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Volumetric and Voxel-Based Morphometry Findings in Autism Subjects With and Without Macrocephaly

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Abstract

This study sought to replicate Herbert et al. (2003a), which found increased overall white matter (WM) volume in subjects with autism, even after controlling for head size differences. To avoid the possibility that greater WM volume in autism is merely an epiphenomena of macrocephaly over-representation associated with the disorder, the current study included control subjects with benign macrocephaly. The control group also included subjects with a reading disability to insure cognitive heterogeneity. WM volume in autism was significantly larger, even when controlling for brain volume, rate of macrocephaly, and other demographic variables. Autism and controls differed little on whole-brain WM voxel-based morphometry (VBM) analyses suggesting that the overall increase in WM volume was non-localized. Autism subjects exhibited a differential pattern of IQ relationships with brain volumetry findings from controls. Current theories of brain overgrowth and their importance in the development of autism are discussed in the context of these findings.

A plausible theory implicates pathological brain overgrowth within the first two years of life in children diagnosed with autism (Courchesne, Redcay, Morgan, & Kennedy, 2005; McCaffery & Deutsch, 2005). Such “overgrowth” helps explain the well-documented observation of increased rates of macrocephaly found in autism (Aylward, Minshew, Field, Sparks, & Singh, 2002; Courchesne, Carper, & Akshoomoff, 2003; Davidovitch, Patterson, & Gartside, 1996; Dementieva et al., 2005; Fidler, Bailey, & Smalley, 2000; Fombonne, Roge, Claverie, Courty, & Fremolle, 1999; Gillberg & de Souza, 2002; Lainhart, 2003; Lainhart et al., 1997; Miles, Hadden, Takahashi, & Hillman, 2000; Stevenson, Schroer, Skinner, Fender, & Simensen, 1997; Woodhouse et al., 1996), as well as the observation by some studies of larger total and regional brain volumes (Carper & Courchesne, 2005; Hazlett, Poe, Gerig, Smith, Provenzale et al., 2005). Occipitofrontal head circumference (OFC) has to exceed the 97th percentile for a subject to be classified as macrocephalic, implying that any random sample of typically developing individuals should have no more than 3% meeting criteria for OFC-defined macrocephaly; however, macrocephaly rates in autism are often 20% or more (Lainhart, Bigler et al., 2006; Lainhart et al., 1997). Likewise, while not universal, numerous studies using volumetric magnetic resonance imaging (MRI) methods have shown larger brain volume in subjects with autism compared to age and demographically matched controls (Courchesne et al., 2001; Hardan et al., 2008; Herbert et al., 2005; Palmen et al., 2005). However, a confound could exist with this later observation, namely, if there is a higher frequency of macrocephaly in autism then macrocephaly becomes overrepresented in the autism group in comparison to the control sample and such overrepresentation could affect volumetric comparisons with a normative sample (Lainhart, Lazar, Alexander, & Bigler, 2006; Lainhart et al., 1997).

If group-dependent macrocephaly effects on total brain volume exist, then purported differences in region of interest (ROI) and tissue-type volumetrics associated with autism could be misleading and biased even after controlling for brain size (Lainhart, Bigler et al., 2006). While early brain overgrowth may be central to the neuropathology associated with autism, it also could be argued that brain size or any specific brain structure is larger in autism simply as epiphenomena of overall increased rate of macrocephaly found in autism. This has very important implications for understanding size–function relationships of brain

morphology to neuropsychological performance. Since benign macrocephaly occurs in the normal population and is associated with no neuropsychiatric or cognitive sequelae (Alper et al., 1999; Artigas, Poo, Rovira, & Cardo, 1999; Bodensteiner, 2000; Wilms et al., 1993), inclusion of such subjects would ensure that the control group has the full range of total brain volume (TBV). Also, given that robust relationships exist between IQ and brain size (Colom, Jung, & Haier, 2007; Haier, Jung, Yeo, Head, & Alkire, 2004, 2005; Toga & Thompson, 2005; Witelson, Beresh, & Kigar, 2006), underscores the importance of matching or controlling for IQ when performing morphometric studies of brain volume.

In addition, autism subjects by the very nature of the disorder, have an over-representation of language-based impairments that would not be found in a control sample (Dominick, Davis, Lainhart, Tager-Flusberg, & Folstein, 2007; Herbert, 2005; Herbert & Kenet, 2007; Whitehouse, Barry, & Bishop, 2007). This becomes significant in volumetric studies, because just like IQ, lowered language abilities can be associated with differences in brain ROIs and overall TBV (Casanova, Araque, Giedd, & Rumsey, 2004; Eckert et al., 2003; Eckert et al., 2005; Herbert, 2005; Phinney, Pennington, Olson, Filley, & Filipek, 2007). These factors raise important research design questions, indicating that in the study of brain volumetric differences between controls and subjects with autism, macrocephaly should be represented in both groups and the control group should include subjects who do not have autism, yet do have some type of language-based deficit.

Herbert et al. (2003a) have demonstrated proportionally greater cerebral white matter (WM) volume in subjects with autism in comparison to controls even after adjustment for TBV, but did not examine the issue of base rate problems with macrocephaly in autism. Since the predominant finding of the Herbert et al. (2003a) study observed larger cerebral WM volume in subjects with autism, even after head size correction, the current study was an attempt to replicate—but with a control sample that included cases of OFC-defined benign macrocephaly—to match the range of head size in the autism sample. If differences in the autism brain versus control are related to WM volume differences (see Lainhart, 2006; Minshew & Williams, 2007), then regardless of issues such as presence of macrocephaly or phenotypic features of the disorder (i.e., presence of a language deficit) the autism group should be different than the control. In the current study, whole brain WM volume was examined in a group of subjects with autism compared to controls.

We also included in our control sample, subjects with a reading disorder (RD), to broaden the range of verbal abilities in the control subjects (see Bigler et al., 2007 for further rationale for inclusion). If proportionally larger WM volume is still found in autism subjects compared to a control sample that includes cases of benign macrocephaly and RD this would support theories of parenchymal overgrowth and neuropathological connectivity involving WM in autism (Barnea-Goraly et al., 2004; Herbert & Kenet, 2007; Herbert et al., 2005; Williams & Minshew, 2007). Herbert's (2005) contention is that the WM increase found in autism is pathologically disproportional and may reflect the early developmental effects of neuroinflammation including microgliosis and astrogliosis and that these abnormalities affect the integration of neural transmission and underlie many of the cognitive and behavioral features of autism. Since studies that have examined birth OFC measures show that this overgrowth is usually not present at birth in those children who go

on to be diagnosed with autism (see Hobbs et al., 2007), increased WM volume in autism is thought to be mostly post-natal in development. Herbert et al. (2003a) also applied factor analytic methods to the various ROIs to assess the underlying importance of brain size in accounting for the variance in regional brain volumes. In addition, their study observed a three-factor model that accounted for the majority of shared variance, where one of the three factors was cerebral WM accounting for 15% of the variance. In the current study, we also applied factor analytic techniques to the ROIs under investigation.

We took several approaches in performing the quantitative MRI analyses to explore the issue of proportionally increased WM volume and other ROI differences in autism: (1) Traditional image segmentation and ROI quantification (Bigler et al., 2003), comparing various groupings of subjects with autism and control subjects with and without macrocephaly with the control group including RD subjects to ensure a broad spectrum of language abilities within the controls; (2) comparing MRI findings using statistical parametric mapping (SPM) to conduct voxel-based morphometry (VBM, see Waiter et al., 2005) comparisons between subjects with autism and controls; and (3) various statistical comparisons that permitted controlling for factors including head size, macrocephaly base rate in autism, presence of RD, and other demographic variables. We only examined non-mentally retarded subjects with autism, since presence of mental retardation is associated with greater heterogeneity in brain size and number of brain anomalies that affect brain size (Greenwood et al., 2005; Hazlett, Poe, Gerig, Smith, & Piven, 2005; Spencer et al., 2006).

ROI volumetry methods permit the direct comparison of brain regions between autism and control subjects, where each individual control ROI is pitted against the same ROI in the autism sample. VBM analyses provide a very different approach for comparing the brains of autism and control subjects where each voxel in the contrasting groups can be compared, voxel-by-voxel determining the concentration of pixels within each voxel that are either WM, gray matter (GM) or cerebrospinal fluid (CSF). Since the SPM methods used for VBM analyses require brains to be normalized, this procedure automatically corrects for head size differences (Buckner et al., 2004; Sanfilipo, Benedict, Zivadinov, & Bakshi, 2004), but such smoothing methods may also eliminate or obscure effects observed by standard ROI volumetry techniques. So, the two methods should be viewed as complementary of each other.

As will be seen, traditional volumetry in this study demonstrated increased WM volume in autism subjects regardless of whether macrocephalic subjects were included or excluded in the analyses and the WM VBM analyses provide an image analysis tool to examine whether regional or widespread differences in WM pixel concentration distinguished the autism group from controls. To that end, we first applied traditional ROI volumetry, including whole brain WM volume followed by SPM methods to conduct WM VBM comparisons between autism and control subjects. Lastly, the relationships between whole brain WM and GM volumetric measures and IQ were assessed for controls and subjects with autism.

METHODS

Subjects and Assessment

Ascertainment—As part of an ongoing investigation, autism and comparison subjects were actively recruited from community sources, including parent support groups, youth groups, and schools, and from clinic social skills groups, the details of which have been thoroughly discussed elsewhere in previous publications (Bigler et al., 2003), including the structured psychiatric assessment by board certified child psychiatrists. Autism subjects were group matched to controls, in terms of the following variables: OFC, performance intelligence quotient (PIQ), age, and height. A disproportionate number of individuals with autism are males (see Baron-Cohen, Knickmeyer, & Belmonte, 2005) and for this investigation to control for sex differences, only male subjects with autism and age-matched male controls were included. Demographic information is provided in Table 1.

Idiopathic autism sample—Autism was rigorously diagnosed. The subject's mother was interviewed using the Autism Diagnostic Interview–Revised (ADI–R), a semi-structured, investigator-based interview with good reliability and validity (Lord, Rutter, & LeCouteur, 1994). All autism subjects were also directly assessed using the Autism Diagnostic Observation Schedule–Generic (ADOS–G), a semi-structured play and interview session designed to elicit social, communication, and stereotyped repetitive behaviors characteristic of autism (Lord et al., 2000). All autistic subjects met ADI–R, ADOS–G, and DSM–IV–TR (American Psychiatric Association, 1994) criteria for autism. History, physical exam, Fragile–X gene testing, and karyotype, performed on all subjects, excluded medical causes of autism. Because psychiatric comorbidity occurs in the majority of children and adults whose primary diagnosis is autism (see Leyfer et al., 2006), existence of a comorbid psychiatric disorder was not an exclusion criteria for the autism group but sample size was insufficient to treat any of these variables as a separate condition or as a control measure. Autism was always the primary diagnosis with approximately half of the autism subjects having a co-morbid DSM–IV psychiatric diagnosis the most common being depression, followed by attention deficit/attention deficit hyperactivity disorder, obsessive-compulsive disorder, and anxiety disorder. Approximately 60% of the autism subjects were being treated with psychotropic medications with selective serotonin reuptake inhibitors being the most frequent, followed by stimulant medications, valproic acid, and neuroleptics.

Control sample—Control subjects were recruited mainly from community schools; none had major developmental, neurological, or severe psychiatric disorders based on history, IQ and language tests, physical examination, and structured psychiatric assessment. A separate reading disorder (RD) group was recruited as explained in Bigler et al. (2007) from the same community schools, where RD was the only identified problem and defined by a discrepancy between IQ and reading level. Control subjects were group matched for age and education irrespective of head size, but because of the need to have a subsample of subjects with benign macrocephaly within the control sample, control subjects with large OFC were selected by sampling students in a public school and selecting those with OFC = 97th percentile.

IQ—Verbal skills are often diminished in autism (Rapin, 1999). In addition, there can be wide splits between verbal and performance IQ (PIQ, Deutsch & Joseph, 2003) in autism, making Full Scale IQ (FSIQ) difficult to interpret. For these reasons, we defined level of intelligence on the basis of non-verbal abilities as measured by the PIQ on either the Wechsler Intelligence Scale for Children—III (WISC—III, Wechsler, 1991) or the Wechsler Adult Intelligence Scale—III (WAIS—III, Wechsler, 1997); all subjects had PIQs > 65. As we have explained elsewhere (see Bigler et al., 2007; Bigler et al., 2003) we included subjects with RD to ensure a full range of language ability within the control sample. RD was defined as reading level on a standardized measure to exceed 1.5 standard deviations below their FSIQ.

Head circumference—OFC and height were measured in all subjects using the standardized methods and reference data described by Farkas, Hreczko, and Katie (1994). Normocephaly was defined as an OFC > 3rd but < 97th percentile for age and sex. Macrocephaly was defined as OFC > 97th percentile for age and sex (Roche, Mukherjee, Guo, & Moore, 1987).

Handedness—Handedness was measured using the Edinburgh Handedness Inventory (Oldfield, 1971) where a score of 100 signifies complete right handedness and -100 indicates complete left handedness. There were no significant differences across groups in handedness.

Neuroimaging

Magnetic resonance (MR) images were acquired on a Philips 1.5 Tesla Scanner. Multiple protocols were run that were used for the clinical review and quantitative analyses of this investigation. However, only the 3D T₁ and T₂ weighted images were used for the quantitative analyses as reported in this study and previously detailed in Bigler et al. (2003). Axial 3D T₁ (TE = 4.47 msec, TR = 13 msec, Flip Angle = 20, Slice Thickness = 1.2 mm, FOV = 25.6 cm) and 3D T₂ FSE Coronal (TE = 114 msec, TR = 3500 msec, Slice Thickness = 1.5 mm, FOV = 25.6 cm) weighted images were used for quantitative image analysis. The images were co-registered to facilitate segmentation into WM, GM, and cerebral spinal fluid (CSF) space. In some cases, sedation was necessary and followed a strict clinical protocol approved by the institutional review board (IRB) by the University of Utah, and performed by an onsite faculty anesthesiologist. The procedure was clearly explained, as best possible, to the subject and parent or guardian. In several situations, rehearsal was used to “practice” lying in the scanner. In all cases, written, informed consent was obtained prior to any imaging. No complications or untoward effects were encountered.

Volumetric image analysis—Quantitative analyses followed well-established protocols as previously published (Bigler, Anderson, & Blatter, 2002; Bigler et al., 1997; Bigler et al., 2003). Briefly, the co-registered T₁ and T₂ weighted images were segmented into white, gray, and CSF pixels using the ANALYZE[®] multispectral tool (Robb, 1995). Total brain volume (TBV) was the combination of WM and gray matter (GM) summed. Total CSF was the sum of subarachnoid and ventricular CSF. By using the inner table of the skull as a landmark, total intracranial volume (TICV) was determined by the total sum of whole brain

parenchyma and CSF. Temporal lobe structures were identified according to the methods outlined by Bigler et al. (2002; 2003) and for this investigation focused on the total amygdala and hippocampal volumes. Volumetric measures of the thalamus, globus pallidus + putamen (lentiform nucleus), caudate, brain stem, and cerebellum were based on ROIs manually identified and followed previously published methods (Fearing et al., 2008; Spanos et al., 2007; Wilde et al., 2007). Total GM was also computed as previously described (Bigler et al., 2002).

VBM analyses—All analyses were based on the T₁ weighted anatomical scan. The methods outlined by Good et al. (2001) and Ashburner and Friston (2000) were used to optimize the VBM protocol. This method involves an extraction and normalization process of pixels that represent brain parenchyma where the native MRI data are stereotactically normalized and segmented into GM, WM, and CSF compartments. Each normalized, segmented and modulated image was finally smoothed with a 12 mm full-width at half-maximum isotropic Gaussian kernel. Because of the numerous comparisons made, only findings that reached a significance of greater than 0.001 were reported and incorporated in to a “glass” 3D depiction where density findings were different. Regions of significant density difference were localized in Talairach space by x, y, and z coordinates based on the peak difference.

Statistical analysis—In general, the same statistical analyses reported by Herbert et al. (2003a) were followed, using a general linear model (GLM) approach for correlated data, controlling for age and TBV where appropriate. ROIs included the following: TBV, total WM volume, total GM volume, and volumes of the cerebellum, globus pallidus-putamen complex (lenticular nucleus), brainstem, caudate, hippocampus-amygdala, and cerebral cortex. The percent of difference between autism and controls on these ROI morphometric measurements was then undertaken, identical to that reported by Herbert et al. (2003a). A maximum likelihood factor analysis was performed. Lastly, WM and GM correlations with IQ measures were compared between control and autism subjects.

RESULTS

Demographic Comparisons

Table 1 outlines the basic comparisons on demographic, psychometric, and head/brain size variables for the different groups examined. Head circumference, height, TBV, and TICV did not differ significantly between the combined autism (normocephalic and macrocephalic subjects) and the combined controls (normocephalic, macrocephalic, and RD subjects). Tables 2 and 3 and Figure 1 present the quantitative neuroimaging findings for the specific brain measures compared to all autism subjects versus all controls. As shown in Tables 2 and 3 an omnibus GLM approached significance for unadjusted and adjusted volumes but univariate analyses for WM and GM were both significant with a significant increase in WM volume and a corresponding decrease in GM volume noted in the autism group. These findings were confirmed when a MANOVA was run with just WM and GM adjusted for age in both the unadjusted and adjusted volume comparisons. Interestingly, a modest effect size was noted with reduced lenticular (caudate + putamen) volume noted in the autism group,

although the mean difference did not reach statistical significance, even when a separate MANOVA was run in either the adjusted or unadjusted conditions.

Autism and Control Comparisons With/Without and With Proportionally OFC-Defined Macrocephalic Subjects Included

As indicated in the introduction, macrocephaly rates are increased in autism. The design of the experiment and the results described earlier are conservative, because macrocephaly was oversampled in the control group and also by having overall head circumference and TICV group matched so that there were no significant differences between the autism and control groups due to these factors. To test sensitivity of our findings with respect to our oversampling, a variety of comparisons were performed, including an autism versus control comparison where *all* macrocephalic subjects were removed. WM volume continued to be significantly larger in the autism subjects. We also ran a comparison of autism subjects where macrocephaly rate in autism was held at approximately 20%, compared to a 3% rate in the controls. In all of these comparisons, WM volume remained significantly larger in the autism group.

Factor Analysis

Factor analysis findings are summarized in Table 4 and Figure 1. Several models were assessed when comparing all subjects irrespective of head size, a two-factor model was observed to be the best fit where WM volume congregated with several other ROI measures, with the second factor being hippocampal-amygdala volume. This model changed when the rate of macrocephaly was adjusted to reflect 20% within the autism subjects compared to 3% in the controls, where WM alone became a separate factor that accounted for approximately 15% of the variance in a two-factor solution, with the other factors grouped as cerebellum, thalamus, GM, brainstem, hippocampus-amygdala, and caudate.

VBM Findings

Given the aforementioned factor analytic findings and increased overall WM volume in autism, WM VBM comparisons were undertaken to determine if regional differences in the distribution of WM pixel density could be identified. Comparing all control subjects to all autism subjects, including both control and autism subjects with macrocephaly, revealed only a few scattered regions of differences as shown in Figure 2. Interestingly, the region of greatest WM concentration difference was within a small region of the right temporal stem as shown in Figure 2, where as a group the autism subjects had lower WM concentration.

IQ and Brain Morphometry Relationships

WM volume differentially correlated with IQ in the autism and controls groups as shown in Table 5. WM volume did not significantly correlate with IQ in controls, but did with PIQ in subjects with autism. GM volume was significantly related to verbal IQ (VIQ) and PIQ in the typically developing controls.

DISCUSSION

While our methods for volumetric assessment were different than Herbert et al. (2003a, see also companion paper Herbert et al., 2003b)—we involved subjects who were older and examined whole brain WM volume—their main finding of greater WM volume in subjects with autism was replicated, even after adjusting for TBV and rate of macrocephaly in the controls and autism subjects. In fact, Figure 1 of the current study is quite similar to the Herbert et al. (2003a) Figure 2. The current replication is particularly important because it examined subjects with a larger age range and the control group included subjects with benign macrocephaly and RD, ensuring heterogeneity in the control sample that matched the autism group. We also explored whether controlling for different prevalence rates of macrocephaly made a difference, but in each analysis the autism subjects had larger WM volume. Since, as a group, the autism and control subjects did not significantly differ in head circumference, TBV, or TICV, the WM volume increase appeared to be specific to the autism group and not a reflection of greater presence of macrocephaly with the autism subjects. Previous studies that have reported larger brain volume in autism have not had OFC defined benign macrocephaly subjects in the control sample and some are not as closely matched with regards to IQ and other demographic variables. Given that the volumetry aspect of this study confirms Herbert et al.'s (2003a) findings of increased WM volume, the current findings add to the literature that increased WM volume is associated with autism.

Herbert et al. (2003a) also applied a factor analysis to their volumetry findings, with a three-factor solution most explanatory of their findings and WM volume alone representing one of the factors. In the current study, when factor analysis was applied, only the two-factor solution was significant. As already mentioned we did not measure all of the regions that Herbert et al. (2003a) did or in the same manner, so it is not surprising that we could not replicate the same factor analysis solution. Interestingly, when we modeled the expected natural prevalence rate of macrocephaly with a 20% rate in the autism group and 3% in the control, a two-factor solution remained but WM volume did represent a single factor explaining approximately 15% of the variance, which was the same value obtained by Herbert et al. (2003a). In the overall factor analysis, hippocampal-amygdala volume constituted a separate factor, and this was also an observation made by Herbert et al. (2003a), although a cerebral cortex volume loading also congregated with hippocampal-amygdala volume in the Herbert et al. (2003a) study.

Limbic abnormalities in autism have long been suspected and therefore it is not surprising that differences in hippocampal and amygdala volumes were noted in this and other studies (see Loveland, Bachevalier, Pearson, & Lane, 2008). Thalamic and basal ganglia volumes also were prominent in the factor analysis findings and several studies have implicated thalamic differences in autism (Hardan et al., 2006; Hardan et al., 2008; Takarae, Minshew, Luna, & Sweeney, 2007), as well as basal ganglia structures (Haznedar et al., 2006; Hollander et al., 2005; Langen, Durston, Staal, Palmen, & van Engeland, 2007; Sears et al., 1999; Singh & Rivas, 2004; Williams, Waiter, Perra, Perrett, & Whiten, 2005). The current volumetry findings suggest that in addition to WM enlargement, differences in basal ganglia structures and the thalamus may be distinguishing features between those with autism and

controls. This has been interpreted by others as disruption of circuitry between subcortical and cortical structures involved in social and other cognitive functions that may distinguish autism (Belmonte et al., 2004; Hardan et al., 2008; Williams & Minshew, 2007).

Before discussing the VBM findings, it is important to highlight the limitations of the VBM method in image analysis and its differences from ROI volumetry (Baron et al., 2001). Since the brains are segmented and normalized, the findings do not represent true volumes but rather a voxel-by-voxel comparison of pixel concentration or density of GM, WM, or CSF within a specified voxel. In other words, VBM has been considered a method of “indirect volumetry” (Brenneis et al., 2005, p. 531), where standard volumetry findings may not mirror VBM findings because of the differences between the two brain image analysis techniques, especially after normalization (see also Testa et al., 2004; Yoshikawa et al., 2006). The advantage of VBM methods is that they permit simultaneous whole brain analyses without limits of pre-defined ROIs and operator-related error in image analysis. Significant VBM findings most distinctly occur when marked differences between the target and reference group are evident such as in aging or injury (Ashburner & Friston, 2000, 2001; Good et al., 2001).

The VBM alpha level in this study was set at 0.001 for all analyses and therefore the findings reported in this study are conservative. With the controls and autism groups so carefully matched and balanced, the current VBM analyses yielded few differences between groups. Thus, while the volumetry shows larger WM volume in this sample of individuals with autism, the VBM studies did not reveal any large regions of difference in WM density, implicating that the increased volume of WM in this autism sample was non-localized and dispersed nonspecifically. However, a particularly interesting observation was that in a small region of the right temporal stem that WM density was actually decreased in the autism group. Using diffusion tensor imaging (DTI) methods, we have previously shown differences in the temporal stem region in autism (see Lee et al., 2007).

Our autism research program is longitudinal, with the current findings based on the initial sampling of subjects at the beginning of the study using a 1.5 Tesla magnet and the Lee et al. (2007) investigation represents data acquired in follow-up with a 3.0 Tesla magnet. Many of the same subjects in the original cohort were re-scanned in the Lee et al. study, so there is some overlap between the two investigations and this may explain some of the temporal stem findings. Nonetheless, the temporal stem is a critical temporal lobe region of afferent-efferent projections with the rest of the brain, so this observation may be particularly relevant to disconnection theories of autism (see Courchesne & Pierce, 2005; Geschwind & Levitt, 2007).

The relationship between whole brain WM and GM volumes and IQ resulted in some distinct differences between the autism and controls groups. Overall GM volume significantly correlated with both VIQ and PIQ in the control sample but only WM volume and only with PIQ was significant in the autism subjects. In typically developing individuals, brain volume correlations with IQ are thought to reflect a relationship between brain growth and cognitive development (see Bigler, 1995). There are now a number of studies showing this relationship, especially between regional GM volumes and normal

intellectual development (Haier et al., 2004; Narr et al., 2007; Toga & Thompson, 2005). The observation that autism and control groups had different patterns of IQ–brain volume relationships suggests different functional organizations between WM and GM and cognitive ability between the two groups. A better understanding of why these differences in size–function relationships occur in autism will undoubtedly prove to be essential in understanding the pathobiology of autism and the clinical significance of increased WM volume in autism as it pertains to differences in cognitive function. For example, is the functional significance of increased WM volume in autism related to aberrant connectivity and redundancy within WM pathways and overall WM integrity in autism (see Casanova, 2007; Hughes, 2007; Minshew & Williams, 2007; Pardo & Eberhart, 2007; Rapin & Tuchman, 2008)?

There are several limitations of the current study, probably most importantly, we only examined what would be considered “high functioning” subjects with autism. High functioning autism (HFA) is only representative of part of the spectrum of the disorder, and findings within HFA subjects may not generalize to all of autism. With a much larger sample size, the full spectrum of potential differences between head and brain size and ROI differences that may distinguish autism subjects from controls could be examined. Also, other neuroimaging methods, such as DTI, magnetic resonance spectroscopy, and functional neuroimaging may provide greater specificity about regional brain integrity and differences that may characterize autism better than the methods of the current study. Lastly, as measures of cognitive functioning, only IQ was examined in this study whereas a broader spectrum of cognitive functions may yield further insights into structure–function relationships in the autism brain.

In conclusion, autism was associated with greater WM volume, regardless of whether the autism subjects had OFC-defined macrocephaly or not, or the natural prevalence rate for macrocephaly was controlled. VBM analyses demonstrated that this increased WM volume was generally evenly distributed throughout the brain. These findings add to the literature on probable aberrant WM structural and functional findings in autism (see Baron-Cohen & Belmonte, 2005; Nayate, Bradshaw, & Rinehart, 2005).

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FIGURE 1.

Bar graph depicting region of interest (ROI) volumes of all subjects with autism compared to all controls regardless of head size. Percentages were calculated identically to that reported by Herbert et al. (2003) as follows: $(\text{mean autistic volume})/(\text{mean control volume}) \times 100$. Values >100 indicate the region is larger in the autism group; values <100 represent larger volumes in the control group. Adjusted and unadjusted volume comparisons are denoted according to the legend inset. This figure should be compared to Figure 2 of Herbert et al. (2003a, p. 1186).

FIGURE 2.

Voxel based morphology (VBM) findings depict few differences in white matter (WM) pixel concentration as shown in the “glass” brain model, where age and IQ were control variables. The arrow points to the region of greatest difference, which was in the right temporal stem as shown in the coronal image in the lower right, which actually showed less WM pixel concentration in the autism subjects. It should be noted that as a result of technical issues and image registration and analysis using the VBM method, two autism subjects, both normocephalic and four control subjects (3 normocephalic, 1 reading disorder [RD]).

TABLE 1

Demographics of Subjects: Means and Standard Deviations (*SD*)

	N	Age (Yrs)	Head Circum (Ins)	zHC	Height Ins	FSIQ	PIQ	VIQ	VIQ-PIQ	TBV cm ³	TICV cm ³
Autism											
Normocephalic	29	15.21 (6.73)	55.62 (2.51)	0.44 (0.97)	154.83 (21.56)	96.07 (20.85)	97.59 (18.87)	94.93 (24.47)	-2.66 (21.79)	1349.66 (106.72)	1470.79 (107.32)
Macrocephalic	13	12.69 (4.25)	58.63 (2.07)	2.93 (0.92)	158.31 (21.89)	109.69 (26.36)	109.15 (17.57)	108.62 (32.98)	-0.54 (21.27)	1520.00 (128.89)	1634.62 (146.13)
Combined	42	14.43 (6.13)	56.55 (2.75)	1.21 (1.50)	155.90 (21.46)	100.29 (23.25)	101.17 (19.05)	99.17 (27.72)	-2.00 (21.40)	1402.38 (137.81)	1521.50 (141.39)
Control											
Normocephalic	45	13.67 (5.85)	55.01 (2.21)	0.11 (1.07)	156.62 (20.53)	102.60 (17.27)	102.47 (15.21)	102.40 (18.73)	-0.07 (13.41)	1326.47 (117.76)	1432.36 (113.37)
Macrocephalic	12	12.75 (3.33)	56.94 (3.20)	1.99 (2.18)	159.67 (17.69)	116.75 (13.97)	113.33 (12.30)	117.25 (14.01)	3.92 (8.59)	1472.50 (177.96)	1608.58 (195.47)
Combined	59 [†]	13.42 (5.35)	55.46 (2.52)	0.52 (1.55)	157.47 (19.79)	105.47 (17.27)	104.76 (15.20)	105.34 (18.45)	0.58 (12.72)	1367.69 (142.21)	1480.59 (150.27)
Reading impaired	24	14.21 (6.21)	54.56 (2.26)	-0.05 (1.30)	153.33 (17.18)	103.38 (17.48)	105.38 (15.74)	101.21 (18.66)	-4.17 (13.90)	1329.38 (100.14)	1442.54 (106.81)
* <i>p</i> -value		0.383	0.032	0.031	0.810	0.201	0.295	0.182	0.451	0.193	0.112

Yrs = years; Head Circum (Ins) = Head Circumference in Inches; FSIQ = full scale intelligence quotient; PIQ = performance IQ; VIQ = verbal IQ; TBV = total brain volume; cm³ = cubic centimeters; TICV = total intracranial volume.

* 2 Sample *t*-Test comparing Combined Autism versus Combined Control Groups.

[†]Two Typically Developing patients unclassified as to whether macrocephalic or normocephalic.

TABLE 2

Descriptive Statistics for Unadjusted Volumes[†]

Brain Region	Autistic Group		Control Group		Between Group Comparison	
	Mean Brain Volume (cm ³)	SD	Mean Brain Volume (cm ³)	SD	ES	p value [*]
Total brain volume (WM + GM)	1402.38	137.81	1364.29	144.59	0.27	0.119
Thalamus	15.66	1.33	15.26	1.27	0.31	0.126
White Matter (WM)	566.12	94.53	493.57	122.79	0.65	0.002
Cerebellum	150.37	15.55	147.98	22.33	0.12	0.533
Globus Pallidus-Putamen	2.85	0.24	2.90	0.33	-0.17	0.508
Brainstem	24.34	3.01	24.33	3.36	0.00	0.946
Caudate	8.89	1.02	9.00	1.29	-0.10	0.659
Grey Matter (GM)	836.21	117.92	871.21	105.20	-0.32	0.211
Hippocampus-Amygdala	12.98	1.09	13.12	1.58	-0.10	0.617

SD = standard deviation; ES = (autistic mean – control mean)/pooled standard deviation.

^{*} p values refer to univariate general linear model (GLM) test of total brain and regional volume differences, adjusting for age.[†] Overall F-test of group differences was obtained using multivariate general linear model (GLM) for correlated data, controlling for age [$F(9,73) = 1.7600, p = 0.0909$]MANOVA group differences in GM and WM, adjusted for age, [$F(2,94) = 5.4207, p = 0.0059$].MANOVA group differences *excluding* GM and WM adjusted for age, [$F(7,75) = 0.8324, p = 0.5646$].

TABLE 3

Descriptive Statistics for Adjusted Volumes[‡]

Brain Region	Autistic Group		Control Group		Between Group Comparison	
	Mean Brain Volume (cm ³)	SD	Mean Brain Volume (cm ³)	SD	ES	p value*
Thalamus	1.12	0.09	1.12	0.10	-0.02	0.855
White Matter (WM)	40.38	5.93	36.07	6.92	0.66	0.003
Cerebellum	10.73	0.87	10.80	1.42	-0.05	0.804
Globus Pallidus-Putamen	0.20	0.02	0.21	0.02	-0.35	0.105
Brainstem	1.74	0.19	1.78	0.20	-0.20	0.141
Caudate	0.64	0.07	0.65	0.07	-0.27	0.157
Grey Matter (GM)	59.62	5.92	63.93	6.90	-0.66	0.002
Hippocampus-Amygdala	0.93	0.09	0.96	0.10	-0.31	0.107

SD = standard deviation; ES = (autistic mean – control mean)/pooled standard deviation.

* *p* values refer to univariate general linear model (GLM) test of total brain and regional volume differences, adjusting for age.[‡]Overall *F*-test of group differences was obtained using multivariate general linear model (GLM) for correlated data, controlling for age [$F(8,74) = 1.8957, p = 0.0733$].MANOVA group differences in GM and WM, adjusted for age, [$F(2,93) = 6.0297, p = 0.0035$].MANOVA group differences excluding GM and WM, adjusted for age, [$F(6,76) = 0.7127, p = 0.6404$].

TABLE 4

Factor Analysis Matrix

Brain Region	Factor	
	1	2
Gray Matter (GM)	0.920	
White Matter (WM)	0.836	
Brainstem	0.641	
Cerebellum	0.604	
Caudate	0.590	
Thalamus	0.525	
Hippocampus–Amygdala		0.535
Percent of Variance	30.30	22.60

Loadings of brain regions on each of three factors and percentage of total variance accounted for by each factor. Absolute loadings < 0.5 are omitted.

TABLE 5
White and Gray Matter Volumes Differentially Correlated With IQ in Autism vs. Controls Subjects

	N	VIQ		PIQ	
		WM	GM	WM	GM
Autism	42	.20	.05	.35**	.25
Controls	59	.17	.33**	.03	.34**

VIQ = verbal intelligence quotients; PIQ = performance intelligence quotient; N = number of subjects; WM = white matter; GM = gray matter.
**
p = 0.02.