the dependent variable and age, sex, site, diagnostic group and IQ entered as predictors. This analysis was repeated including the IQ by group interaction term to determine if the relationship between TBV and IQ differed between the ASD and TD groups.

Results

Total brain and tissue volumes in ASD and TD

TBV and tissue volumes for the All Subjects and Matched Samples cohorts are presented in Fig. 1. Results within each site are presented in Supplemental Figures 2 and 3.

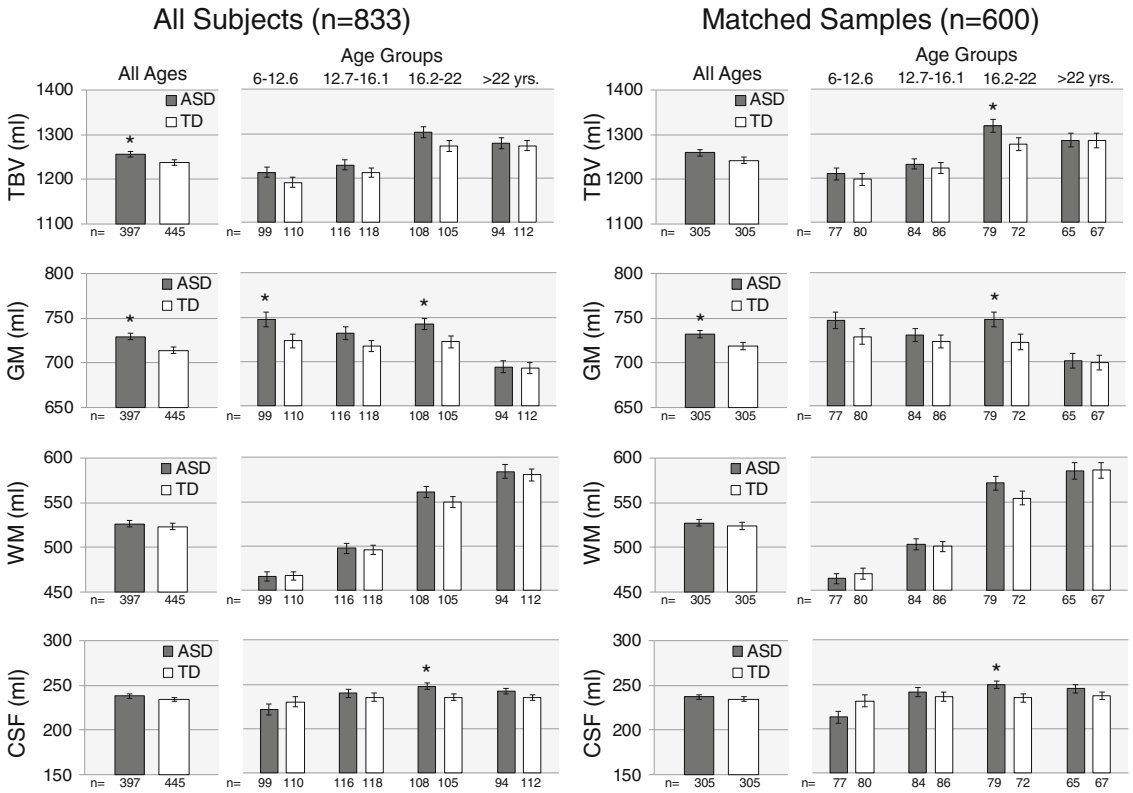

Fig. 1 Total brain and tissue volumes in individuals with autism spectrum disorder (*ASD*) and typical development (*TD*). *Left panel*: results of the "All Subjects" analysis which included all individuals within the ABIDE with usable structural neuroimaging data. *Right panel*: results of the "Matched Samples" analysis which included ASD and TD individuals matched within each site on the basis of age (± 2 years) and sex. All volumes adjusted for age, sex, and site. Error bars indicate standard error of the mean. Abbreviations: *CSF* Cerebrospinal Fluid, *GM* Grey Matter, *TBV* Total Brain Volume, *WM* White Matter. * Significant difference between groups ($p \leq .05$)

All Subjects Cohort TBV was significantly larger in ASD compared to TD by 1.58 % (adjusted volumes: 1257.9 ml vs. 1238.3 ml; $F(1828) = 5.63$, $p = .018$). The MANOVA with grey matter, white matter, and CSF entered as dependent variables revealed a main effect of group ($F(3826) = 5.16$, $p = .002$). As shown in Fig. 1, the tissue main effect of group was due to a 2.17 % enlargement in total gray matter volume in ASD (adjusted volumes: 730.6 ml vs. 714.4 ml; $F(1828) = 10.45$, $p = .001$); no group differences were detected for white matter (527.3 ml vs. 523.8 ml; $F(1828) = 0.62$, $p = .432$) and CSF volumes (237.5 ml vs. 233.9 ml; $F(1828) = 1.22$, $p = .270$).

Matched Subjects Cohort Consistent with the analysis of all subjects, TBV was approximately 1.27 % larger in ASD compared to TD (1260.4 vs. 1244.6 ml) within the Matched Samples cohort; however, this difference did not reach statistical significance ($F(1595) = 2.56$, $p = .110$). Also consistent with the analysis of all subjects, total grey matter volume was significantly larger in ASD by approximately 1.75 % (732.6 vs. 720.0 ml; $F(1595) = 4.58$, $p = .033$); however, the overall MANOVA with tissue type entered as the dependent variables only reached trend significance ($F(3593) = 2.42$, $p = .065$).

Regional grey matter volume in ASD: voxel-based morphometry

Results of the VBM analyses of voxel-wise grey matter volume are presented in Table 2 and Fig. 2. In light of modest group differences in TBV between ASD and TD, it is important to reiterate that the analysis of modulated, normalized images in VBM, as performed here, controls for individual differences in TBV. Within the All Subjects cohort, VBM analysis revealed a single cluster located in the left anterior superior temporal gyrus (STG) (MNI coordinates: −66 −6 −2) of increased grey matter volume in ASD compared to TD. There were no areas of grey matter where the TD group demonstrated significantly greater volume than the ASD group. No significant group differences were detected in the Matched Samples cohort.

Age effects

All Subjects Cohort Results of total tissue volumes comparing ASD and TD within each age band are presented in Fig. 1. In Children (age range 6 to 12.7 years), there was a non-significant trend towards increased TBV in ASD (1221.0 ml vs. 1191.0 ml; ($F(1197) = 3.25$, $p = .073$). MANOVA with grey

Table 2 Voxel-based morphometry results

	Cohort											
	All subjects ($n = 833$)						Matched Samples ($n = 600$)					
	MNI			t-value	p[a]	Cluster Size[b]	MNI			t-value	p[a]	Cluster Size[b]
	x	y	z				x	y	z			
Entire Sample												
ASD > TD							No Significant Differences					
Left Superior Temporal Gyrus	−66	−6	−2	4.41	.023	574						
TD > ASD	No Significant Differences						No Significant Differences					
Children (age 6–12.6 years)												
ASD > TD	No Significant Differences						No Significant Differences					
TD > ASD	No Significant Differences						No Significant Differences					
Young Adolescents (age 12.7–16.1 year)												
ASD > TD	No Significant Differences						No Significant Differences					
TD > ASD	No Significant Differences						No Significant Differences					
Older Adolescents (age 16.2–22 years)												
ASD > TD	No Significant Differences						No Significant Differences					
TD > ASD							No Significant Differences					
Left Central Sulcus	−48	−15	43	4.10	.002	891						
Adults (age > 22 years)												
ASD > TD	No Significant Differences						No Significant Differences					
TD > ASD	No Significant Differences						No Significant Differences					

Abbreviations: *ASD* Autism Spectrum Disorder, *MNI* Montreal Neurological Institute, *TD* Typically Developed

[a] cluster-level Family-Wise Error (*FWE*) corrected p=.05 for voxel-wise $p = .001$

[b] in voxels (voxel size = 1.5 mm isotropic)

matter, white matter, and CSF entered as dependence variables was significant (F(3195) = 2.88, $p = 037$) due to significant enlargement of grey matter in ASD (752.6 ml vs. 724.2 ml; F(1197) = 6.33, $p = .013$), but not white matter and CSF (F-values < 1.56, $p > .213$). In the Young Adolescent cohort (age range 12.7 to 16.1 years), no significant differences in TBV or total tissue volumes were detected (TBV: F(1208) = 0.86, $p = .355$; MANOVA F(3206) = 1.60, $p = .192$). In Older Adolescents, TBV was increased in ASD compared to TD at the trend significance level (1303.2 ml vs. 1272.2 ml; F(1208) = 3.33, $p = .069$). The MANOVA examining group differences in tissue volumes was significant (F(3206) = 3.07, $p = .029$) due to the fact that grey matter volume was significantly increased in ASD (742.4 ml vs. 722.4; F(1208) = 4.45, $p = .036$), as was CSF volume (247.7 ml vs. 235.5 ml; F(1208) = 5.30, $p = .022$). In Adults, no significant differences in TBV (F(1200) = 0.19, $p = .891$) and total tissue volumes were detected (MANOVA F(3198) = 0.90, $p = .445$).

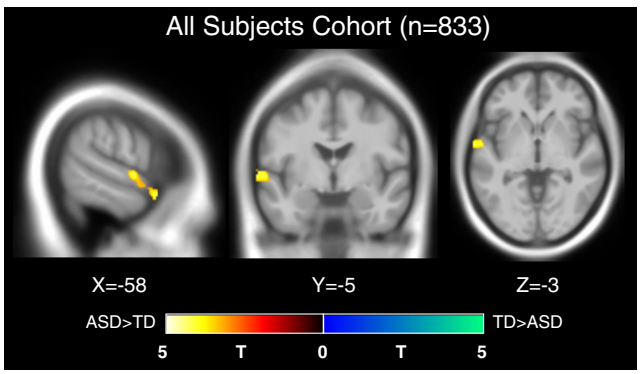

Fig. 2 Grey matter abnormalities in individuals with autism spectrum disorder (*ASD*). *Top Panel*: within the All Subjects cohort ($n = 833$), individuals with ASD exhibited greater grey matter volume in the left anterior superior temporal gyrus (MNI coordinates: −66 − 6 − 2, cluster size = 574 voxels) compared to typical development (*TD*) individuals. No significant differences were detected in the Matched Samples cohort ($n = 600$)

Matched Samples Cohort Results of total tissue volumes comparing ASD and TD within each age band presented in Fig. 1. There was no difference in TBV between TD and ASD groups within the children age band (F(1146) = 0.40, $p = .527$). Similarly, the MANOVA did not reveal any group differences for tissue type (F(3144) = 1.64, $p = .184$). No group differences in TBV and total tissue volumes were detected in the Young Adolescents age band (all F-values < 0.54, p-values > .618). In the Older Adolescents age band, TBV was

significantly increased in ASD (1318.6 ml vs. 1276.2 ml; F(1146) = 4.17, $p = .043$). The MANOVA was significant (F(3144) = 3.07, $p = .030$) due to the fact that grey matter and CSF volumes were increased in ASD (grey matter: 747.6 ml vs. 722.2 ml, F(1146) = 4.70, $p = .032$; CSF: 249.9 ml vs. 234.7 ml, F(1146) = 6.12, $p = .015$).

No group differences in TBV and tissue volumes were detected in the Adult age band (all F-values < 0.77, p-values > .517).

VBM Results of the voxel-wise analysis in each age band are presented in Table 2 and Fig. 2. Within the All Subjects cohort, no group differences were detected in the children, young adolescents and adult age groups. In the Older Adolescent group, there were no regions in the grey matter where ASD demonstrated greater volume than TD. However, older adolescents with ASD demonstrated reduced grey matter volume in a single cluster located in the left central sulcus (MNI coordinates −48 −15 43). Within the Matched Subjects cohort, no group differences were detected in any age band.

IQ Effects

All Subjects Cohort IQ was available on 814 of the 833 individuals included in the All Subjects cohort. Three subjects with IQ < 70 were excluded leaving a total of 811 subjects (ASD $n = 381$; TD $n = 430$) in the following analyses. Consistent with the results of the primary analysis, TBV remained significantly enlarged in ASD by 2.02 % compared to TD after covarying for IQ (1259.0 ml vs. 1234.0 ml; F(5805) = 8.71, $p = .003$). Similarly, the group effect for the MANOVA of tissue types also remained significant (F(3803) = 4.90, $p = .002$) due significant enlargement of grey matter in ASD (732.2 ml vs. 714.1 ml; F(1805) = 12.48, $p < .001$). No group differences in white matter and CSF were detected (F-values < 2.37, p-values > .124). As shown in Supplementary Figure 4, the results of the voxel-wise analysis also remained unchanged when FIQ was added as a covariate. Grey matter volume in a cluster located in the left anterior STG (MNI coordinates −66 −4 −2) was significantly increased in ASD (t = 4.38, p_{FWE} cluster level corrected = .002; cluster size = 993 voxels). No regions of decreased grey matter volume were detected in ASD.

The linear regression analysis with TBV entered as the dependent variable and age, sex, site, diagnostic group, and FIQ entered as predictors was significant (F(5805) = 44.56, $p < .001$). This was due, in part, to a significant correlation between TBV and IQ (partial r = 0.16, $p < .001$). Scatterplots for the Correlations between TBV and IQ are presented in Supplemental Figure 5. In the TD group, the partial correlation between TBV and IQ was r = .20, $p < .001$, indicating that IQ accounted for 4.0 % of the variance in TBV. The partial correlation in ASD was r = .13, $p < .011$ indicating that IQ accounted for about 1.7 % of the variance in TBV. Repetition of the linear regression analysis after including an IQ by group interaction term indicated that the correlation between TBV and IQ, while diminished in ASD, did not significantly differ between groups (group x IQ interaction term t(804) = 1.38, $p = .169$).

Matched Samples Cohort IQ was available on 592 subjects. Two individuals with IQ < 70 were excluded leaving a total of 590 subjects (ASD $n = 297$; TD $n = 293$) in the following analyses. Adjusted for IQ, TBV was significantly larger in ASD by approximately 1.94 % (1263.8 ml vs. 1239.8 ml; (F(1584) = 5.73, $p = .017$). The group effect within the MANOVA was significant (F(3582) = 2.90, $p = .034$) due to the fact that grey matter volume increased in ASD (735.3 ml vs. 718.6 ml; F(1584) = 7.73, $p = .006$). For the VBM analysis, no significant differences were detected with IQ included as a covariate which is consistent with the Matched Subjects analysis that did not include IQ as a covariate.

The linear regression analysis with TBV entered as the dependent variable and age, sex, site, diagnostic group, and FIQ entered as predictors was significant (F(5584) = 27.39, $p < .001$) due, in part, to a significant correlation between TBV and IQ (partial r = 0.19, $p < .001$). Scatterplots for the Correlations between TBV and IQ are presented in Supplemental Figure 5. In the TD group, the partial correlation between TBV and IQ was r = .21, $p < .001$, indicating that IQ accounted for 4.4 % of the variance in TBV. The partial correlation in ASD was r = .17, $p < .003$ indicating that IQ accounted for about 2.9 % of the variance in TBV. Repetition of the linear regression analysis after including an IQ by group interaction term indicated that the correlation between TBV and IQ, while diminished in ASD, did not significantly differ between groups (group x FIQ interaction term t(583) = 0.77, $p = .441$).

Discussion

Using the vast resource of the ABIDE, we were able to examine brain structure in a large sample of individuals with and without ASD. In keeping with previous studies (Courchesne et al. 2003; Freitag et al. 2009; Hazlett et al. 2005), we found that TBV was enlarged in ASD due to a selective increase in total grey matter volume. This effect was significant in the All Subjects cohort, which included 833 individuals, but only reached trend significance in the smaller Matched Samples cohort ($n = 600$) which provided stringent control over potential confounds inherent to multi-site studies by matching cases to controls on age and sex within each site. However, after controlling for IQ, significant TBV enlargement in ASD was also detected in the Matched Samples cohort. Despite different image processing tools (i.e. VBM vs. FreeSurfer), statistical

methods, quality control criteria, and outcome variables (TBV vs. ICV), the current results are very similar to the previous investigation of the ABIDE by Haar and colleagues which reported a very slight increase in ICV in ASD (Haar et al. 2014). Consequently, it appears that TBV and grey matter enlargement in ASD is remarkably subtle, on the order of 1–2 %, and the generally modest significance level reached for most analyses is striking given the large sample sizes.

The ABIDE does not contain longitudinal data; however, we were able to examine age effects cross-sectionally. TBV and gray matter volume peaked in adolescence, while white matter continued to increase, which is consistent with prior developmental studies and meta-analyses (Durston et al. 2001; Giedd et al. 1999; Hedman et al. 2012). Although larger total cerebral and gray matter volumes in the ASD group contributed to more pronounced peaks in childhood and adolescence, the overall growth trajectories were very similar in the ASD and the TD groups. This suggests that the same basic processes are at play, but the extent and timing may differ subtly in ASD, at least for individuals aged 6 and older. The adults had remarkably similar volumes for all tissue classes, suggesting normalization of global structural differences over time, which is consistent with a recent VBM study of high functioning adults (Riedel et al. 2014) as well as Duerden et al.'s (Duerden et al. 2012) meta-analysis reporting no grey matter differences in adults with ASD. This resolution in adulthood may result from a compensatory drop in grey matter volume sometime in late adolescence or early adulthood for individuals with ASD that is enhanced relative to the drop seen in typical adolescents. The lack of group differences in TBV and total tissue volumes in adults with ASD clarifies a mixed literature on the developmental extent of brain volume differences in ASD, with some studies reporting increased volume persisting into adulthood (Freitag et al. 2009; Hazlett et al. 2006; Piven et al. 1995), but others reporting resolution of group differences by adulthood (Aylward et al. 2002; Courchesne et al. 2001; Ecker et al. 2012; Hallahan et al. 2009).

In addition to examining total brain and tissue volumes, a major goal of this investigation was to identify regional grey matter abnormalities in ASD. Using VBM, we found that grey matter expansion in ASD was relatively more pronounced in the left anterior STG. This finding is generally consistent with prior studies identifying altered morphometry in the temporal lobe in ASD (Brieber et al. 2007; McAlonan et al. 2005), and the STG as a potentially important biomarker of ASD (Mueller et al. 2013; Pierce 2011; Waiter et al. 2004). This finding remained significant even after controlling for IQ. However, it is critical to point out that no group differences in regional grey matter were identified in the Matched Samples cohort, which included 300 case–control pairs. This is consistent with Haar and colleagues who reported no volumetric differences in grey matter using an ROI approach with date from the ABIDE (Haar et al. 2014). They did, however, find increased cortical thickness in several ROIs, including the left STG. The anterior region of the left STG we identified in the larger sample is associated with semantic language comprehension (Lau et al. 2013) and response selectivity for human speech sounds (DeWitt and Rauschecker 2012), corroborating previous findings that the structure of the STG impacts aberrant language and communication development in ASD (Bigler et al. 2007).

When examining age effects, older adolescents with ASD in the All Subjects cohort exhibited a single cluster of decreased grey matter volume in the left central sulcus. No significant regional differences were found in other age bands, or in any age band within the Matched Samples cohort. Decreased left central sulcus grey matter volume in older adolescents is consistent with functional findings of less coherent central sulcus response in ASD during a sensorimotor task (Muller et al. 2001).

As touched upon earlier, we were struck by the minimal, highly localized group differences in morphometry in a very large sample of individuals with ASD. This is particularly striking given the extensive neural network models that have been hypothesized to be involved in the neuropathology of ASD (McAlonan et al. 2005; Muller 2007). It is noteworthy that within a sample of over 800 individuals, significant group differences were so minimal and localized to regions that are more involved with language and sensorimotor function than with reciprocal social interaction, the defining clinical feature of ASD. This contrasts with previous studies of much smaller samples that have reported widespread group differences in the insula (Radeloff et al. 2014), cingulate (Greimel et al. 2013), as well as various temporal (Greimel et al. 2013), parietal (Ecker et al. 2012; Greimel et al. 2013), and prefrontal (Duerden et al. 2012; Ecker et al. 2012) lobe structures. It's possible that the relative lack of such findings in the current study is due to methodological differences between studies and symptom heterogeneity. However, the possibility that some, possibly many of the neuroanatomical findings in ASD are false positives must also be considered. As touched upon earlier, the vast majority of anatomical imaging studies included relatively few subjects, less than 25 individuals with ASD in many cases (Duerden et al. 2012). Small studies are prone to producing unreliable results; an effect that is compounded by publication bias and the use of samples of convenience in neuroimaging studies (Falk et al. 2013; Ioannidis et al. 2014).

In conclusion, the current study leveraged the unprecedented power of the ABIDE to investigate brain structure differences in individuals with ASD. While increased total brain/gray matter volume in ASD was replicated, it was a small increase, and was absent in the adult subgroup. It was, however, robust to IQ effects as group differences remained after accounting for IQ differences. This was in spite of a

significant amount of variance in total brain volume that was accounted for by IQ, which has been reported in previous studies (Freitag et al. 2009). These findings represent the largest VBM study to date of brain structure in ASD; the ABIDE will undoubtedly provide the autism research community with unprecedented opportunity to assess brain structure and function in ASD on a scale that will help to clarify discrepancies in the literature.

Compliance with ethical standards

Disclosures No commercial support was received for the preparation of this manuscript and the authors have no conflicts of interest to report.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the original data sources on which this study is based.

Funding This research was supported by funding from NIMH R21MH101321 (C.J.C. & N.D.W.) and the Jack Martin, MD., Research Professorship in Psychopharmacology (held by N.D.W.).

References

Ashburner, J. (2007). A fast diffeomorphic image registration algorithm. *NeuroImage, 38*, 95–113.

Aylward, E. H., Minshew, N. J., Field, K., Sparks, B. F., & Singh, N. (2002). Effects of age on brain volume and head circumference in autism. *Neurology, 59*, 175–183.

Bigler, E. D., Mortensen, S., Neeley, E. S., Ozonoff, S., Krasny, L., Johnson, M., Lu, J., Provencal, S. L., McMahon, W., & Lainhart, J. E. (2007). Superior temporal gyrus, language function, and autism. *Developmental Neuropsychology, 31*, 217–238.

Biswal, B. B., Mennes, M., Zuo, X. N., Gohel, S., Kelly, C., Smith, S. M., Beckmann, C. F., Adelstein, J. S., Buckner, R. L., Colcombe, S., Dogonowski, A. M., Ernst, M., Fair, D., Hampson, M., Hoptman, M. J., Hyde, J. S., Kiviniemi, V. J., Kotter, R., Li, S. J., Lin, C. P., Lowe, M. J., Mackay, C., Madden, D. J., Madsen, K. H., Margulies, D. S., Mayberg, H. S., McMahon, K., Monk, C. S., Mostofsky, S. H., Nagel, B. J., Pekar, J. J., Peltier, S. J., Petersen, S. E., Riedl, V., Rombouts, S. A., Rypma, B., Schlaggar, B. L., Schmidt, S., Seidler, R. D., Siegle, G. J., Sorg, C., Teng, G. J., Veijola, J., Villringer, A., Walter, M., Wang, L., Weng, X. C., Whitfield-Gabrieli, S., Williamson, P., Windischberger, C., Zang, Y. F., Zhang, H. Y., Castellanos, F. X., & Milham, M. P. (2010). Toward discovery science of human brain function. *Proceedings of the National Academy of Sciences of the United States of America, 107*, 4734–4739.

Brieber, S., Neufang, S., Bruning, N., Kamp-Becker, I., Remschmidt, H., Herpertz-Dahlmann, B., Fink, G. R., & Konrad, K. (2007). Structural brain abnormalities in adolescents with autism spectrum disorder and patients with attention deficit/hyperactivity disorder. *Journal of Child Psychology and Psychiatry, 48*, 1251–1258.

Campbell, M., Rosenbloom, S., Perry, R., George, A. E., Kricheff, I. I., Anderson, L., Small, A. M., & Jennings, S. J. (1982). Computerized axial tomography in young autistic children. *The American Journal of Psychiatry, 139*, 510–512.

Courchesne, E., Chisum, H. J., Townsend, J., Cowles, A., Covington, J., Egaas, B., Harwood, M., Hinds, S., & Press, G. A. (2000). Normal brain development and aging: quantitative analysis at in vivo MR imaging in healthy volunteers. *Radiology, 216*, 672–682.

Courchesne, E., Karns, C. M., Davis, H. R., Ziccardi, R., Carper, R. A., Tigue, Z. D., Chisum, H. J., Moses, P., Pierce, K., Lord, C., Lincoln, A. J., Pizzo, S., Schreibman, L., Haas, R. H., Akshoomoff, N. A., & Courchesne, R. Y. (2001). Unusual brain growth patterns in early life in patients with autistic disorder: an MRI study. *Neurology, 57*, 245–254.

Courchesne, E., Carper, R., & Akshoomoff, N. (2003). Evidence of brain overgrowth in the first year of life in autism. *JAMA, 290*, 337–344.

Courchesne, E., Pierce, K., Schumann, C. M., Redcay, E., Buckwalter, J. A., Kennedy, D. P., & Morgan, J. (2007). Mapping early brain development in autism. *Neuron, 56*, 399–413.

DeRamus, T. P., & Kana, R. K. (2015). Anatomical likelihood estimation meta-analysis of grey and white matter anomalies in autism spectrum disorders. *Neuroimage Clinical, 7*, 525–536.

DeWitt, I., & Rauschecker, J. P. (2012). Phoneme and word recognition in the auditory ventral stream. *Proceedings of the National Academy of Sciences of the United States of America, 109*, E505–E514.

Di Martino, A., Yan, C. G., Li, Q., Denio, E., Castellanos, F. X., Alaerts, K., Anderson, J. S., Assaf, M., Bookheimer, S. Y., Dapretto, M., Deen, B., Delmonte, S., Dinstein, I., Ertl-Wagner, B., Fair, D. A., Gallagher, L., Kennedy, D. P., Keown, C. L., Keysers, C., Lainhart, J. E., Lord, C., Luna, B., Menon, V., Minshew, N. J., Monk, C. S., Mueller, S., Muller, R. A., Nebel, M. B., Nigg, J. T., O'Hearn, K., Pelphrey, K. A., Peltier, S. J., Rudie, J. D., Sunaert, S., Thioux, M., Tyszka, J. M., Uddin, L. Q., Verhoeven, J. S., Wenderoth, N., Wiggins, J. L., Mostofsky, S. H., & Milham, M. P. (2014). The autism brain imaging data exchange: towards a large-scale evaluation of the intrinsic brain architecture in autism. *Molecular Psychiatry, 19*, 659–667.

Duerden, E. G., Mak-Fan, K. M., Taylor, M. J., & Roberts, S. W. (2012). Regional differences in grey and white matter in children and adults with autism spectrum disorders: an activation likelihood estimate (ALE) meta-analysis. *Autism Research, 5*, 49–66.

Durston, S., Hulshoff Pol, H. E., Casey, B. J., Giedd, J. N., Buitelaar, J. K., & van Engeland, H. (2001). Anatomical MRI of the developing human brain: what have we learned? *Journal of the American Academy of Child and Adolescent Psychiatry, 40*, 1012–1020.

Ecker, C., Suckling, J., Deoni, S. C., Lombardo, M. V., Bullmore, E. T., Baron-Cohen, S., Catani, M., Jezzard, P., Barnes, A., Bailey, A. J., Williams, S. C., & Murphy, D. G. (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.

Falk, E. B., Hyde, L. W., Mitchell, C., Faul, J., Gonzalez, R., Heitzeg, M. M., Keating, D. P., Langa, K. M., Martz, M. E., Maslowsky, J., Morrison, F. J., Noll, D. C., Patrick, M. E., Pfeffer, F. T., Reuter-Lorenz, P. A., Thomason, M. E., Davis-Kean, P., Monk, C. S., & Schulenberg, J. (2013). What is a representative brain? Neuroscience meets population science. *Proceedings of the National Academy of Sciences of the United States of America, 110*, 17615–17622.

Freitag, C. M., Luders, E., Hulst, H. E., Narr, K. L., Thompson, P. M., Toga, A. W., Krick, C., & Konrad, C. (2009). Total brain volume and corpus callosum size in medication-naive adolescents and young adults with autism spectrum disorder. *Biological Psychiatry, 66*, 316–319.

Fusar-Poli, P., Radua, J., Frascarelli, M., Mechelli, A., Borgwardt, S., Di, F. F., Biondi, M., Ioannidis, J. P., & David, S. P. (2014). Evidence of

reporting biases in voxel-based morphometry (VBM) studies of psychiatric and neurological disorders. *Human Brain Mapping, 35*, 3052–3065.

Giedd, J. N., Blumenthal, J., Jeffries, N. O., Castellanos, F. X., Liu, H., Zijdenbos, A., Paus, T., Evans, A. C., & Rapoport, J. L. (1999). Brain development during childhood and adolescence: a longitudinal MRI study. *Nature Neuroscience, 2*, 861–863.

Greimel, E., Nehrkorn, B., Schulte-Ruther, M., Fink, G. R., Nickl-Jockschat, T., Herpertz-Dahlmann, B., Konrad, K., & Eickhoff, S. B. (2013). Changes in grey matter development in autism spectrum disorder. *Brain Structure and Function, 218*, 929–942.

Gupta, C. N., Calhoun, V. D., Rachakonda, S., Chen, J., Patel, V., Liu, J., Segall, J., Franke, B., Zwiers, M. P., Arias-Vasquez, A., Buitelaar, J., Fisher, S. E., Fernandez, G., van Erp, T. G., Potkin, S., Ford, J., Mathalon, D., McEwen, S., Lee, H. J., Mueller, B. A., Greve, D. N., Andreassen, O., Agartz, I., Gollub, R. L., Sponheim, S. R., Ehrlich, S., Wang, L., Pearlson, G., Glahn, D. C., Sprooten, E., Mayer, A. R., Stephen, J., Jung, R. E., Canive, J., Bustillo, J., & Turner, J. A. (2015). Patterns of gray matter abnormalities in schizophrenia based on an international mega-analysis. *Schizophrenia Bulletin, 41*, 1133–1142.

Haar, S., Berman, S., Behrmann, M., & Dinstein, I. (2014) Anatomical Abnormalities in Autism? *Cerebral Cortex*

Hallahan, B., Daly, E. M., McAlonan, G., Loth, E., Toal, F., O'Brien, F., Robertson, D., Hales, S., Murphy, C., Murphy, K. C., & Murphy, D. G. (2009). Brain morphometry volume in autistic spectrum disorder: a magnetic resonance imaging study of adults. *Psychological Medicine, 39*, 337–346.

Hardan, A. Y., Muddasani, S., Vemulapalli, M., Keshavan, M. S., & Minshew, N. J. (2006). An MRI study of increased cortical thickness in autism. *The American Journal of Psychiatry, 163*, 1290–1292.

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

Hazlett, H. C., Poe, M. D., Gerig, G., Smith, R. G., & Piven, J. (2006). Cortical gray and white brain tissue volume in adolescents and adults with autism. *Biological Psychiatry, 59*, 1–6.

Hedman, A. M., van Haren, N. E., Schnack, H. G., Kahn, R. S., & Hulshoff Pol, H. E. (2012). Human brain changes across the life span: a review of 56 longitudinal magnetic resonance imaging studies. *Human Brain Mapping, 33*, 1987–2002.

Herbert, M. R., Ziegler, D. A., Deutsch, C. K., O'Brien, L. M., Lange, N., Bakardjiev, A., Hodgson, J., Adrien, K. T., Steele, S., Makris, N., Kennedy, D., Harris, G. J., & Caviness, V. S., Jr. (2003). Dissociations of cerebral cortex, subcortical and cerebral white matter volumes in autistic boys. *Brain, 126*, 1182–1192.

Ioannidis, J. P., Munafo, M. R., Fusar-Poli, P., Nosek, B. A., & David, S. P. (2014). Publication and other reporting biases in cognitive sciences: detection, prevalence, and prevention. *Trends in Cognitive Sciences, 18*, 235–241.

Jou, R. J., Mateljevic, N., Minshew, N. J., Keshavan, M. S., & Hardan, A. Y. (2011). Reduced central white matter volume in autism: implications for long-range connectivity. *Psychiatry and Clinical Neurosciences, 65*, 98–101.

Kamdar, M. R., Gomez, R. A., & Ascherman, J. A. (2009). Intracranial volumes in a large series of healthy children. *Plastic and Reconstructive Surgery, 124*, 2072–2075.

Lau, E. F., Gramfort, A., Hamalainen, M. S., & Kuperberg, G. R. (2013). Automatic semantic facilitation in anterior temporal cortex revealed through multimodal neuroimaging. *The Journal of Neuroscience, 33*, 17174–17181.

Lenroot, R. K., Gogtay, N., Greenstein, D. K., Wells, E. M., Wallace, G. L., Clasen, L. S., Blumenthal, J. D., Lerch, J., Zijdenbos, A. P., Evans, A. C., Thompson, P. M., & Giedd, J. N. (2007). Sexual dimorphism of brain developmental trajectories during childhood and adolescence. *NeuroImage, 36*, 1065–1073.

Lord, C., Rutter, M., & Le, C. 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*, 659–685.

Lord, C., Risi, S., Lambrecht, L., Cook, E. H., Jr., Leventhal, B. L., DiLavore, P. C., Pickles, A., & Rutter, M. (2000). The autism diagnostic observation schedule-generic: a standard measure of social and communication deficits associated with the spectrum of autism. *Journal of Autism and Developmental Disorders, 30*, 205–223.

McAlonan, G. M., Cheung, V., Cheung, C., Suckling, J., Lam, G. Y., Tai, K. S., Yip, L., Murphy, D. G., & Chua, S. E. (2005). Mapping the brain in autism. A voxel-based MRI study of volumetric differences and intercorrelations in autism. *Brain, 128*, 268–276.

Mueller, S. G., Weiner, M. W., Thal, L. J., Petersen, R. C., Jack, C., Jagust, W., Trojanowski, J. Q., Toga, A. W., & Beckett, L. (2005). The Alzheimer's disease neuroimaging initiative. *Neuroimaging Clinics of North America, 15*, 869–xii.

Mueller, S., Keeser, D., Samson, A. C., Kirsch, V., Blautzik, J., Grothe, M., Erat, O., Hegenloh, M., Coates, U., Reiser, M. F., Hennig-Fast, K., & Meindl, T. (2013). Convergent findings of altered functional and structural brain connectivity in individuals with high functioning Autism: a multimodal MRI study. *PloS One, 8*, e67329.

Muller, R. A. (2007). The study of autism as a distributed disorder. *Mental Retardation and Developmental Disabilities Research Reviews, 13*, 85–95.

Muller, R. A., Pierce, K., Ambrose, J. B., Allen, G., & Courchesne, E. (2001). Atypical patterns of cerebral motor activation in autism: a functional magnetic resonance study. *Biological Psychiatry, 49*, 665–676.

Nickl-Jockschat, T., Habel, U., Michel, T. M., Manning, J., Laird, A. R., Fox, P. T., Schneider, F., & Eickhoff, S. B. (2012). Brain structure anomalies in autism spectrum disorder–a meta-analysis of VBM studies using anatomic likelihood estimation. *Human Brain Mapping, 33*, 1470–1489.

Palmen, S. J., Hulshoff Pol, H. E., Kemner, C., Schnack, H. G., Durston, S., Lahuis, B. E., Kahn, R. S., & Van, E. H. (2005). Increased gray-matter volume in medication-naive high-functioning children with autism spectrum disorder. *Psychological Medicine, 35*, 561–570.

Pierce, K. (2011). Early functional brain development in autism and the promise of sleep fMRI. *Brain Research, 1380*, 162–174.

Piven, J., Arndt, S., Bailey, J., Havercamp, S., Andreasen, N. C., & Palmer, P. (1995). An MRI study of brain size in autism. *The American Journal of Psychiatry, 152*, 1145–1149.

Radeloff, D., Ciaramidaro, A., Siniatchkin, M., Hainz, D., Schlitt, S., Weber, B., Poustka, F., Bolte, S., Walter, H., & Freitag, C. M. (2014). Structural alterations of the social brain: a comparison between schizophrenia and autism. *PloS One, 9*, e106539.

Redcay, E., & Courchesne, E. (2005). When is the brain enlarged in autism? A meta-analysis of all brain size reports. *Biological Psychiatry, 58*, 1–9.

Riedel, A., Maier, S., Ulbrich, M., Biscaldi, M., Ebert, D., Fangmeier, T., Perlov, E., & van Tebartz, E. L. (2014). No significant brain volume decreases or increases in adults with high-functioning autism spectrum disorder and above average intelligence: a voxel-based morphometric study. *Psychiatry Research, 223*, 67–74.

Sparks, B. F., Friedman, S. D., Shaw, D. W., Aylward, E. H., Echelard, D., Artru, A. A., Maravilla, K. R., Giedd, J. N., Munson, J., Dawson, G., & Dager, S. R. (2002). Brain structural abnormalities in young children with autism spectrum disorder. *Neurology, 59*, 184–192.

Stanfield, A. C., McIntosh, A. M., Spencer, M. D., Philip, R., Gaur, S., & Lawrie, S. M. (2008). Towards a neuroanatomy of autism: a systematic review and meta-analysis of structural magnetic resonance imaging studies. *European Psychiatry, 23*, 289–299.

Stein, J. L., Medland, S. E., Vasquez, A. A., Hibar, D. P., Senstad, R. E., Winkler, A. M., Toro, R., Appel, K., Bartecek, R., Bergmann, O., Bernard, M., Brown, A. A., Cannon, D. M., Chakravarty, M. M., Christoforou, A., Domin, M., Grimm, O., Hollinshead, M., Holmes, A. J., Homuth, G., Hottenga, J. J., Langan, C., Lopez, L. M., Hansell, N. K., Hwang, K. S., Kim, S., Laje, G., Lee, P. H., Liu, X., Loth, E., Lourdusamy, A., Mattingsdal, M., Mohnke, S., Maniega, S. M., Nho, K., Nugent, A. C., O'Brien, C., Papmeyer, M., Putz, B., Ramasamy, A., Rasmussen, J., Rijpkema, M., Risacher, S. L., Roddey, J. C., Rose, E. J., Ryten, M., Shen, L., Sprooten, E., Strengman, E., Teumer, A., Trabzuni, D., Turner, J., van Eijk, K., van Erp, T. G., van Tol, M. J., Wittfeld, K., Wolf, C., Woudstra, S., Aleman, A., Alhusaini, S., Almasy, L., Binder, E. B., Brohawn, D. G., Cantor, R. M., Carless, M. A., Corvin, A., Czisch, M., Curran, J. E., Davies, G., de Almeida, M. A., Delanty, N., Depondt, C., Duggirala, R., Dyer, T. D., Erk, S., Fagerness, J., Fox, P. T., Freimer, N. B., Gill, M., Goring, H. H., Hagler, D. J., Hoehn, D., Holsboer, F., Hoogman, M., Hosten, N., Jahanshad, N., Johnson, M. P., Kasperaviciute, D., Kent, J. W., Jr., Kochunov, P., Lancaster, J. L., Lawrie, S. M., Liewald, D. C., Mandl, R., Matarin, M., Mattheisen, M., Meisenzahl, E., Melle, I., Moses, E. K., Muhleisen, T. W., Nauck, M., Nothen, M. M., Olvera, R. L., Pandolfo, M., Pike, G. B., Puls, R., Reinvang, I., Renteria, M. E., Rietschel, M., Roffman, J. L., Royle, N. A., Rujescu, D., Savitz, J., Schnack, H. G., Schnell, K., Seiferth, N., Smith, C., Steen, V. M., Valdes Hernandez, M. C., Van den Heuvel, M., van der Wee, N. J., van Haren, N. E., Veltman, J. A., Volzke, H., Walker, R., Westlye, L. T., Whelan, C. D., Agartz, I., Boomsma, D. I., Cavalleri, G. L., Dale, A. M., Djurovic, S., Drevets, W. C., Hagoort, P., Hall, J., Heinz, A., Jack, C. R., Jr., Foroud, T. M., Le, H. S., Macciardi, F., Montgomery, G. W., Poline, J. B., Porteous, D. J., Sisodiya, S. M., Starr, J. M., Sussmann, J., Toga, A. W., Veltman, D. J., Walter, H., Weiner, M. W., Bis, J. C., Ikram, M. A., Smith, A. V., Gudnason, V., Tzourio, C., Vernooij, M. W., Launer, L. J., DeCarli, C., Seshadri, S., Andreassen, O. A., Apostolova, L. G., Bastin, M. E., Blangero, J., Brunner, H. G., Buckner, R. L., Cichon, S., Coppola, G., de Zubicaray, G. I., Deary, I. J., Donohoe, G., de Geus, E. J., Espeseth, T., Fernandez, G., Glahn, D. C., Grabe, H. J., Hardy, J., Hulshoff Pol, H. E., Jenkinson, M., Kahn, R. S., McDonald, C., McIntosh, A. M., McMahon, F. J., McMahon, K. L., Meyer-Lindenberg, A., Morris, D. W., Muller-Myhsok, B., Nichols, T. E., Ophoff, R. A., Paus, T., Pausova, Z., Penninx, B. W., Potkin, S. G., Samann, P. G., Saykin, A. J., Schumann, G., Smoller, J. W., Wardlaw, J. M., Weale, M. E., Martin, N. G., Franke, B., Wright, M. J., & Thompson, P. M. (2012). Identification of common variants associated with human hippocampal and intracranial volumes. *Nature Genetics, 44*, 552–561.

Takao, H., Hayashi, N., & Ohtomo, K. (2014). Effects of study design in multi-scanner voxel-based morphometry studies. *NeuroImage, 84*, 133–140.

van Erp, T.G., Hibar, D.P., Rasmussen, J.M., Glahn, D.C., Pearlson, G.D., Andreassen, O.A., Agartz, I., Westlye, L.T., Haukvik, U.K., Dale, A.M., Melle, I., Hartberg, C.B., Gruber, O., Kraemer, B., Zilles, D., Donohoe, G., Kelly, S., McDonald, C., Morris, D.W., Cannon, D.M., Corvin, A., Machielsen, M.W., Koenders, L., de Haan, L., Veltman, D.J., Satterthwaite, T.D., Wolf, D.H., Gur, R.C., Gur, R.E., Potkin, S.G., Mathalon, D.H., Mueller, B.A., Preda, A., Macciardi, F., Ehrlich, S., Walton, E., Hass, J., Calhoun, V.D., Bockholt, H.J., Sponheim, S.R., Shoemaker, J.M., van Haren, N.E., Pol, H.E., Ophoff, R.A., Kahn, R.S., Roiz-Santianez, R., Crespo-Facorro, B., Wang, L., Alpert, K.I., Jonsson, E.G., Dimitrova, R., Bois, C., Whalley, H.C., McIntosh, A.M., Lawrie, S.M., Hashimoto, R., Thompson, P.M., & Turner, J.A. (2015). Subcortical brain volume abnormalities in 2028 individuals with schizophrenia and 2540 healthy controls via the ENIGMA consortium. *Molecule Psychiatry*.

Van Essen, D. C., Smith, S. M., Barch, D. M., Behrens, T. E., Yacoub, E., & Ugurbil, K. (2013). The WU-Minn human connectome project: an overview. *NeuroImage, 80*, 62–79.

Waiter, G. D., Williams, J. H., Murray, A. D., Gilchrist, A., Perrett, D. I., & Whiten, A. (2004). A voxel-based investigation of brain structure in male adolescents with autistic spectrum disorder. *NeuroImage, 22*, 619–625.