J Autism Dev Disord (2012) 42:419–427
DOI 10.1007/s10803-011-1261-6

ORIGINAL PAPER

Measures of Cortical Grey Matter Structure and Development in Children with Autism Spectrum Disorder

Kathleen M. Mak-Fan · Margot J. Taylor · Wendy Roberts · Jason P. Lerch

Published online: 10 May 2011

Abstract The current study examined group differences in cortical volume, surface area, and thickness with age, in a group of typically developing children and a group of children with ASD aged 6–15 years. Results showed evidence of age by group interactions, suggesting atypicalities in the relation between these measures and age in the ASD group. Additional vertex-based analyses of cortical thickness revealed that specific regions in the left inferior frontal gyrus (BA 44) and left precuneus showed thicker cortex for the ASD group at younger ages only. These data support the hypothesis of an abnormal developmental trajectory of the cortex in ASD, which could have profound effects on other aspects of neural development in children with ASD.

Keywords Autism spectrum disorder · Brain structure · Volume · Surface area · Cortical thickness · Development

K. M. Mak-Fan · M. J. Taylor
Department of Psychology, University of Toronto, Toronto, ON, Canada

K. M. Mak-Fan (✉) · M. J. Taylor
Diagnostic Imaging, Hospital for Sick Children, 555 University Avenue, Toronto, ON M5G 1X8, Canada
e-mail: katie@psych.utoronto.ca

W. Roberts
Autism Research Unit, Toronto, ON, Canada

M. J. Taylor · J. P. Lerch
NMH Research Institute, Hospital for Sick Children, Toronto, ON, Canada

J. P. Lerch
Department of Medical Biophysics, University of Toronto, Toronto, ON, Canada

W. Roberts
Bloorview Kids Rehab, Toronto, ON, Canada

Introduction

Autism is a neurodevelopmental disorder characterized by communication impairments, social deficits and rigid, repetitive behaviour (DSM-IV; American Psychiatric Association (1994). Recent research suggests that cortical development and organization follows an abnormal trajectory in children with autism spectrum disorder (ASD). One of the most consistent pieces of supporting evidence has been the repeated finding of abnormalities in brain volume, both white and grey matter, which appear to be more pronounced in younger children and to decrease with age (Courchesne 2002; Hardan et al. 2001; Carper et al. 2002; Aylward et al. 2002; Sparks et al. 2002; Carper and Courchesne 2005; and see Redcay and Courchesne 2005 and Amaral et al. 2008 for reviews), most noticeably in the frontal lobes (e.g., Carper et al. 2002; Carper and Courchesne 2005). These findings are further supported by abnormalities in rates of developmental change in head circumference and brain volume for children with ASD (e.g., Courchesne et al. 2003; Carper et al. 2002; Carper and Courchesne 2005). Overall, a "growth dysregulation hypothesis" of neuropathology of ASD has emerged, characterized by brain overgrowth early in life, followed by abnormally slowed or even arrested growth in some regions (Akshoomoff et al. 2002).

Cortical grey matter volume is a product of the surface area and thickness of the cortex, which are thought to reflect different maturational processes. It has been hypothesized that cortical thickness reflects dendritic arborisation and pruning within grey matter or changes in myelination at the interface of grey and white matter (Sowell et al. 2004), whereas surface area is dependent on division of progenitor cells in the periventricular area during embryogenesis (Chenn and Walsh 2002) and varies

with degree of cortical folding/gyrification. Although there have been a number of studies investigating regional differences in brain volume in children with ASD, studies examining surface area and cortical thickness are lacking.

Surface area is determined by cortical folding, and there is some evidence that this may be altered in ASD. In a preliminary study including children and adults with ASD, Hardan et al. (2004) showed a greater gyrification index in the left frontal lobe for children and adolescents with ASD, but not in adults, as well as decreased cortical folding with age for the ASD participants relative to control participants. Sulcal location (Levitt et al. 2003) and sulcal depth (Nordahl et al. 2007) may also be atypical in children with ASD.

Most reports of cortical thickness have shown that cortical thickness is increased in ASD relative to controls in adult samples (e.g., Bailey et al. 1998; Hutsler et al. 2007, but see Hadjikhani et al. 2006, for an exception). In the study by Hutsler et al. (2007), the difference in cortical thickness between matched pairs tended to decrease with age, suggesting that cortical thickness differences were more pronounced at younger ages, although this relation failed to reach significance. A study of adolescents by Chung et al. (2005), using a vertex-by-vertex analysis allowing for regional specificity of cortical thickness differences also showed evidence of areas of thicker cortex in the ASD group, in right inferior orbitofrontal cortex, left superior temporal sulcus, and left occipitotemporal gyrus. Hyde et al. (2009), also using a vertex-based approach, found further evidence of increased cortical thickness in an adult ASD group relative to a matched control group in regions from all four lobes. A small number of regions had thinner cortex in the autism group (the pre- and post-central gyri, and the paracentral gyrus); however, the majority of findings were in the direction of increased cortical thickness (Hyde et al. 2009).

Studies of cortical thickness in children with ASD, although only two have been reported, have also tended to show evidence of increased cortical thickness. Using measures of average cortical thickness across hemispheres and lobes, Hardan et al. (2006) found no differences in overall brain volume between the two groups, but significantly thicker cortex in the whole brain overall for the boys with autism, with similar findings in the temporal and parietal lobes. In a follow up report, Hardan et al. (2009) showed evidence of decreases in total grey matter and cortical thickness with time for the ASD group relative to the control group. In contrast to the Hardan (2009) study, in a sample spanning 10–45 years of age, Raznahan et al. (2010) found that in regions showing an age by group interaction, there was no relation between age and changes in volume or cortical thickness in the ASD group, compared to significant decreases in cortical thickness and volume with age in the control group. Raznahan et al. (2010) also found that at younger ages, cortical thickness in typically developing children was decreased relative to children with ASD, but increased relative to the ASD group at later ages. In addition, cortical surface area showed minimal changes with age and this pattern did not differ between the ASD and typically developing control group (Raznahan et al. 2010).

Overall, there are relatively few investigations on detailed measures of grey matter comparing children with and without ASD, despite the consistent findings of structural brain differences in ASD; further investigations of these measures across age are needed. Given that ASD is a developmental disorder and there is now a body of work documenting significant changes in grey matter indices over childhood (Shaw et al. 2008; Lenroot et al. 2009), it is important to have a greater understanding of the age-related changes in these brain measures in ASD and the impact that they may have on behaviour.

In the present study of children from 6 to 15 years of age, we investigated the relation between age and structural measures of volume, surface area and cortical thickness in ASD relative to a typically developing control group. To our knowledge, this is the first report to examine cortical thickness in a larger group of only school-aged children with ASD using a vertex-by-vertex whole-brain approach. We hypothesized that children with ASD would show abnormalities in the typical maturation of cortex, evident in age by group interactions in measures of volume, surface area and cortical thickness, particularly in the frontal lobes, and that these abnormalities would be more pronounced at earlier ages.

Materials and Methods

Participants

Participants were 25 children, all male, diagnosed with an autism spectrum disorder (ASD) (mean age = 10.9 years, range 6.8–15.4) and 63 male, typically developing (TD) control children (mean age = 11.3 years, range 6.5–15.8). Of the 25 ASD participants, 24 were recruited through the Autism Research Unit at the Hospital for Sick Children (Toronto, Canada), and were diagnosed by clinician experts supported by a research reliable Autism Diagnostic Observation Schedule (ADOS-G) (Lord et al. 2000) and Autism Diagnostic Interview-Revised (ADI-R) (Lord et al. 1994). One ASD participant was recruited by parent interest in the study, and was not available for ADI/ADOS assessment, but had been given a diagnosis by a community clinician.

One of the ASD participants had a previous diagnosis of Generalized Anxiety Disorder, and two had a previous diagnosis of Attention Deficit Hyperactivity Disorder. Two ASD participants had an early childhood history of seizures, but had been deemed seizure free. One ASD participant was on medication (selective serotonin reuptake inhibitor, risperidol and methylphenidate). TD participants were screened and had no known history of psychiatric or neurological disorders.

Full scale IQ was measured using the 4-subtest Wechsler Abbreviated Scale of Intelligence (WASI, Wechsler 2002) for 23 of the participants with ASD, and the majority ($n = 39$) of the typically developing controls. One ASD participant was previously assessed with the Wechsler Intelligence Scales for Children (WISC-IV, Wechsler 2003), and one with the Leiter International Performance Scale Revised (Leiter-R, Roid and Miller 1997). All ASD participants had IQ > 70.

Imaging Parameters

High-resolution axial T1-weighted images were obtained for all of the children on a 1.5 Tesla GE scanner (FSPGR sequence, 116 slices; TR = 9 ms, TE = 4.2 ms, flip angle = 15). Voxel size was 0.9375 × 0.9375 × 1.5 mm at 2 NEX.

Image Processing

T1 images were registered to the symmetric ICBM 152 template with a 12-parameter linear transformation (Collins et al. 1994), RF inhomogeneity corrected (Sled et al. 1998), skull stripped (Smith 2002) and tissue classified (Zijdenbos et al. 2002; Tohka et al. 2004). Deformable models were then used to first fit the white matter surface for each hemisphere separately, followed by an expansion outward to find the grey matter/CSF intersection (MacDonald et al. 2000; Kim et al. 2005), resulting in 4 surfaces of 40,962 vertices each. From these surfaces the distance between the white and grey surfaces was used to measure cortical thickness (Lerch and Evans 2005). The thickness data were blurred using a 20 mm surface-based diffusion blurring kernel (Chung et al. 2005) and non-linearly aligned using surface based registration (Robbins et al. 2004; Lyttelton et al. 2007) prior to statistical analyses. Un-normalized, native-space thickness values were used in all analyses owing to the poor correlation between cortical thickness and brain volume (Ad-Dab'bagh et al. 2005; Sowell et al. 2007). Along with measures of cortical thickness at each of 81,924 vertices across the cortex, total volumes and surface area were estimated for the whole brain and each cortical lobe. This was accomplished by non-linearly warping each T1 image towards a segmented atlas (Collins et al. 1995; Chakravarty et al. 2008).

Statistical Analyses

Statistical analyses were performed on the brain volume, surface area and cortical thickness data. Effects of age and group alone were examined using analysis of variance, and differences in these effects were examined using an analysis of covariance linear model. Here we allowed for separate age by imaging metric (thickness, surface area, etc.) slopes for the two groups (TD and ASD), and computed the marginal significance of the difference in intercepts and difference in slopes between the groups. In order for the intercept to be interpretable, we centred it at three different ages within the range of available data; at the younger end of the age range (7.5 years), in the middle (11 years) and at the older end of the age range (14.5 years). Results of vertex-based cortical thickness analyses were thresholded for statistical significance using the False Discovery Rate (FDR) correction at $q < 0.05$, and at $q < 0.10$ to indicate trends (Genovese et al. 2002).

Behavioural Results

There was no significant difference in age between the two groups ($t(86) = -0.68$, $p = 0.50$, n.s.). ASD participants had significantly lower full-scale IQ than the subset of typically developing children with IQ measures (ASD = 104.52 vs. TD = 114.95, $t(32.3) = -2.49$, $p = 0.02$).

Imaging Results

Brain Volume

Differences between the ASD and TD groups in the relation between age and overall brain volume were evident in an age by group interaction in total brain volume (Fig. 1) ($t(84) = -2.13$, $p = 0.036$). Inspection of this interaction revealed that brain volume was increased for the ASD group relative to the TD group at younger ages, but was significantly decreased relative to the TD group at older ages ($t(84) = -2.16$, $p = 0.033$).

For grey matter volume alone, the results were similar, with a trend toward an age by group interaction ($t(84) = -1.79$, $p = 0.076$), and a pattern of increased grey matter volume in ASD relative to the TD group at younger ages, and decreased grey matter at older ages (Fig. 2). At the lobar level, the age by group interaction was also significant in occipital grey matter volume ($t(84) = -2.24$, $p = 0.03$) and approached significance in frontal grey matter volume ($t(84) = -1.85$, $p = 0.07$). Significant decreases with age were seen in the ASD group only in overall grey matter volume ($t(23) = -2.27$, $p = 0.025$), as well as frontal ($t(23) = -2.31$, $p = 0.023$), parietal

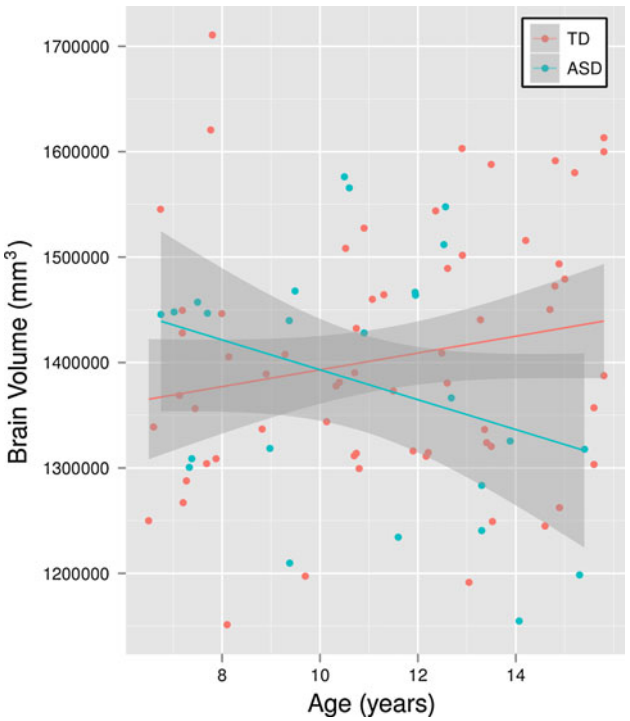

Fig. 1 Brain volume by age for the ASD and TD children. Shading represents the 95% confidence interval around the linear fits for each group. Pattern shows increased brain volume at younger ages for the ASD children compared to the TD children, and the opposite, decreased volume, at older ages

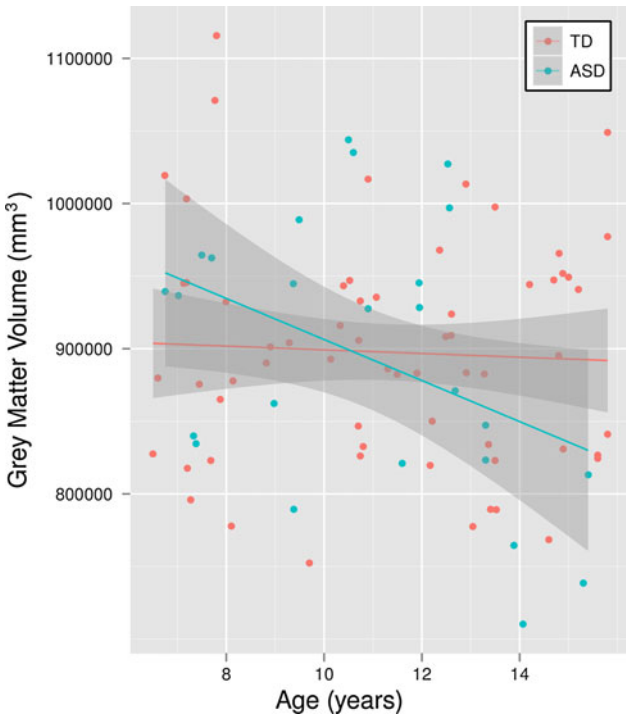

Fig. 2 Grey matter volume by age for ASD and TD groups, showing the same pattern of increased volume at younger ages for ASD children and decreased volume at older ages as seen in overall brain volume

($t(23) = -2.061$, $p = 0.042$), and occipital lobe grey matter ($t(23) = -2.41$, $p = 0.018$).

Surface Area

Results of the age by group ANCOVA for surface area (Fig. 3) showed the same pattern of results as in volume, with increased surface area at younger ages and decreased surface area at older ages. Although the age by group interaction did not reach statistical significance, there was a trend for overall surface area to decrease with age for the ASD group only ($t(23) = -1.95$, $p = 0.054$). In addition, at the lobar level an age by group interaction was seen in occipital lobe surface area ($t(84) = -2.30$, $p = 0.023$), and approached significance in frontal surface area ($t(84) = -1.78$, $p = 0.078$). Surface area was significantly increased in the ASD group relative to the TD group at the older end of the age range (centered at 14.5 years) in occipital lobes ($t(84) = -2.31$, $p = 0.023$).

Cortical Thickness

A similar pattern of results was seen in mean cortical thickness, with increased thickness at younger ages and decreased thickness at older ages in the ASD group

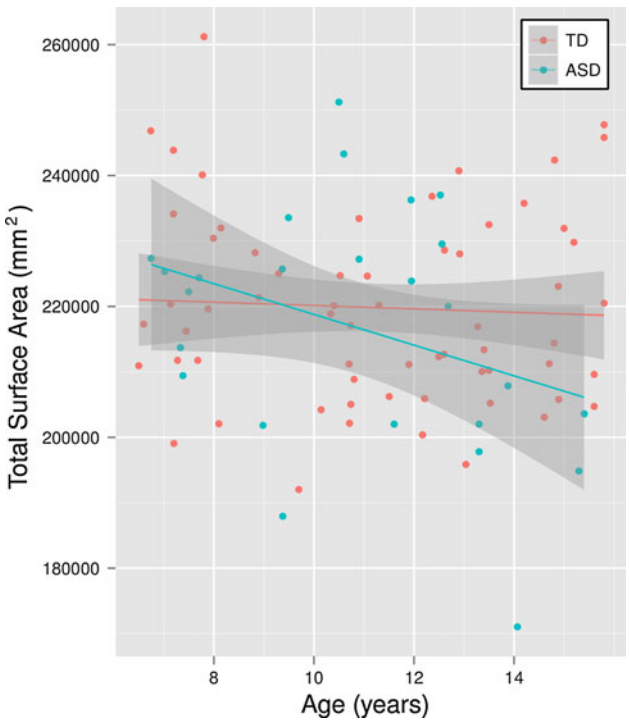

Fig. 3 Surface area by age for both ASD and TD groups, showing pattern of increased SA at younger ages in ASD, and decreased SA at older ages, similar to overall and grey matter volume

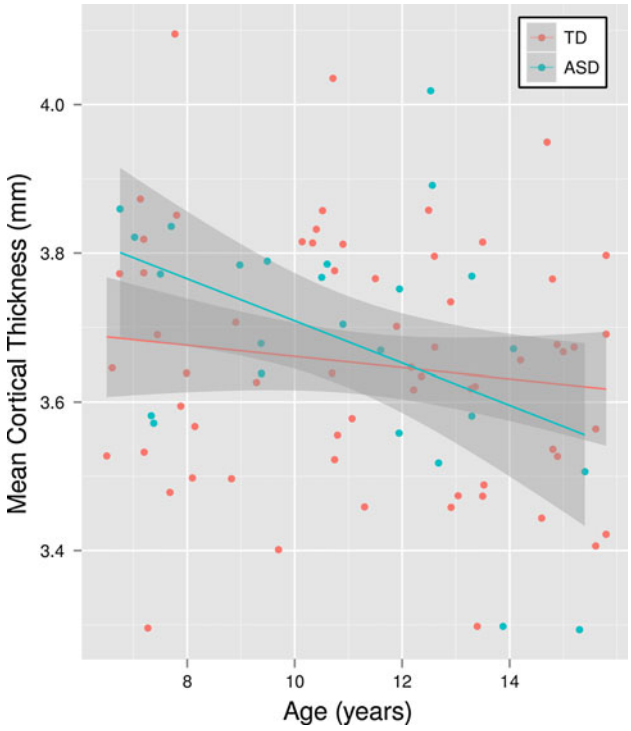

Fig. 4 Mean cortical thickness with age in ASD and TD groups, showing pattern of increased CT at younger ages in the children with ASD and decreased CT at older ages, compared to TD children

(Fig. 4). Although the age by group interaction was not significant, mean cortical thickness decreased significantly with age in the ASD group only ($t(23) = -2.37$, $p = 0.027$). The same pattern was also significant in parietal lobes ($t(23) = -2.76$, $p = 0.011$) and approached significance in frontal lobes ($t(23) = -2.03$, $p = 0.054$).

The strongest effects seen in the regional analysis of cortical thickness were age effects, including thickening of the temporal pole, pre-central and superior temporal gyri and thinning of multiple other cortical areas in the TD group. In ASD children, similar results were seen. However, additional regions of decreased cortical thickness with age were also observed in the ASD group in bilateral medial parieto-occipital fissure/precuneus (LH: $t(23) = -4.75$, $p = 0.00009$, $q < 0.05$; RH: $t(23) = -4.06$, $p = 0.00049$, $q < 0.10$), medial cingulate/paracentral lobule (LH: $t(23) = -4.02$, $p = 0.0005$, $q < 0.05$; RH: $t(23) = -3.93$, $p = 0.0007$, $q < 0.10$) and left inferior frontal gyrus/BA 44 ($t(23) = -3.66$, $p = 0.001$, $q < 0.05$), that were not observed in the TD group. In two of these regions the cortex was significantly thicker for the ASD group relative to TD children at the younger end of the age range (centered at 7.5 years): the left medial parieto-occipital fissure/precuneus ($t(84) = 4.88$, $p = 0.000005$, $q < 0.05$) and left inferior frontal gyrus (BA44) ($t(84) = 4.25$, $p = 0.00005$, $q < 0.10$) (Fig. 5).

To address any issues in matching, the results detailed above were verified to hold in a smaller sample excluding the ASD participant without ADOS/ADI-R characterization and TD participants without measured IQ, and full-scale IQ was added as a covariate. Overall patterns remained the same, and most statistical results remained significant or were even improved. For example, the age by group interaction of grey matter went from a p-value of $t(84)$ $p = 0.076$ to $t(58)$ $p = 0.092$, whereas the local cortical thickness results in precuneus remained unchanged, from $t(84)$ $p = 0.00003$ to $t(58)$ $p = 0.000003$. The full sample employed in this study is thus very likely an accurate reflection of the smaller, better-characterized cohort of subjects, and differences in IQ between the groups do not appear to account for the results found in this study.

Discussion

Overall, we found atypicalities in the relation between age and structural measures of the cortex in ASD children. Evidence came from different relations between structural measures and age seen in brain volume, surface area and in cortical thickness for children with ASD compared to typically developing children. The results suggest a pattern of increased volume, surface area and cortical thickness at younger end of the age range of this sample (around 7.5 years), but decreased or similar volume, surface area and cortical thickness at the older end of this age range (around 14.5 years). The difference in developmental progression appeared most robust in overall brain volume (grey and white matter combined), where the age by group interaction was significant, and in occipital and frontal lobes for overall grey matter and surface area. Although the age by group interaction was not significant in mean cortical thickness, age effects were significant in the ASD group only, and at the lobar level appeared stronger in parietal and frontal lobes. When examined using a regionally specific approach, two regions showed thicker cortex for the ASD group relative to the TD group at the younger end of the age range. Lastly, overall group differences were not seen for children with ASD relative to typically developing controls in these structural measures when age was not considered in the model. These findings strongly indicate that development is an important factor to consider in analyses of neural correlates of ASD and that cortical abnormalities associated with ASD change with age. The age range of this sample does not include pre-school children, where differences in brain volume are most evident, suggesting that neuroanatomical effects persist past the pre-school period, at least until mid-childhood.

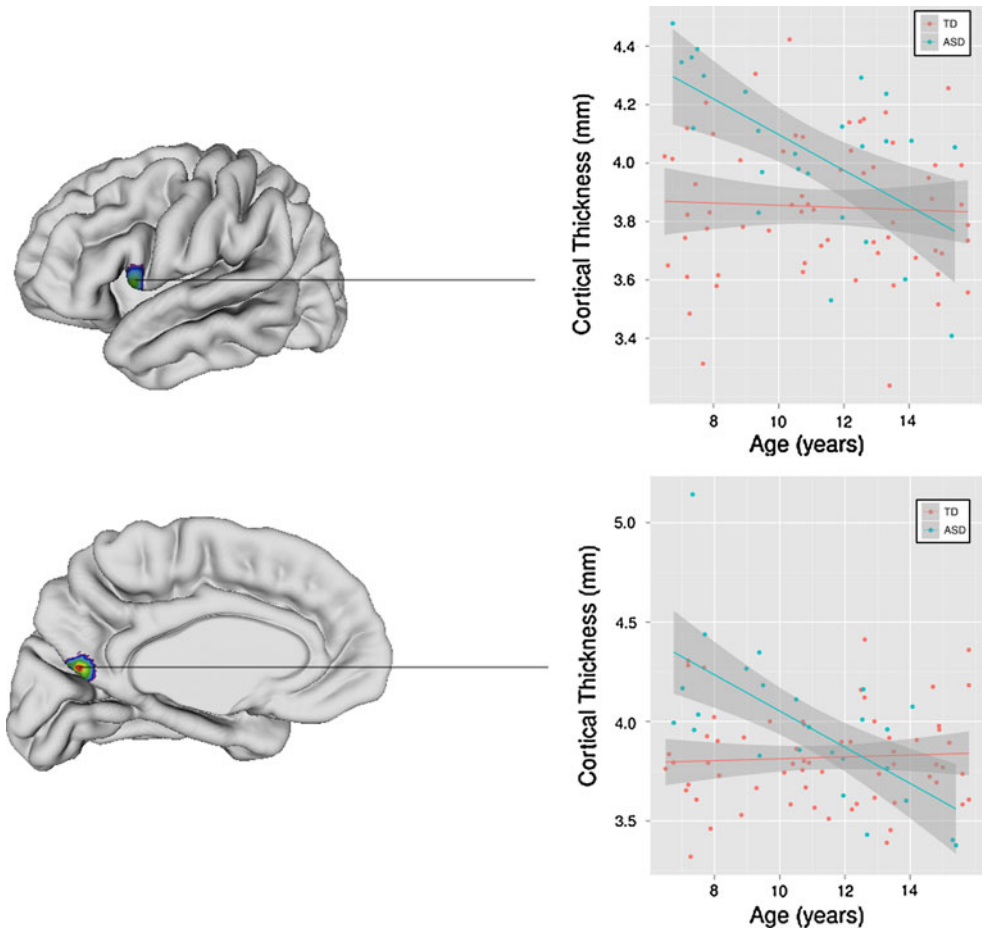

Fig. 5 Cortical thickness was significantly increased for children with ASD in **a** BA44 and **b** medial precuneus at the younger end of the age range, but not at older ages

Brain volume results from the current study are generally consistent with the existing literature on this measure. The pattern of increased brain volume seen at the younger end of our age range is concordant with other studies that have found evidence of increased volume peaking in the preschool years. Although the majority of previous studies have suggested that differences in brain volume between ASD and TD individuals eventually normalize, there is debate about when this occurs, with some researchers finding continued increased volume in studies of older individuals with ASD. Our current results show a greater decrease in brain volume with age in the ASD group that eventually results in significantly decreased brain volume at the later ages of our sample (mid-teenage years), a result not seen in the majority of previous volume analyses. However, the overall pattern of decrease with age is similar, and significantly decreased volume for an ASD group at older ages has been shown in at least one previous study.

Because of the small number of existing studies of surface area in ASD, an overall pattern has yet to emerge from the literature. Findings from the present study suggest that surface area may tend to decrease with age in children with ASD and that this may differ from typically developing children, contrary to some previous findings of a lack of relation between these measures (Raznahan et al. 2010). In our results, surface area was increased in ASD children at younger ages and decreased at older ages, relative to TD children, which is generally consistent with the findings of increased gyrification at younger ages, and decreasing gyrification with age in ASD (Hardan et al. 2004).

Cortical thickness is generally increased in studies of adults with ASD. Due to the small number of studies of cortical thickness conducted in ASD children only, a consensus has yet to emerge, but Hardan et al. (2006) found thicker cortex overall, as well as in temporal and parietal lobes, in a group of children with ASD aged 8–12 years, relative to an age-matched group of TD children, using average measures of cortical thickness across lobes as opposed to a vertex-based analysis. Here we did not find evidence of an overall increase in cortical thickness or in cortical thickness averaged across lobes for the whole group. However, we did find a pattern of increased cortical thickness in two regions of cortex, which were significantly increased at the younger end of the age range, and a relation between decreasing overall, parietal and frontal cortical thickness and age in the ASD group only.

Since Hardan et al. (2006) did not use age as a covariate in their analyses it is not possible to know if they would have found any variation in lobar cortical thickness based on age. In addition, it is difficult to compare results from an averaging method to a vertex-based approach, which provides regionally specific detail.

When examining subjects from a much larger age range (10–65 years) Raznahan et al. (2010) found that at younger ages cortical thickness was decreased in ASD relative to typically developing controls, but increased relative to controls at older ages. They also reported that in regions showing an age by group interaction, there was no relation between age and changes in cortical thickness in the ASD group, compared to a significant decrease in cortical thickness with age in the control group. Our results are in contradistinction to these findings; however, the age ranges of the two studies are quite different and the number of subjects overlapping with our age range was likely small, making it difficult to be sure of the sources of these discrepancies. In contrast, when examining change over time (on average 2 years), Hardan et al. (2009) found that there was evidence of a greater decrease in average cortical thickness in children with ASD relative to controls, in the whole brain, in the temporal and occipital lobes, and a trend in the frontal lobes, but significant in occipital cortex only. This overall pattern is consistent with the results observed in the present study, where decreases with age for overall and lobar cortical thickness were observed in the ASD group only, and where both regions emerging from the ANCOVA (left medial parieto-occipital fissure/precuneus and left IFG/BA44) showed steeper decreasing slopes with age in children with ASD across age compared to the typically developing children.

Our vertex-based analysis further showed that both groups showed similar regions of age-related changes in cortical thickness, except for the additional regions observed in the ASD group (the same regions that had group differences at the younger end of the age range). Therefore, our results suggest that there are indeed regions showing greater age-related cortical changes in ASD children 6–15 years of age, relative to typically developing children. Results may differ from the previous studies because of methods (vertex-based approach versus lobular averaging, allowing more detailed cortical analyses), age range of the sample and investigation of developmental change across this specific age range.

Of the two regions that emerged from the ANCOVA, the left IFG area has been implicated in previous structural studies of individuals with ASD. In general, the frontal lobes may be particularly affected by abnormal brain maturation processes in ASD (e.g., Carper et al. 2002), and abnormalities in the frontal lobes are one of the most consistently reported findings in the study of brain volume (Amaral et al. 2008). This hypothesis was also partially confirmed by the trends in the present study toward increased grey matter volume, surface area, and cortical thickness in the frontal lobes in the younger children with ASD. Furthermore, this region is known to be important both for language (Broca's area) and executive function (Hill 2004), two functional domains that are impaired in ASD (DSM-IV; American Psychiatric Association APA (1994), Hill 2004).

The second area, the precuneus, is unique because of the strategic position that it occupies in the structural hierarchy of the cerebral cortex (Bullmore and Sporns 2009). Parts of the medial posterior cortex, including the precuneus and posterior cingulate, are identified as putative hub regions due to their unusual anatomical properties, including dense connectivity, short average path length to other regions and the participation in a large proportion of short paths between other regions, both in anatomical (Iturria-Medina et al. 2008) and in functional brain networks (Achard et al. 2006). We have shown developmental changes in brain complexity are most marked in the precuneus region (Misic et al. 2010). Atypical development of this area in ASD may have far-reaching effects and relate to the poorer development of functional connectivity in ASD (see further discussion below).

Overall, these findings lend support to the growth dysregulation hypothesis (Akshoomoff et al. 2002) by providing further evidence that maturation of the cortex is atypical in children with ASD. Our data demonstrate that these changes are found in volume, surface area and cortical thickness, and evolve over childhood. This model of abnormal cortical maturation holds great promise for understanding the neuropathology of ASD. According to this hypothesis, early overgrowth followed by abnormal slowing essentially decouples neuronal development from the normal timing of learning and experience that shapes typical development (Akshoomoff et al. 2002) and that is necessary for typical synaptic and functional connectivity within the brain. In addition, abnormalities of cortical maturation could have profound effects on the structural aspects of neural connectivity. For example, increases in cortical folding (Hardan et al. 2004) and abnormalities in grey matter minicolumns (Casanova et al. 2002) may promote the formation of more short distance connections in the brain and impede the formation of longer distance connections, resulting in a lack of large-scale connectivity within the brain. Brain underconnectivity may indeed characterize individuals with ASD; a theory supported by evidence from DTI research (e.g., Barnea-Goraly et al. 2004; Keller et al. 2007; Conturo et al. 2008; Ke et al. 2009), white matter volumetric studies (e.g., Courchesne et al. 2001; Ke et al. 2009) and functional connectivity analyses (e.g., Just et al. 2007; Kana et al. 2007; Koshino et al. 2008).

Future research with larger numbers and age ranges of children is needed to further explore this developmental disorder and to better characterise atypical maturation patterns of the cortex in ASD, their implications for brain development and mechanisms by which they contribute to ASD symptomatology.

Acknowledgments This work was supported by the Canadian Institutes of Health Research [MOP-81161 to MJT], the National Alliance for Autism Research/Autism Speaks [1468 to MJT and WR] and the Ontario Council of Graduate Studies [Autism Scholar's Award to KMM]. The authors thank Drew Morris for technical support, and Marion Malone, Laura Hopf, and staff at the Autism Research Unit, Hospital for Sick Children, for help with behavioural testing and recruitment. We would also like to thank all the wonderful families and children who participated in this study and made this research possible.

References

Achard, S., Salvador, R., Whitcher, B., Suckling, J., & Bullmore, E. (2006). A resilient, low-frequency, small-world human brain functional network with highly connected association cortical hubs. *Journal of Neuroscience, 26*, 63–72.

Ad-Dab'bagh, Y., Singh, V., Robbins, S, Lerch, J., Lyttelton, O., Fombonne, E., & et al. (2005). *Native-space cortical thickness measurement and the absence of correlation to cerebral volume*. Poster presented at the 11th Annual meeting of the organization for human brain mapping (OHBM), Toronto.

Akshoomoff, N., Pierce, K., & Courchesne, E. (2002). The neurobiological basis of autism from a developmental perspective. *Development and Psychopathology. Special Issue: Multiple Levels of Analysis, 14*(3), 613–634.

Amaral, D. G., Schumann, C. M., & Nordahl, C. W. (2008). Neuroanatomy of autism. *Trends in Neurosciences, 31*(3), 137–145.

American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders* (4th ed.). Washington, DC: American Psychiatric Association.

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*(2), 175–183.

Bailey, A., Luthert, P., Dean, A., Harding, B., Janota, I., Montgomery, M., et al. (1998). A clinicopathological study of autism. *Brain, 121*(Pt 5), 889–905.

Barnea-Goraly, N., Kwon, H., Menon, V., Eliez, S., Lotspeich, L., & Reiss, A. L. (2004). White matter structure in autism: Preliminary evidence from diffusion tensor imaging. *Biological Psychiatry, 55*(3), 323–326.

Bullmore, E., & Sporns, O. (2009). Complex brain networks: Graph theoretical analysis of structural and functional systems. *Nature Reviews.Neuroscience, 10*(3), 186–198.

Carper, R. A., & Courchesne, E. (2005). Localized enlargement of the frontal cortex in early autism. *Biological Psychiatry, 57*(2), 126–133.

Carper, R. A., Moses, P., Tigue, Z. D., & Courchesne, E. (2002). Cerebral lobes in autism: Early hyperplasia and abnormal age effects. *NeuroImage, 16*(4), 1038–1051.

Casanova, M. F., Buxhoeveden, D. P., Switela, A. E., & Roy, E. (2002). Minocolumnar pathology in autism. *Neurology, 58*(3), 428–432.

Chakravarty, M. M., Sadikot, A. F., Germann, J., Hellier, P., Bertrand, G., & Collins, D. L. (2009). Comparison of piecewise linear, linear, and nonlinear atlas-to-patient warping techniques: Analysis of the labeling of subcortical nuclei for functional neurosurgical applications. *Human Brain Mapping, 30*(11), 3574–3595.

Chenn, A., & Walsh, C. A. (2002). Regulation of cerebral cortical size by control of cell cycle exit in neural precursors. *Science, 297*(5580), 365–369.

Chung, M. K., Robbins, S. M., Dalton, K. M., Davidson, R. J., Alexander, A. L., & Evans, A. C. (2005). Cortical thickness analysis in autism with heat kernel smoothing. *NeuroImage, 25*(4), 1256–1265.

Collins, L., Holmes, C. J., Peters, T. M., & Evans, A. C. (1995). Automatic 3-D model-based neuroanatomical segmentation. *Human Brain Mapping, 3*(3), 190–208.

Collins, D. L., Neelin, P., Peters, T. M., & Evans, A. C. (1994). Automatic 3D intersubject registration of MR volumetric data in standardized talairach space. *Journal of Computer Assisted Tomography, 18*(2), 192–205.

Conturo, T. E., Williams, D. L., Smith, C. D., Gultepe, E., Akbudak, E., & Minshew, N. J. (2008). Neuronal fiber pathway abnormalities in autism: An initial MRI diffusion tensor tracking study of hippocampo-fusiform and amygdalo-fusiform pathways. *Journal of International Neuropsychological Society, 14*(6), 933–946.

Courchesne, E. (2002). Abnormal early brain development in autism. *Molecular Psychiatry, 7*, S21–S23.

Courchesne, E., Carper, R., & Akshoomoff, N. (2003). Evidence of brain overgrowth in the first year of life in autism. *JAMA: Journal of the American Medical Association, 290*(3), 337–344.

Courchesne, E., Karns, C. M., Davis, H. R., Ziccardi, R., Carper, R. A., Tigue, Z. D., et al. (2001). Unusual brain growth patterns in early life in patients with autistic disorder: An MRI study. *Neurology, 57*(2), 245–254.

Genovese, C. R., Lazar, N. A., & Nichols, T. (2002). Thresholding of statistical maps in functional neuroimaging using the false discovery rate. *NeuroImage, 15*(4), 870–878.

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

Hardan, A. Y., Jou, R. J., Keshavan, M. S., Varma, R., & Minshew, N. J. (2004). Increased frontal cortical folding in autism: A preliminary MRI study. *Psychiatry Research, 131*, 263–268.

Hardan, A. Y., Libove, R. A., Keshavan, M. S., Melhem, N. M., & Minshew, N. J. (2009). A preliminary longitudinal magnetic resonance imaging study of brain volume and cortical thickness in autism. *Biological Psychiatry, 66*(4), 320–326.

Hardan, A. Y., Minshew, N. J., Mallikarjuhn, M., & Keshavan, M. S. (2001). Brain volume in autism. *Journal of Child Neurology, 16*(6), 421–424.

Hardan, A. Y., Muddasani, S., Vemulapalli, M., Keshavan, M. S., & Minshew, N. J. (2006). An MRI study of increased cortical thickness in autism. *American Journal of Psychiatry, 163*(7), 1290–1292.

Hill, E. L. (2004). Evaluating the theory of executive dysfunction in autism. *Developmental Review, 24*(2), 189–233.

Hutsler, J. J., Love, T., & Zhang, H. (2007). Histological and magnetic resonance imaging assessment of cortical layering and thickness in autism spectrum disorders. *Biological Psychiatry, 61*(4), 449–457.

Hyde, K. L., Samson, F., Evans, A. C., & Mottron, L. (2009). Neuroanatomical differences in brain areas implicated in perceptual and other core features of autism revealed by cortical thickness analysis and voxel-based morphometry. *Human Brain Mapping* [Epub ahead of print].

Iturria-Medina, Y., Sotero, R. C., Canales-Rodriguez, E., Aleman-Gomez, Y., & Melie-Garcia, L. (2008). Studying the human brain anatomical network via diffusion-weighted MRI and graph theory. *NeuroImage, 40*(3), 1064–1076.

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

Kana, R. K., Keller, T. A., Minshew, N. J., & Just, M. A. (2007). Inhibitory control in high-functioning autism: Decreased activation and underconnectivity in inhibition networks. *Biological Psychiatry, 62*(3), 198–206.

Ke, X., Tang, T., Hong, S., Hang, Y., Zou, B., Li, H., et al. (2009). White matter impairments in autism, evidence from voxel-based morphometry and diffusion tensor imaging. *Brain Research, 1265*, 171–177.

Keller, T. A., Kana, R. K., & Just, M. A. (2007). A developmental study of the structural integrity of white matter in autism. *Neuroreport, 18*(1), 23–27.

Kim, J. S., Singh, V., Lee, J. K., Lerch, J., Ad-Dab'bagh, Y., MacDonald, D., et al. (2005). Automated 3-D extraction and evaluation of the inner and outer cortical surfaces using a laplacian map and partial volume effect classification. *NeuroImage, 27*(1), 210–221.

Koshino, H., Kana, R. K., Keller, T. A., Cherkassky, V. L., Minshew, N. J., & Just, M. A. (2008). fMRI investigation of working memory for faces in autism: Visual coding and underconnectivity with frontal areas. *Cerebral Cortex, 18*(2), 289–300.

Lenroot, R. K., Schmitt, J. E., Ordaz, S. J., Wallace, G. L., Neale, M. C., Lerch, J. P., et al. (2009). Differences in genetic and environmental influences on the human cerebral cortex associated with development during childhood and adolescence. *Human Brain Mapping, 30*(1), 163–174.

Lerch, J. P., & Evans, A. C. (2005). Cortical thickness analysis examined through power analysis and a population simulation. *NeuroImage, 24*(1), 163–173.

Levitt, J. G., Blanton, R. E., Smalley, S., Thompson, P. M., Guthrie, D., McCracken, J. T., et al. (2003). Cortical sulcal maps in autism. *Cerebral Cortex, 13*(7), 728–735.

Lord, C., Risi, S., Lambrecht, L., Cook, E. H. J., Leventhal, B. L., DiLavore, P. C., et al. (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*(3), 205–223.

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

Lyttelton, O., Boucher, M., Robbins, S., & Evans, A. (2007). An unbiased iterative group registration template for cortical surface analysis. *NeuroImage, 34*(4), 1535–1544.

MacDonald, D., Kabani, N., Avis, D., & Evans, A. C. (2000). Automated 3-D extraction of inner and outer surfaces of cerebral cortex from MRI. *NeuroImage, 12*(3), 340–356.

Misic, B. V., Mills, T., & Taylor, M. J. (2010). *& McIntosh*. Barcelona, June: A. R. The regional specificity and task dependence of brain signal complexity in human development. Presented at HBM.

Nordahl, C. W., Dierker, D., Mostafavi, I., Schumann, C. M., Rivera, S. M., Amaral, D. G., et al. (2007). Cortical folding abnormalities in autism revealed by surface-based morphometry. *Journal of Neuroscience, 27*(43), 11725–11735.

Raznahan, A., Toro, R., Daly, E., Robertson, D., Murphy, C., Deeley, Q., et al. (2010). Cortical anatomy in autism spectrum disorder: An in vivo MRI study on the effect of age. *Cerebral Cortex, 20*(6), 1332–1340.

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

Robbins, S., Evans, A. C., Collins, D. L., & Whitesides, S. (2004). Tuning and comparing spatial normalization methods. *Medical Image Analysis, 8*(3), 311–323.

Roid, G. H., & Miller, L. J. (1997). *Leiter international performance scale–revised*. Wood Dale, IL: Stoelting.

Shaw, P., Greenstein, D., Lerch, J., Clasen, L., Lenroot, R., Gogtay, N., et al. (2006). Intellectual ability and cortical development in children and adolescents. *Nature, 440*(7084), 676–679.

Shaw, P., Kabani, N. J., Lerch, J. P., Eckstrand, K., Lenroot, R., Gogtay, N., et al. (2008). Neurodevelopmental trajectories of the human cerebral cortex. *Journal of Neuroscience, 28*(14), 3586–3594.

Sled, J. G., Zijdenbos, A. P., & Evans, A. C. (1998). A nonparametric method for automatic correction of intensity nonuniformity in MRI data. *IEEE Trans Medical Imaging, 17*(1), 87–97.

Smith, S. M. (2002). Fast robust automated brain extraction. *Human Brain Mapping, 17*(3), 143–155.

Sowell, E. R., Peterson, B. S., Kan, E., Woods, R. P., Yoshii, J., Bansal, R., et al. (2007). Sex differences in cortical thickness mapped in 176 healthy individuals between 7 and 87 years of age. *Cerebral Cortex, 17*(7), 1550–1560.

Sparks, B. F., Friedman, S. D., Shaw, D. W., Aylward, E. H., Echelard, D., Artru, A. A., et al. (2002). Brain structural abnormalities in young children with autism spectrum disorder. *Neurology, 59*(2), 184–192.

Tohka, J., Zijdenbos, A., & Evans, A. (2004). Fast and robust parameter estimation for statistical partial volume models in brain MRI. *NeuroImage, 23*(1), 84–97.

Wechsler, D. (2002). *Wechsler Abbreviated Scales of Intelligence*. San Antonio, TX: Psychological Corporation.

Wechsler, D. (2003). *Wechsler Intelligence Scale for Children* (4th ed ed.). San Antonio, TX: Psychological Corporation.

Zijdenbos, A. P., Forghani, R., & Evans, A. (2002). Automatic "pipeline" analysis of 3-D MRI data for clinical trials: application to multiple sclerosis. *IEEE Transactions on Medical Imaging, 21*, 1280–1291.