Alterations in Regional Shape on Ipsilateral and Contralateral Cortex Contrast in Children With Unilateral Cerebral Palsy and Are Predictive of Multiple Outcomes

Alex M. Pagnozzi,^{1,2,*} Nicholas Dowson,¹ Simona Fiori,³ James Doecke,¹
Andrew P. Bradley,² Roslyn N. Boyd,⁴ and Stephen Rose¹

¹CSIRO Health and Biosecurity, The Australian e-Health Research Centre, Brisbane, Australia

²The School of Information Technology and Electrical Engineering, The University of Queensland, Brisbane, Australia

³Stella Maris Scientific Institute, Pisa, Italy

⁴School of Medicine, The University of Queensland, Queensland Cerebral Palsy and Rehabilitation Research Centre, Brisbane, Australia

Abstract: Congenital brain lesions result in a wide range of cerebral tissue alterations observed in children with cerebral palsy (CP) that are associated with a range of functional impairments. The relationship between injury severity and functional outcomes, however, remains poorly understood. This research investigates the differences in cortical shape between children with congenital brain lesions and typically developing children (TDC) and investigates the correlations between cortical shape and functional outcome in a large cohort of patients diagnosed with unilateral CP. Using 139 structural magnetic resonance images, including 95 patients with clinically diagnosed CP and 44 TDC, cortical segmentations were obtained using a modified expectation maximization algorithm. Three shape characteristics (cortical thickness, curvature, and sulcal depth) were computed within a number of cortical regions. Significant differences in these shape measures compared to the TDC were observed on both the injured hemisphere of children with CP ($P < 0.004$), as well as on the apparently uninjured hemisphere, illustrating potential compensatory mechanisms in these children. Furthermore, these shape measures were significantly correlated with several functional outcomes, including motor, cognition,

Additional Supporting Information may be found in the online version of this article.

Compliance with ethical standards: The authors declare that they have no conflict of interest. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethics standards. Informed parental consent was obtained for all participants included in the study.

Contract grant sponsor: The University of Queensland and Commonwealth Scientific Industrial and Research Organisation (CSIRO) (Australian Postgraduate Award [APA]; to A.M.P.); Contract grant sponsor: Foundation for Children Grant (to R.N.B.); Contract grant sponsor: NHMRC Career Development Fellowship (to R.N.B.); Contract grant number: 1037220; Contract grant sponsor:

NHMRC Project Grant COMBIT (to R.N.B.); Contract grant number: 1003887; Contract grant sponsor: Smart Futures Co-Investment Program Grant (to R.N.B. and S.R.); Contract grant sponsor: Andrew Bradley is supported by an ARC Future fellowship; Contract grant number: FT110100623

*Correspondence to: Alex M. Pagnozzi, Australian e-Health Research Centre, Level 5, UQ Health Sciences Building, Royal Brisbane and Women's Hospital, Herston, QLD 4029, Australia. E-mail: Alex.Pagnozzi@csiro.au

Received for publication 30 October 2015; Revised 4 May 2016; Accepted 6 May 2016.

DOI: 10.1002/hbm.23262

Published online 3 June 2016 in Wiley Online Library (wileyonlinelibrary.com).

vision, and communication ($P < 0.012$), with three out of these four models performing well on test set validation. This study highlights that cortical neuroplastic effects may be quantified using MR imaging, allowing morphological changes to be studied longitudinally, including any influence of treatment. Ultimately, such approaches could be used for the long term prediction of outcomes and the tailoring of treatment to individuals. *Hum Brain Mapp* 37:3588–3603, 2016. © 2016 Wiley Periodicals, Inc.

Key words: magnetic resonance imaging; cerebral palsy; cortical gray matter; morphology

INTRODUCTION

Cerebral palsy (CP) is the most common form of childhood disability worldwide [Oskoui et al., 2013], describing a range of brain injury caused by disturbances during prenatal development [Luhmann et al., 2014]. Alterations of the cortical surface are the result of several types of lesions observed in children with CP [Bax et al., 2006], as it relates to either environmental or genetic insult [Barkovich et al., 2012; Leventer et al., 2008] to the neuronal architecture critical for brain function [Collin et al., 2014]. The injury appears as a heterogeneous group of congenital cerebral alterations, which results in several clinical types. In particular, in unilateral CP, the type of injury includes (by frequency): periventricular white matter lesions (45%), gray matter lesions (30%), and brain maldevelopments (14%) [Cioni et al., 1999]. All these abnormalities can result in abnormal cortical folding, altered gyri, abnormally thick folds (pachygyria), and abnormal fluid filled clefts arising from primary (for cortical gray matter involvement) or secondary (for white matter involvement) origin, which contribute to functional impairments irrespective of aetiology. Magnetic resonance imaging (MRI) is pivotal for defining alterations due to cerebral injury; however, the current qualitative clinical assessments based on aetiology [Cioni et al., 1999; Krägeloh-Mann and Horber, 2007] are too broad, and not sufficient to describe the large variability in appearance or impact of these alterations [Feys et al., 2010]. Quantitative image analysis techniques are needed to develop models which can quantify the severity of abnormalities due to injury, and to link cortical structure to patient function.

The automated quantitative analysis of cortical shape has the potential to comprehensively characterize the shape of the cortex and relate this shape to a range of functional outcomes. In the CP setting, the heterogeneity of possible alterations due to lesions necessitates the use of several measures of shape to fully characterize cortical morphology. Cortical thickness is one important measure that increases during development [Shaw et al., 2006], which can be used to detect and quantify primary or secondary pachygyria. Cortical thickness has been used in many studies to characterize healthy development [Sowell et al., 2004], abnormal development [Moeskops et al., 2015], and to investigate cortical thinning due to schizophrenia [Rimol et al., 2012] and Alzheimer's disease [Hai-

dar and Soul, 2006]. The curvature of the cortex [Rodriguez-Carranza et al., 2008] and sulcal depth [van Essen, 2005] are alternative measures that reflect the changes in cortical surface area arising from gyrification during development [Dubois et al., 2008a]. Consequently, these measures are important for identifying changes in cortical folding related to several brain malformations such as lissencephaly, polymicrogyria, or schizencephaly, with multiple studies highlighting the sensitivity of these measures in detecting cortical abnormalities [Nordahl et al., 2007; van Essen et al., 2006; White et al., 2003; Zhang et al., 2015].

Current cortical analyses typically use combinations of these shape measures within surface-based morphometry frameworks to identify statistically significant differences between diseased or injured brains and healthy controls [Dierker et al., 2015; Park et al., 2009; Schaer et al., 2008]. However, the severity of alterations observed in children with CP, such as those illustrated in Figure 1, introduces significant errors into the registration of cortical surfaces required by morphometric analyses. In the CP setting, FreeSurfer is frequently used to extract and parcellate the cortical surface [Kelly et al., 2015; Papadelis et al., 2014; Rose et al., 2011] and to compute multiple measures of cortical shape [Danti et al., 2015; Ma et al., 2015; Shollenbarger et al., 2015]. This method however relies on an accurate deformation of a surface mesh, necessitating manual intervention or the exclusion of severely injured data. Voxel-Based Morphometry (VBM) [Ashburner and Friston, 2000] is also a commonly used approach for assessing cortical gray matter changes between healthy and unhealthy groups [Giménez et al., 2006], correlating image features to outcome [Northam et al., 2011; Soria-Pastor et al., 2008], and investigating longitudinal changes in structure related to plasticity [Giuliani et al., 2011; Sterling et al., 2013; Thomas et al., 2009]. This approach has been found to be susceptible to false positives due to the complicated structure of the neocortex [Scarpazza et al., 2015], and is similarly hindered by severe injury, which affects the accuracy of the image registration. Additionally, although a combination of these cortical shape measures have been correlated with brain volume [Im et al., 2008], intelligence quotient [Im et al., 2006] and cognitive scores [Dubois et al., 2008a; Jouvent et al., 2008], and have been tracked longitudinally over the development of pre-term infants [Chung et al., 2003; Dubois et al., 2008b], no such

Figure 1.

An illustration of the extensive injury common in CP patients resulting in abnormal folding and abnormal fluid filled areas (bilateral perisylvian polymicrogyria [arrow, **a**], ventriculomegaly [**b–d**] and abnormal fluid filled clefts [arrow, **b** and **c**], or cysts [arrowhead, **d** and **e**]). Secondary alterations of the cortical surface were caused by: (**b** and **c**) periventricular white matter lesions and (**d** and **e**) cortical and deep gray matter lesions.

correlations have been made for CP specifically, primarily due to the difficulty in segmenting and labeling gray matter tissue on regions of severe injury.

Provided these technical difficulties can be overcome and a robust and sensitive characterization of the cortical surface can be obtained, several aspects related to cortical injury and compensatory mechanisms in children with CP can be investigated. First, since cortical shape is an important consideration of clinicians reviewing abnormalities that are visible in MRIs [Guerrini and Dobyns, 2014; Lev-enter et al., 2008], automated measures of cortical shape could readily be applied to identify and quantify the differences between children with cortical alterations and typically development children (TDC). Second, in cases with unilateral injury, abnormalities in the uninjured hemisphere relative to the typical population will occur as a result of either secondary microstructural damage due to altered influences of the injured hemisphere, or potential plasticity mechanisms which have been observed in animal models [Kolb and Gibb, 2007], stroke patients [Ward, 2005], and children with CP [Krägeloh-Mann, 2004]. It could also help establish whether subtle cortical alterations exist in children with other forms of injury such as periventricular white matter lesions (i.e., periventricular leukomalacia or ventricular enlargement due to loss of periventricular white matter). Finally, measures of healthy (or unhealthy) cortical shape taken from multiple cortical regions with a known functional role could be correlated to patient function, revealing the structure-function models of the brain.

In this article, we hypothesize that shape measures in the injured classes (alterations present within the ipsilateral hemisphere or bilateral alterations due to brain injury in clinically unilateral CP) are different from TDC. We also hypothesize that cortical shape contralateral to the side of injury differs from TDC, potentially due to mechanisms of plasticity. Finally, we hypothesize that children with clinically diagnosed unilateral CP but with other

(non-cortical) forms of injury will nevertheless contain subtle changes in cortical measures relative to the TDC. To test these hypotheses, we investigated the differences in shape measures between healthy and altered brains of children with unilateral CP independently on the sides ipsilateral and contralateral to injury. We also establish the extent of the relationship between the severity of cortical alteration and multiple clinical scores of function in a cohort of patients diagnosed with unilateral CP. To achieve this, we use the Expectation Maximization (EM) segmentation algorithm with a modified Markov Random Field (MRF) implementation which removes the reliance on atlas based priors to obtain segmentations that are robust in the presence of injury [Pagnozzi et al., 2015]. Such robustness is necessary when alterations are as severe as those often observed in patients with CP. Using the segmented regions, measures of cortical thickness, curvature and sulcal depth are computed to capture the heterogeneous range of values observed in children with CP and TDC. Comparisons were performed between the TDC and children with unilateral alterations, bilateral alterations, and CP cases without visible cortical alterations. Subsequent correlation to clinical performance scores including motor function, cognitive function, visual acuity and communicative ability were performed using the cortical measures in units of z-score normalized by the variance of individuals within the healthy population. The derived models of structure and function are intended to facilitate future improvements to the selection of therapies tailored to individual patients.

MATERIALS AND METHODS

Subjects

A total of 139 patients were included in this study: 95 patients with clinically diagnosed unilateral CP (50 male, 45 female, mean age 11.4, age range 5–17), and 44 TDC (15

male, 29 female, mean age 10.8, age range 7–16) were included. Images were acquired at the Royal Brisbane and Women's Hospital and were supplied by the Queensland Cerebral Palsy and Rehabilitation Research Centre (QCPRRRC), as well as from the Stella Maris Institute, Pisa. Study participants included children who were recruited as part of ongoing studies of children with CP [Boyd et al., 2013a,b]. Diagnoses of CP were made based on clinical assessment by experienced clinicians in the field of CP. For both studies, ethical approval was granted and informed parental consent was obtained for all participants.

MRI Data Acquisition

All 139 MR scans were acquired from one of two scanners, and one of three sets of scanning parameters: a 3T Siemens scanner (TR = 1,900 ms, TE = 2.32 ms, flip angle = 9 degrees, $n = 106$ images), and a 1.5T GE scanner for which the scanning parameters were either (TR = 12.36 ms, TE = 5.17 ms, flip angle = 13 degrees, $n = 19$ images) or (TR = 124.29 ms, TE = 4.37 ms, flip angle = 10 degrees, $n = 14$ images).

Clinical Measures

To evaluate patient motor function, the Assisted Hand Assessment (AHA) [Krumlinde-Sundholm et al., 2007] was measured. This is a score between 0 and 100 that measures how well the impaired hand is used as an assisting hand during bimanual activities, with larger scores indicating greater assistance from the impaired hand during these tasks. The Behavior Rating Inventory of Executive Function (BRIEF) [Gioia et al., 2002] was also measured, which is a parent reported questionnaire scoring their child's emotional and behavioral function in daily life. Visual acuity, including the ability to discriminate and memorize visual cues, was measured using the Test of Visual Perception Skills (TVPS) measure [Frostig et al., 1961], while communicative ability was assessed using the vocabulary (VOC) subtest of the Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III) [Wechsler, 1967].

Image Pre-Processing

Bias correction was performed using the N4 algorithm [Tustison et al., 2010]. All images were then aligned using an affine block matching registration algorithm [Rivest-Hénault et al., 2015] to the Colin 27 Average Brain Atlas. Image de-noising was performed using anisotropic diffusion [Perona and Malik, 1990] with modified curvature diffusion equation [Yezzi, 1998] to reduce the influence of image noise. Skull stripping was performed in MATLAB (Mathworks, Natick, MA) using an approach that identified intracranial cerebrospinal fluid (CSF) at locations proximal to the skull using intensity thresholding. Brain tissue was segmented as the region encapsulated by this

intracranial CSF segmentation, with morphological operations implemented to ensure consistent segmentations between adjacent MR slices, and manually verified. This method is capable of accurately segmenting brains in cases of large lesions by including abnormal regions of CSF, caused by the absence of tissue, to be included in the brain mask.

EM-Weighted MRF Segmentation Algorithm

Accurate gray matter segmentation remains a challenging task as the organization of the cortical surface can differ significantly in patients with cerebral injury. The EM algorithm [Dempster et al., 1977] has frequently been used for the automated segmentation of brain MRI data [Van Leemput et al., 1999; Wells et al., 1996], often with interleaved methods for enforcing spatial homogeneity using MRF [Zhang et al., 2001]. For neonatal datasets, EM provides robust segmentations even in the presence of high noise, significant partial volume effects, lack of tissue contrast, and extensive anatomical variability typical of these datasets [Cardoso et al., 2011; Makropoulos et al., 2012; Murgasova et al., 2006], highlighting its potential application to CP.

The limitation of the EM approach, particularly in the presence of severe injury, is its reliance on atlas priors during initialization, and when iterative scaling voxel-wise tissue likelihoods based on the expected tissue type. Although non-rigid alignment of the atlas priors to the data is performed, non-rigid registration typically fails in cases of severe injury. Additionally, while a number of a priori relaxation strategies allow for more data-driven segmentation in later iterations [Cardoso et al., 2011; Makropoulos et al., 2012], the discrepancies between the anatomical assumptions of the normative atlases and CP patients are too great to provide a robust initialization [Pagnozzi et al., 2015].

In this study, segmentation of the cerebral tissues on all 139 T1-weighted MRIs was performed using a modified EM-MRF, from which cortical gray matter segmentations were subsequently identified. To avoid making assumptions about the volume of different tissues, the segmentation was initialized using a peak finding algorithm that searches the intensity histogram for the two sufficiently separated dominant peaks from the brain mask, labeled as gray and white matter. The mean intensity of the CSF distribution was estimated by searching backwards from the gray matter peak. The standard deviation of each distribution is computed from the gradient of the Gaussian intensity histogram on either side of the respective maximum.

In the EM approach, the segmentation problem is formulated as an incomplete data problem where given the set of n voxel intensities in the image, $y = \{y_i | i \in [1; n]\}$, the algorithm attempts to compute a set of labels, $z = \{z_i | i \in [1; K]\}$, describing which of K tissue classes each voxel belongs to, with k denoting a specific tissue class

$1 \leq k \leq K$. Voxels are indexed by i . Intensity distributions for each tissue class k are assumed to be normally distributed, with mean and standard deviation $\Phi_k = (\mu_k, \sigma_k)$. The estimation of the maximum likelihood parameters, $\hat{\Phi}$, is obtained by interleaving the estimation of the hidden segmentation, $\hat{z}$, (E-step), followed by the update of the class distributions, Φ , based on the observed image y and segmentation z (M-step).

In the E-step, tissue labels at each voxel, i , were selected as the tissue class k that has the minimum posterior likelihood p_{ik} , which at iteration $m+1$ takes the form:

$$p_{ik}^{(m+1)} = \frac{\frac{1}{\sqrt{2\pi\sigma_k^2}} \exp\left(-\frac{y_i - \mu_k}{2\sigma_k^2}\right) f(z|\Phi_z)}{\sum_{j=1}^K \left[\frac{1}{\sqrt{2\pi\sigma_j^2}} \exp\left(-\frac{y_i - \mu_j}{2\sigma_j^2}\right) f(z|\Phi_z) \right]} \quad (1)$$

Given a set of labels z , the parameters were updated in the M-step as follows:

$$\mu_k^{(m+1)} = \frac{\sum_i p_{ik}^{(m+1)} y_i}{\sum_i p_{ik}^{(m+1)}} \quad (2)$$

$$\left(\sigma_k^{(m+1)}\right)^2 = \frac{\sum_i p_{ik}^{(m+1)} \left(y_i - \mu_k^{(m+1)}\right)^2}{\sum_i p_{ik}^{(m+1)}} \quad (3)$$

The form of $f(z|\Phi_z)$ in Eq. (1), which is related to the MRF implementation, is critical to the performance of the algorithm. This modification is proposed to provide necessary robustness to the segmentation of MRI scans with extensive CP-related injuries. Commonly, the spatial relationship between a voxel and its six adjacent neighbors is assumed to be a random field following a Gibbs distribution:

$$f(z|\Phi_z) = Z(\Phi_z)^{-1} \exp(-U_{\text{mrf}}), \quad (4)$$

where $Z(\Phi_z) = \sum_z \exp(-U_{\text{mrf}})$ is called the partition function and U_{mrf} is the energy function. The energy function is the sum of clique potentials $V_c(z)$ over all possible cliques, C :

$$U_{\text{mrf}}(z) = \sum_{c \in C} V_c(z). \quad (5)$$

Traditionally, clique potentials compute the sum of mismatched labels between the voxel x_i and its clique neighbors:

$$V_c(z_i, z_j) = \begin{cases} \frac{1}{2} & \text{if } z_i \neq z_j \\ 0 & \text{if } z_i = z_j \end{cases}. \quad (6)$$

This standard formulation of the clique potential is implemented in the Atropos software [Avants et al., 2011]. Other modulations of the MRF parameters are proposed in the seminal works of Geman and Geman, and Mumford and Shah [Geman and Geman, 1984; Mumford and Shah,

1989]. These techniques modulate clique potentials based on gradients or smooth edges in the label field, z . Both FSL's FAST and NiftySeg use a clique potential discretely weighted by gradients in the label field, as in Geman and Geman [Geman and Geman, 1984].

To compensate for the lack of an informative atlas-based prior, the proposed modification instead incorporates a new assumption in the model, that a mismatch of labels at a clique edge will have an associated mismatch of intensity at defined tissue boundaries. In comparison to previous studies, in the proposed modification the cost of neighboring voxels with different labels is down scaled by the presence of intensity gradients between the voxels in the image, y . Correspondingly, the cost of neighboring voxels with identical labels is upscaled in the presence of intensity gradients between the voxels. Hence, in the modified MRF the cost of neighboring labels is weighted by the gradient of intensity between the neighboring voxels, which is congruous with the concept that different labels in a clique should have a different intensity, and vice versa. Therefore, the cost of neighboring voxels as follows:

$$V_c(z_i, z_j) = \begin{cases} \frac{1}{2} \left(\exp\left(-\frac{|y_i - y_j|}{w}\right) \right) & \text{if } z_i \neq z_j \\ \frac{1}{2} \left(1 - \exp\left(-\frac{|y_i - y_j|}{w}\right) \right) & \text{if } z_i = z_j \end{cases} \quad (7)$$

In Eq. (7), w is a global parameter to control the influence of the gradient across tissue boundaries present in the MRI, typically based on the expected difference between classes y_i and y_j . In the experiments, this parameter was chosen to be half of the difference in intensity between white matter and gray matter at initialization, which was consistent due to intensity normalization in MRI preprocessing.

To validate this proposed segmentation approach, we compared the accuracy of multiple segmentation approaches, including FreeSurfer, NiftySeg, ANTs Atropos, and FSL's FAST, and the proposed approach, to manual segmentations provided by two independent raters. This comparison was performed on 23 of the 139 MRIs, of which 17 contained severe alterations, and 6 were TDC. This analysis is shown in the Supporting Information. We note here that the proposed segmentation approach yielded the highest Dice Similarity Coefficient (DSC) among the 17 cases with severe injury (DSC = 0.783), with Atropos having the second highest performance (DSC = 0.757). The improvement in results compared favorably to the inter-rater agreement of 0.797 and was hence used in the subsequent methodology.

As this study is primarily focused on identifying cortical alterations and not on other lesion sites, including white and deep gray matter lesions, as well as secondary ventricular enlargement, the effects of these other lesion types were removed from the analysis. Specifically, secondary

ventricular enlargement was removed by masking out the segmented lateral ventricles from the brain mask, which otherwise could influence measures of sulcal depth if the ventricle extended to the skull. In cases where entire cortical regions are missing due to tissue loss, resulting in secondary enlargement of the ventricles, shape measures from these cortical regions would be subsequently be masked out in this process, and treated as a missing value in the statistical methodology. Additionally, the presence of lesions was not accounted for in the brain segmentation, as the presence of gray matter lesions subtracted from the cortical gray matter mask could affect measures of cortical thickness and curvature.

Shape Analysis of Cortical Segmentations

Three measures of cortical shape; cortical thickness, sulcal depth and curvature were computed for all 139 gray matter segmentations obtained using the proposed EM-weighted MRF method. A description of how these shape measures were computed, and how cortical regions were segmented, is given below.

Computing cortical thickness and sulcal depth

For all MRIs, cortical thickness and sulcal depth measures were computed by solving Laplace's equation [Jones et al., 2000]. This voxel-based approach for measuring the distance between non-intersecting surfaces was used due to its computational efficiency compared to the relatively time-consuming surface-based methods [Das et al., 2009]. To measure cortical thickness, the voxels adjacent to the white-matter/gray matter boundary were labeled as such, as were the voxels adjacent to the gray matter/CSF boundary. The remaining voxels from this segmentation were iteratively recomputed as the average of its six adjacent neighboring voxels. After several iterations, a local gradient was computed for every voxel within the segmentation and normalized to have unit magnitude. Subsequently, each location of the outer surface was propagated along the gradient field until the inner surface was reached, forming one path per voxel. This approach yields a smooth topological one-to-one mapping between each surface of the cortex, allowing thickness measures to be computed as the cumulative distance from the interior of the cortex to its corresponding point on the exterior of the cortex. Similarly, both sides of the subdural CSF segmentation were identified from the EM-MRF segmentation, and Laplace's approach was used to compute a smooth mapping between the CSF adjacent to the skull and the CSF adjacent to the sulci and gyri of the cortical surface. The distance between these two regions (i.e. surfaces) of CSF was called the sulcal depth. These two measures are illustrated in Figure 2.

Cortical thickness and sulcal depth measures computed from the 44 healthy MR scans were isolated, and the mean and standard deviation was identified for each cortical

Figure 2.

An illustration of the cortical thickness and sulcal depth shape measures on a region from a healthy brain shown in (a). In (b), the outer (subdural) surface of the CSF is shown in yellow, the CSF/gray matter interface is shown in green, and the gray matter/white matter interface is shown in red. Measures of cortical thickness and sulcal depth are demonstrated as white arrows between the yellow and green, and green and red contours, respectively. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

region labeled on the Colin 27 Automated Anatomical Labeling (AAL) atlas. This models the healthy variation of these shape measures in each cortical region as a Gaussian distribution. The computed shape cortical thickness and sulcal depth measures obtained from target MR scans, which may or may not have a malformed cortex, were converted to a z-score using the distribution of parameters obtained from the TDC, as shown in Eq. (8). The signed value of the z-score was then used as independent variables in the subsequent linear regression models, for example, for cortical thickness:

$$z_{\text{thick}} = \text{abs} \left(\frac{x_{\text{thick,target}} - \mu_{\text{thick,healthy}}}{\sigma_{\text{thick,healthy}}} \right) \quad (8)$$

Computing exterior surface mesh and cortical curvature

The 139 gray matter segmentations were also converted to meshes using The Visualization Toolkit (VTK) [Shroeder et al., 2006]. This mesh was decimated and smoothed, before measures of curvature are computed, also using VTK. Using this 3D mesh, absolute curvature measures computed from the 44 healthy MR scans were extracted, and the standard deviation was identified for each cortical region labeled on the AAL atlas. The mean and standard deviation of the measured curvature from MR scans of children with CP is computed in each cortical region. As alterations may appear as either excessively folded gyri or an excessively smooth cortex, a signed z-score was again used for curvature.

Anatomical Labeling of Cortical Regions

Labels of cortical regions were obtained from the AAL atlas, and propagated to the exterior surface of the cortical gray matter from all 139 MRIs using level sets [Adalsteins-son and Sethian, 1995; Osher and Sethian, 1988]. The level set approach computes the propagation of fronts, taking into account topological properties such as curvature and surface normal vectors, by solving the Eikonal equation [Sethian, 1996]. This method yields a level set function, which contains the topological evolution mapping from one surface (in our case, the outer gray matter surface of the subject) to the other (the outer surface of the atlas). Unlike the Laplacian method, the level set function although more computationally expensive, can produce a topological mapping between intersecting surfaces, which occurs frequently in the comparison between atlas and subject. Furthermore, this mapping can extend across large distances, allowing for correspondences between healthy and severely malformed cortical surfaces, as illustrated in Figure 3. Using a MATLAB implementation of level sets described here [Li et al., 2011], the level set function was fitted to the subtraction of the outer gray matter surface of the atlas, which was given a positive value, and the outer gray matter surface of the subject, which was given a negative value. Voxels where curves intersect cancel out to give a zero value, indicating no label propagation was required. Paths are extracted by placing a seed at each location on the surface of the subject and propagating the seed along the gradient of the level set function until the cortical surface of the atlas is reached. The paths provide a one to one mapping between each location on the subject's cortical surface and the cortical surface of the atlas, enabling propagation the atlas label to the subject.

Selection of Cortical Gray Matter Regions

A succinct set of 12 cortical regions related to each of the six clinical scores were chosen from the AAL atlas for the subsequent statistical analyses. For the AHA test of bimanual hand function, areas critical to motor tasks such as the primary motor cortex, supplementary motor area and the primary somatosensory cortex [Shibasaki et al., 1993] were included, as well as the posterior parietal cortex which has a role in reaching tasks [Kertzman et al., 1997]. These regions have also been identified as important for hand motor function from several functional MRI studies examining cortical activation following hand tapping tasks [Jäncke et al., 2000; Lotze et al., 1999; Lutz et al., 2005].

For the BRIEF score of executive function, the insular and cingulate cortices were chosen based on their known role in both cognitive tasks [Sridharan et al., 2008] and emotional processes [Bush et al., 2000] respectively. Regions selected for the TVPS test for visual perception include the primary visual cortex which is involved in visual processing [Lee et al., 1998], the inferior temporal

Figure 3.

The propagation of the AAL gray matter labels using the level set function for an image with severe alteration. The in-plane gradient of the level set is illustrated with the white contour lines, and the multicolored cortical surface represents the cortical labels from the AAL atlas. Propagation of three points from the atlas label to locations on the subject's cortex is shown, with two points being close to their target and the third being relatively distant from its target, yet still generating a successful labeling. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

gyrus which is involved in visual memory [Eskandar et al., 1992], and both the lingual and fusiform gyri which have a role in processing letters [Mechelli et al., 2000] and faces [Gorno-Tempini et al., 1998]. The inferior frontal gyrus was included for the VOC score as it contains Broca's area, which has a known role in speech production [Papoutsis et al., 2009], and the superior temporal gyrus which contains the primary auditory cortex and has a known role in speech perception and production [Buchsbaum et al., 2001]. An outline of the selected cortical regions for each clinical score is outlined in Table I.

Statistical Methodology

To investigate the differences in measured cortical shape between scanner sequences, a Hotelling's *t*-squared test was performed on the mean cortical thickness, mean curvature and mean sulcal depth of each patient with each of the three scanner sequences.

A linear mixed-effects model was fitted to examine differences in cortical shape measure based on the categorical class of injury, as detailed below, controlling for cortical

TABLE I. The manually selected cortical regions from the AAL atlas used as predictor variables for the linear models

Motor regions (AHA)	Executive function regions (BRIEF)	Visual regions (TVPS)	Vocabulary regions (VOC)
Primary motor cortex	Insular cortex	Primary visual cortex	Inferior frontal gyrus
Supplementary motor area	Cingulate cortex	Lingual gyrus	Superior temporal gyrus
Primary somatosensory cortex		Fusiform gyrus	
Posterior parietal cortex		Inferior temporal gyrus	

region, scanner and sequence, patient age and gender. Twelve models were constructed, one for each of the three cortical shape measures, and stratified by the four functional groupings of cortical regions, as outlined in Table I. Bonferroni correction ($\alpha = 0.05/12$ tests = 0.004) was performed to account for multiple comparisons. In each model, a categorical predictor variable describing the aetiological class of injury was included, as well as three covariates, patient age, gender, and cortical region defined in the previous section. Patient ID was included in the model as a mixed effect, to account for the fact that shape measures of each cortical region are quantified for individual patients. The five defined categories for the class of injury include cortical measures obtained from the TDC ($n = 44$), cortical measures obtained from the ipsilateral hemisphere of children with unilateral alterations ($n = 34$), cortical measures obtained from the contralateral hemisphere of children with unilateral alterations ($n = 34$), cortical measures obtained from children with bilateral alterations ($n = 7$), and cortical measures obtained from children diagnosed with CP but with other (non-cortical) forms of injury ($n = 54$). This latter class included children with periventricular white matter injury and ventricular enlargement.

Multivariable regression analyses were conducted to identify the significant cortical shape predictors of multiple patient outcomes. Using the three measures of cortical shape in the cortical regions propagated from the AAL atlas, four models were constructed with the absolute z-scores of the shape measures (relative to the cortical regions of the TDC) being the independent (predictor) variable, and the four clinical scores of patient function being the dependent variable in each model. Patient age, gender, and scanner sequence were also included as covariates in the models. Due to the slight mismatch in age between CP and TDC cohorts, children with CP aged between 5 and 7 were removed from the dataset, prior to training the regression models. Trained models constructed on the full dataset are provided in the Supporting Information. To identify optimal sets of markers associated with outcome, we utilized a data-driven variable selection using the “stepAIC” package in R. This package aims to remove variables that do not explain sufficient variance in the clinical score based on their Akaike information criterion [Sugiura, 2007]. Note that variable selection was performed on different sets of independent variables, based

on the different groups of cortical regions shown in Table I, and used different outcome variables also highlighted by this table, hence there was no overlap between the models. This process was completed using 75% of the data (training), with optimal sets of markers then used to validate the models performance using the remaining test dataset (25%). Multiple comparisons on the trained regression models was accounted for using Bonferroni correction ($\alpha = 0.05/4$ tests = 0.0125).

Optimal training models yielded partial regression coefficients, indicating the relative influence of each shape measure and cortical region affecting the neurological outcome used in the model, and a multiple R -squared, which describes the amount of variance in the clinical score explained by the weighted measures of cortical shape. All statistical calculations were performed using then R statistical software environment, version 3.2.2 [The R Development Core Team, 2008].

RESULTS

Demographic Information

Demographic information, including age, gender, of the cohort of children with CP, and the TDC, are provided in Table II below. This table additionally includes the number of children at each Gross Motor Function Classification System (GMFCS) level, for the 85 children with CP who were scored with this measure. Additionally, a validated, semi-quantitative measure of brain injury [Fiori et al., 2014], obtained manually from observed radiological injury by the same expert clinician, is provided in this table. For the TDC cohort, their GMFCS level and injury severity score were not obtained.

Investigating Cortical Shape Differences Between MR Scanner Sequence

Hotelling’s t -squared test statistics quantifying the differences in mean cortical shape measures between the 3T Siemen’s scanner sequence and the first 1.5T GE scanner sequence was 1.425 ($P = 0.258$), between the 3T scanner sequences and the second 1.5T scanner sequence was 1.764 ($P = 0.197$), and between the two different 1.5T scanner sequences was 1.764 ($P = 0.178$). None of these differences was found to be significant, signifying that despite the

TABLE II. Demographic characteristics for the TDC and CP cohorts

Cohort	TDC cohort	CP cohort
Number of patients	44	95
Gender		
Male	15	84
Female	29	83
Age at scan (years)		
Mean $\pm$ standard deviation	12.35 $\pm$ 2.40	11.41 $\pm$ 3.08
Range (minimum – maximum)	7–16	5–17
Global brain injury severity score [Fiori et al., 2015]		
Mean $\pm$ standard deviation	0.00 $\pm$ 0.00	9.20 $\pm$ 4.88
Range (minimum – maximum)	0–0	1–21
Gross Motor Function Classification System (GMFCS)		
Level I	NA	52
Level II	NA	33
Level III	NA	0
Level IV	NA	0
Level V	NA	0

differences in scanner sequence and image quality, these differences were resolved by the image alignment and resampling pre-processing steps of the proposed pipeline, hence the computed cortical shape measures were not significantly different.

Measured Cortical Shape Changes Due to Alteration

The three measures of cortical shape compared between the five aetiological classes of injury are outlined in Table III. Note that all comparisons between these groups have been performed taking into account cortical region, patient age, and gender.

Table III shows that there were significant decreases in cortical thickness observed for children with ipsilateral alterations on the side of injury, compared to the TDC, for the motor and visual regions ($P < 0.004$). In contrast, there were significant increases in cortical thickness observed on the contralateral side for both motor regions compared to TDC ($P < 0.004$), with executive function and VOC regions also being thicker than the corresponding healthy measure, however this latter finding was not significant ($P > 0.004$). No significant differences were observed between children with CP but without cortical alterations, and the TDC.

Table III also shows that there were significant reductions in the curvature of the ipsilateral hemisphere of children with unilateral injury compared to the TDC for executive function regions ($P < 0.004$). In many of the remaining cases, the curvature of children with any type of observed radiological injury were also less curved than the TDC, albeit these did not reach significance ($P > 0.004$).

There were significant increases in sulcal depth observed for children with ipsilateral cortical alterations (on the side of injury) compared to the TDC for motor, executive function, and visual cortical regions ($P < 0.004$). Sulcal depth on the contralateral side, however, was significantly decreased compared to the TDC, for VOC regions ($P < 0.004$).

Modelling Cortical Shape Biomarkers to Clinical Outcomes

The shape features from the multivariable regression analyses that were retained following data-driven variable selection are as follows. For the AHA motor score, retained regions include thickness, curvature, and sulcal depth of the primary motor cortex and primary somatosensory cortex, and thickness and sulcal depth of the posterior parietal cortex. Retained regions for the BRIEF score include all three shape measures for the cingulate cortex, and the thickness and sulcal depth of the insular cortex. For this model, the data-driven variable selection only removed one cortical shape feature, suggesting that all these predictor variables explain a unique portion of variance in the executive function score. For the TVPS model, retained predictors include the curvature and sulcal depth in the primary visual cortex, curvature of the inferior temporal gyrus, and thickness of the fusiform gyrus. For the VOC model, cortical thickness and curvature of the inferior frontal gyrus, and the cortical thickness of the superior temporal gyrus, were retained. All retained predictors following the data-driven variable selection in the training set were statistically significant ($P < 0.05$), except for the curvature and sulcal depth of the cingulate cortex, and the thickness and sulcal depth of the insular cortex in the BRIEF model. The regression coefficients and standard errors of the strongly significant cortical features ($P < 0.005$), as well as patient age, gender, and scanner sequence, are provided in Table IV.

The R -squared of the linear models for each of the clinical scores, provided in Table IV, represents the proportion of variance in the clinical score explained by the model constructed on the training set while the r^2 derived from the model validation represents how well the model performed on the test set.

Although all trained models were statistically significant ($P < 0.0125$), only three obtained significant correlations in the independent test set ($P < 0.0125$). Interestingly, reductions in curvature and increases in sulcal depth in the primary somatosensory cortex were strongly associated with poorer AHA outcomes, reflecting that reduced surface area, and hence cortical volume, of this cortical region is predictive of motor function. We note that for communication outcomes, decreases in cortical thickness in the inferior frontal gyrus (the cortical region containing Broca's area) were also strongly significant ($P < 0.005$), suggesting that tissue loss, reflected in

TABLE III. The measured differences in cortical shape measure between TDC ($n = 44$), the ipsilateral hemisphere of children with unilateral alterations ($n = 34$), the contralateral hemisphere of children with unilateral alterations ($n = 34$), both hemispheres from children with bilateral alterations ($n = 7$), and both hemispheres of children diagnosed with CP but with other (non-cortical) forms of injury ($n = 54$)

In cortex:	Cortical thickness (mm)			Curvature (mm^{-2})			Sulcal depth (mm)		
	Mean	Difference	S.E.	Mean	Difference	S.E.	Mean	Difference	S.E.
Motor regions									
Healthy	2.947			0.490			8.627		
With bilateral alterations	3.210	0.263	0.248	0.424	-0.066	0.064	10.296	1.669	0.549
Ipsilateral to alterations	2.442	-0.505*	0.132	0.418	-0.072	0.030	10.421	1.794*	0.456
Contralateral to alterations	3.378	0.431*	0.153	0.470	-0.020	0.039	7.583	-1.044	0.408
With other (non-cortical) forms of injury	3.325	0.378	0.202	0.455	-0.035	0.034	8.327	-0.300	0.427
Executive function regions									
Healthy	2.788			0.882			26.963		
With bilateral alterations	2.391	-0.397	0.196	0.668	-0.214	0.198	26.339	-0.624	1.382
Ipsilateral to alterations	2.701	-0.087	0.130	0.219	-0.663**	0.135	31.075	4.112**	0.834
Contralateral to alterations	2.872	0.084	0.128	0.609	-0.273	0.252	25.244	-1.719	1.16
With other (non-cortical) forms of injury	2.752	-0.036	0.117	0.812	-0.070	0.123	27.938	0.975	0.754
Visual regions									
Healthy	1.960			0.442			6.633		
With bilateral alterations	1.286	-0.537	0.201	0.400	-0.042	0.058	5.493	-1.140	0.976
Ipsilateral to alterations	1.380	-0.580**	0.144	0.390	-0.052	0.032	8.388	1.755*	0.625
Contralateral to alterations	1.762	-0.198	0.167	0.461	0.019	0.033	5.834	-0.799	0.599
With other (non-cortical) forms of injury	1.664	-0.296	0.154	0.401	-0.041	0.030	6.497	-0.136	0.553
Vocabulary regions									
Healthy	2.962			0.449			7.893		
With bilateral alterations	2.545	-0.417	0.175	0.391	-0.058	0.046	8.010	0.117	0.641
Ipsilateral to alterations	2.836	-0.126	0.104	0.389	-0.060	0.024	8.694	0.801	0.356
Contralateral to alterations	3.051	0.089	0.004	0.396	-0.053	0.024	6.601	-1.292**	0.348
With other (non-cortical) forms of injury	2.977	0.015	0.090	0.404	-0.045	0.021	7.005	-0.888	0.307

Asterisked correlations were found to be statistically significant: * $P < 0.004$; ** $P < 0.0008$. Correlations in bold have a statistical significance of $P < 0.004$.

The differences between injured and healthy cortices are also shown along with the significance of the difference and the corresponding standard error (S.E.). For these models, cortical region, age, and gender are included as covariates, and patient ID was included as a mixed effect, taking into account that multiple observations per patient corresponding to different regions were used.

the cortical thickness measure, is an important cortical predictor of these outcomes. For vision, only curvature features were found to be strongly significant ($P < 0.005$), potentially a result of the thinner cortex and shallower sulci present in the posterior sections of the brain. Nevertheless, reductions in the curvature of the primary visual cortex, which again may be a reflection of reduced cortical volume in this area, were the most indicative predictor of patient vision.

Patient age was observed to be a significant predictor of all clinical outcomes ($P < 0.001$), indicating older children performed better at the different tasks. Patient gender was only significantly related to the BRIEF outcome, with girls performing better on the survey of executive functioning compared to boys. Despite age and gender being significant in this model, these findings did not generalize to the test set. MR scanner and sequence was not significant in any regression model, highlighting that differences in sources of data did not explain a significant portion of variance in the clinical outcomes.

DISCUSSION

Using the proposed cortical analysis pipeline, significant differences in cortical shape measures were identified between children with cortical alterations due to congenital brain injury that resulted in unilateral CP, and TDC, that were consistent with known developmental processes. It was observed that children with alterations within the hemisphere of injury had significantly reduced cortical thickness compared to the TDC. The reduced cortical thickness observed in motor and visual cortical regions may be the result of tissue loss due to injury, as well as the cortical alterations interrupting the regional increases in cortical density that occur during healthy development [Gogtay et al., 2004; Sowell et al., 2004]. This finding is consistent with the regional reduction in cortical thickness associated with schizophrenia [Goldman et al., 2009; Narr et al., 2005] and children with a very low birth weight [Martinussen et al., 2005], which are both conditions which bear some relationship to CP [Beaino et al., 2010; Wu

TABLE IV. Summary of the four trained, age-matched regression models, including the regression coefficients and standard errors of only the significant ($P < 0.005$) cortical regions retained from the data-driven variable selection, as well as patient age, gender, and scanner sequence for all models

Cortical region	Regression coefficient	Standard error	R-squared
AHA			
Primary somatosensory cortex - cortical thickness	-26.612***	6.445	
Primary somatosensory cortex - curvature	-14.169***	3.181	
Primary somatosensory cortex - sulcal depth	8.426***	1.931	
Posterior parietal cortex - cortical thickness	12.962**	4.543	
Age	2.009***	0.262	
Gender (Reference: male)	5.548	3.809	
Scanner & sequence (Reference: UQCPRRC)	-0.625	3.323	
R-squared of trained model			0.78***
Predicted r^2 on the test set			0.33**
BRIEF			
Age	0.851***	0.092	
Gender (Reference: male)	4.246**	1.388	
Scanner & sequence (Reference: UQCPRRC)	-0.818	1.337	
R-squared of trained model			0.89***
Predicted r^2 on the test set			0.03
TVPS			
Primary visual cortex - curvature	-4.621**	1.182	
Inferior temporal gyrus - curvature	5.065**	1.565	
Age	2.897***	0.512	
Gender (Reference: male)	1.311	3.999	
Scanner & sequence (Reference: UQCPRRC)	0.514	3.316	
R-squared of trained model			0.82***
Predicted r^2 on the test set			0.44**
VOC			
Inferior frontal gyrus - cortical thickness	-2.065**	0.565	
Age	2.017***	0.366	
Gender (Reference: male)	5.595	3.224	
Scanner & sequence (Reference: UQCPRRC)	0.890	2.784	
R-squared of trained model			0.90***
Predicted r^2 on the test set			0.39**

Asterisk regression coefficients were found to be statistically significant: ** $P < 0.01$, *** $P < 0.001$. Model correlations in bold have a statistical significance of $P < 0.0125$. Asterisk model and validation correlations were found to be statistically significant: ** $P < 0.0025$, *** $P < 0.00025$.

The multiple R-squared of the trained models and the squared correlation between the predictions of the trained model on the test set and the test set outcomes are provided, with the significance of these values compared against a Bonferroni corrected alpha value ($\alpha = 0.05/4, 0.0125$). However, the P -values of each feature were not corrected, and simply reflects the strength of that feature within the chosen model.

et al., 2013]. The ipsilateral cortical surface of children with unilateral injury was also found to have a reduced curvature compared to the TDC in motor, executive function and VOC regions. This reduction in curvature may be the result of injury interrupting the gyrification of the cortex that results in significant cortical expansion during healthy development [Hill et al., 2010], and is also consistent with findings of reduced gyrification in patients with schizophrenia [Sallet et al., 2003; White et al., 2003]. There were also significant increases in sulcal depth observed on the ipsilateral side of children with unilateral alterations compared to the TDC for motor, executive function and visual cortical regions. Although higher sulcal depth implies increased cortical surface area [Im et al., 2006], the

larger sulcal depth observed in most cases arises from reduced cortical migration due to dysplasia, or the presence of schizencephalic clefts. Observed differences between children with bilateral injury and the TDC were largely not significant, most likely due to the reduced number of children in our data with bilateral injury ($n = 7$).

Children with lesions that do not involve the cortex, which in our data were mostly periventricular white matter injury, were found to have significantly reduced cortical thickness in visual regions, and significant decreases in curvature and sulcal depth compared to the TDC for VOC regions. These findings all reflect a decrease in cortical volume, which is consistent with previous findings for

children with periventricular white matter injury [Inder et al., 1999]. Overall, the contralateral hemisphere of children with unilateral alterations was observed to be significantly thicker, smoother and have reduced sulcal depth compared to the TDC, for all functional cortical regions. The reduced curvature and sulcal depth also reflect a reduced cortical volume on the contralateral side. The increase in cortical thickness, however, may be the result of plasticity as a mechanisms to compensate for injury [He et al., 2007] on the side contralateral to injury, which is in line with previous findings [Kolb and Gibb, 2007; Krägeloh-Mann, 2004; Ward, 2005]. Overall, the measurable change in impaired cortical regions highlight the utility of the three shape measures used in this study to quantify cortical injury. There is value in characterizing shape using a number of different shape measures as opposed to a single cortical volume measure, as the combination of increased thickness and reduced cortical folding may counteract the measure of cortical volume, making it more difficult to discriminate between altered and preserved cortical volumes. Furthermore, these findings highlight the utility in the proposed method for characterizing cortical shape, as subtle cortical alterations arising from white matter injury, or subtle cortical alterations observed on the apparently non-injured hemisphere, which may not be clearly visible in the MRI, may still be quantified using this approach, and hence contribute to the clinical assessment of children with CP.

The constructed multivariable linear regression models show a moderate multiple R -squared, that is, goodness of fit, to all four clinical scores, with ranges between 0.78 and 0.90 in the training set. These measures represent the variance explained by the succinct set of shape descriptors from specific cortical regions, which included 5 or fewer regions for all models. Additionally, it should be noted that the proposed processing pipeline only quantifies one of the classes of injury present in children with CP. Other classes of injury, including white matter lesions or ventricular enlargement, would also contribute to observed patient outcome and would be expected to explain a unique portion of variance in the clinical scores. As expected, the multiple R -squared was reduced in the test set for all clinical scores, yet was still statistically significant for three of the four scores. The significant correlation on the independent test set highlights the ability of these models to generalize to unseen data and hence the general patient population. The BRIEF model of executive function was observed to not retain any cortical measures, and additionally did not perform well on test set validation. This may be a reflection of the typically wider cortical involvement and the important role of white matter for cognitive function, and the consequent limitation of only using a sparse set of cortical regions to model this function. We note that the specific cortical regions and shape measures retained by the data-driven variable selection were from within a set of cortical regions pre-selected

based on the literature. However, the final subset of variables included by the model, as shown in Table IV, as well as the sign of the regression coefficients, is a reflection of the patterns of injury present in our data, and should ideally be verified independently using another cohort of data. What these models demonstrate, however, is the ability to extract a succinct set of morphological biomarkers of cortical shape that are strongly linked to clinical outcome and generalize to unseen data.

A limitation of this work is that the proposed modification to the EM algorithm has only been applied to the segmentation of tissue types, with specific focus on improving cortical gray matter segmentations. The proposed modification was observed to mislabel partial volume voxels around the third ventricle. Furthermore, there are a number of technical challenges limiting the sensitivity of the cortical shape analyses, including subtle occipital sulci that may be incorrectly delineated by the segmentation approach, thus yielding inaccurate shape measures in this location, as well as the presence of dura mater not fully resolved from the brain surface. However, segmentation results were visually inspected and manually corrected where necessary. Other injury related to premature birth, but unrelated to CP, may also be detected by the proposed cortical analysis if this injury affects cortical morphology. Although many patterns of injury associated with CP are linked to preterm birth, this remains a limitation as these injuries unrelated to CP have altered cortical shape measures, and hence, the observed relationships between brain structure and function. A final limitation is that the predictive models did not include other non-cortical, primary and secondary injuries, which would contribute to reduced patient functional outcomes. Future work will investigate characterizing these forms of injury, and combining them into improved predictive models.

We note that this study does not account for potentially altered structure-function relationships caused by plasticity to compensate for the presence of injury [Carmichael, 2003; Thiel et al., 2001]. These mechanisms may cause shifts in where particular functions are performed, confounding the structure-function relationships of the brain which the linear models attempt to elucidate. This would consequently reduce the multiple R -squared of these models as it introduces variance in the clinical score potentially not explained by cortical shape in the chosen cortical regions. Furthermore, as the data used in this study are cross-sectional, the obtained results cannot be causally linked to plasticity-related mechanisms. Instead, longitudinal data are required in future studies to validate that such changes are indeed related to plasticity. Although VBM has frequently been used to identify longitudinal changes in gray matter density in the investigation of plasticity [Giuliani et al., 2011; Sterling et al., 2013; Thomas et al., 2009], the characterization of cortical shape analysis used in this study can complement such approaches by quantifying alternate cortical changes caused by plasticity,

such as the thickening of cortical gray matter or alternate changes in neuronal architecture [Feldman, 2009]. Combined with diffusion MRI, such a cortical analysis could help identify both the underlying white and gray matter mechanisms of plasticity.

CONCLUSIONS

A quantifiable and reliable relationship between regional brain structure and function appears to exist in our data, although a broader interpretation would require independent validation on another cohort. Significant decreases in cortical thickness, curvature, and significant increases in sulcal depth were observed within the injured hemisphere(s) of children with unilateral CP compared to children with healthy development. Significant increases in cortical thickness and significant decreases in curvature and sulcal depth were observed on the uninjured hemisphere of children with unilateral CP, highlighting potential compensatory mechanisms in these children. Using a succinct set of shape measures chosen from specific cortical regions, significant correlations with outcome were observed for three clinical functions, including motor function, visual function and communication, and performed well on test set validation. Care needs to be taken when segmenting the gray matter and labeling cortical substructures, specifically, atlas-based priors need adapting to deal with the problem of severe alterations that frequently occur in CP, which nullifies the efficacy of atlas priors. Automated approaches have the potential to quantify cortical shape automatically and predict patient outcomes. This has a potential role in tailoring treatment strategies for children with CP. In future, it will be of interest to examine how structure-function relationships vary longitudinally in individuals during development, and how plasticity impacts this relationship in instances of brain injury.

ACKNOWLEDGMENTS

The funding bodies have not contributed to the study design, the collection, management, analysis and interpretation of data, the writing of final reports or the decision to submit findings for publication. No other authors have potential conflicts of interest to declare.

REFERENCES

- Adalsteinsson D, Sethian JA (1995): A fast level set method for propagating interfaces. *J Comput Phys* 118:269–277.
- Ashburner J, Friston KJ (2000): Voxel-based morphometry. *The Methods Neuroimage* 821:805–821.
- Avants BB, Tustison NJ, Wu J, Cook PA, Gee JC (2011): An open source multivariate framework for n-tissue segmentation with evaluation on public data. *Neuroinformatics* 9:381–400.
- Barkovich AJ, Guerrini R, Kuzniecky RI, Jackson GD, Dobyns WB (2012): A developmental and genetic classification for malformations of cortical development: Update. 2012. *Brain* 135:1348–1369.
- Bax M, Tydeman C, Flodmark O (2006): Clinical and MRI correlates of cerebral palsy: The European Cerebral Palsy Study. *JAMA* 296:1602–1608.
- Beaino G, Khoshnood B, Kaminski M, Pierrat V, Marret S, Matis J, Ledésert B, Thiriez G, Fresson J, Rozé J-C, Zupan-Simunek V, Arnaud C, Burguet A, Larroque B, Bréart G, Ancel P-Y (2010): Predictors of cerebral palsy in very preterm infants: The EPI-PAGE prospective population-based cohort study. *Dev Med Child Neurol* 52:e119–e125.
- Boyd RN, Mitchell LE, James ST, Ziviani J, Sakzewski L, Smith A, Rose S, Cunningham R, Whittingham K, Ware RS, Comans TA, Scuffham PA (2013a): Move it to improve it (Mitii): Study protocol of a randomised controlled trial of a novel web-based multimodal training program for children and adolescents with cerebral palsy. *BMJ Open* 3:e002853.
- Boyd RN, Ziviani J, Sakzewski L, Miller L, Bowden J, Cunningham R, Ware R, Guzzetta A, Al Macdonell R, Jackson GD, Abbott DF, Rose S (2013b): COMBIT: Protocol of a randomised comparison trial of COMbined modified constraint induced movement therapy and bimanual intensive training with distributed model of standard upper limb rehabilitation in children with congenital hemiplegia. *BMC Neurol* 13:68.
- Buchsbaum BR, Hickock G, Humphries C (2001): Role of left posterior superior temporal gyrus in phonological processing for speech perception and production. *Cogn Sci* 25:663–678.
- Bush G, Luu P, Posner MI (2000): Cognitive and emotional influences in anterior cingulate cortex. *Trends Cogn Sci* 4:215–222.
- Cardoso MJ, Melbourne A, Kendall GS, Modat M, Haggmann CF, Robertson NJ, Marlow N, Ourselin S (2011): Adaptive neonate brain segmentation. In: *Medical Image Computing and Computer-Assisted Intervention–MICCAI 2011*. Springer Berlin Heidelberg. pp 378–386.
- Carmichael ST (2003): Plasticity of cortical projections after stroke. *Neuroscientist* 9:64–75.
- Chung MK, Worsley KJ, Robbins S, Paus TT, Taylor J, Giedd JN, Rapoport JL, Evans AC (2003): Deformation-based surface morphometry applied to gray matter deformation. *Neuroimage* 18:198–213.
- Cioni G, Sales B, Paolicelli P, Petacchi E, Scusa M, Canapicchi R (1999): MRI and clinical characteristics of children with hemiplegic cerebral palsy. *Neuropediatrics* 30:249–255.
- Collin G, Sporns O, Mandl RCW, van den Heuvel MP (2014): Structural and functional aspects relating to cost and benefit of rich club organization in the human cerebral cortex. *Cereb Cortex* 24:2258–2267.
- Danti S, Toschi N, Diciotti S, Tessa C, Poletti M, Del Dotto P, Lucetti C (2015): Cortical thickness in de novo patients with Parkinson disease and mild cognitive impairment with consideration of clinical phenotype and motor laterality. *Eur J Neurol* 22:1564–1572.
- Das SR, Avants BB, Grossman M, Gee JC (2009): Registration based cortical thickness measurement. *Neuroimage* 45:867–879.
- Dempster AP, Laird NM, Rubin DB (1977): Maximum likelihood from incomplete data via the EM algorithm. *J R Stat Soc Ser B* 39:1–38.
- Dierker DL, Feczko E, Pruett JR, Petersen SE, Schlaggar BL, Constantino JN, Harwell JW, Coalson TS, Van Essen DC (2015): Analysis of cortical shape in children with simplex autism. *Cereb Cortex* 25:1042–1051.
- Dubois J, Benders M, Borradori-Tolsa C, Cachia A, Lazeyras F, Leuchter RH-V, Sizonenko SV, Warfield SK, Mangin JF, Hüppi

- PS (2008a): Primary cortical folding in the human newborn: An early marker of later functional development. *Brain* 131: 2028–2041.
- Dubois J, Benders M, Cachia A, Lazeyras F, Leuchter RH-V, Sizonenko SV, Borradori-Tolsa C, Mangin JF, Hüppi PS (2008b): Mapping the early cortical folding process in the pre-term newborn brain. *Cereb Cortex* 18:1444–1454.
- Eskandar EN, Richmond BJ, Optican LM (1992): Role of inferior temporal neurons in visual memory. I. Temporal encoding of information about visual images, recalled images, and behavioral context. *J Neurophysiol* 68:1277–1295.
- van Essen DC (2005): A Population-Average, Landmark- and Surface-based (PALS) atlas of human cerebral cortex. *Neuroimage* 28:635–662.
- van Essen DC, Dierker D, Snyder AZ, Raichle ME, Reiss AL, Korenberg J (2006): Symmetry of cortical folding abnormalities in Williams Syndrome revealed by surface-based analyses. *J Neurosci* 26:5470–5483.
- Feldman DE (2009): Synaptic mechanisms for plasticity in neocortex. *Annu Rev Neurosci* 32:33–55.
- Feys H, Eyssen M, Jaspers E, Klingels K, Desloovere K, Molenaers G, De Cock P (2010): Relation between neuroradiological findings and upper limb function in hemiplegic cerebral palsy. *Eur J Paediatr Neurol* 14:169–177.
- Fiori S, Cioni G, Klingels K, Ortibus E, Van Gestel L, Rose S, Boyd RN, Feys H, Guzzetta A (2014): Reliability of a novel, semi-quantitative scale for classification of structural brain magnetic resonance imaging in children with cerebral palsy. *Dev Med Child Neurol* 56:839–845.
- Fiori S, Guzzetta A, Pannek K, Ware RS, Rossi G, Klingels K, Feys H, Coulthard A, Cioni G, Rose S, Boyd RN (2015): Validity of semi-quantitative scale for brain MRI in unilateral cerebral palsy due to periventricular white matter lesions: Relationship with hand sensorimotor function and structural connectivity. *NeuroImage Clin* 8:104–109.
- Frostig M, Lefever DW, Whittlesey JRB (1961): A developmental test of visual perception for evaluating normal and neurologically handicapped children. *Percept Mot Skills* 12:383–394.
- Geman S, Geman D (1984): Stochastic relaxation, Gibbs distributions, and the Bayesian Restoration of Images. *IEEE Trans Pattern Anal Mach Intell PAMI* 6:721–741.
- Giménez M, Junqué C, Narberhaus A, Bargalló N, Botet F, Mercader JM (2006): White matter volume and concentration reductions in adolescents with history of very preterm birth: A voxel-based morphometry study. *Neuroimage* 32:1485–1498.
- Gioia GA, Isquith PK, Retzlaff PD, Espy KA (2002): Confirmatory factor analysis of the Behavior Rating Inventory of Executive Function (BRIEF) in a clinical sample. *Child Neuropsychol* 8: 249–257.
- Giuliani NR, Drabant EM, Bhatnagar R, Gross JJ (2011): Emotion regulation and brain plasticity: Expressive suppression use predicts anterior insula volume. *Neuroimage* 58:10–15.
- Gogtay N, Giedd JN, Lusk L, Hayashi KM, Greenstein D, Vaituzis AC, Nugent TF, Herman DH, Clasen LS, Toga AW, Rapoport JL, Thompson PM (2004): Dynamic mapping of human cortical development during childhood through early adulthood. *Proc Natl Acad Sci USA* 101:8174–8179.
- Goldman AL, Pezawas L, Mattay VS, Fischl B, Verchinski BA, Chen Q, Weinberger DR, Meyer-Lindenberg A (2009): Widespread reductions of cortical thickness in schizophrenia and spectrum disorders and evidence of heritability. *Arch Gen Psychiatry* 66:467–477.
- Gorno-Tempini ML, Price CJ, Josephs O, Vandenberghe R, Cappa SF, Kapur N, Trackowiak RS (1998): The neural systems sustaining face and proper-name processing. *Brain* 121:2103–2118.
- Guerrini R, Dobyns WB (2014): Malformations of cortical development: Clinical features and genetic causes. *Lancet Neurol* 13: 710–726.
- Haidar H, Soul JS (2006): Measurement of cortical thickness in 3D brain MRI data: Validation of the Laplacian Method. *J Neuroimaging* 16:146–153.
- He Y, Chen ZJ, Evans AC (2007): Small-world anatomical networks in the human brain revealed by cortical thickness from MRI. *Cereb Cortex* 17:2407–2419.
- Hill J, Inder T, Neil J, Dierker D, Harwell J, Van Essen D (2010): Similar patterns of cortical expansion during human development and evolution. *Proc Natl Acad Sci USA* 107:13135–13140.
- Im K, Lee JM, Lyttelton O, Kim SH, Evans AC, Kim SI (2008): Brain size and cortical structure in the adult human brain. *Cereb Cortex* 18:2181–2191.
- Im K, Lee JM, Yoon U, Shin YW, Hong SB, Kim IY, Kwon JS, Kim SI (2006): Fractal dimension in human cortical surface: Multiple regression analysis with cortical thickness, sulcal depth, and folding area. *Hum Brain Mapp* 27:994–1003.
- Inder TE, Hüppi PS, Warfield S, Kikinis R, Zientara GP, Barnes PD, Jolesz F, Volpe JJ (1999): Periventricular white matter injury in the premature infant is followed by reduced cerebral cortical gray matter volume at term. *Ann Neurol* 46:755–760.
- Jäncke L, Peters M, Himmelbach M, Nösselt T, Shah J, Steinmetz H (2000): fMRI study of bimanual coordination. *Neuropsychologia* 38:164–174.
- Jones SE, Buchbinder BR, Aharon I (2000): Three-dimensional mapping of cortical thickness using Laplace’s equation. *Hum Brain Mapp* 11:12–32.
- Jouvent E, Mangin J-F, Porcher R, Viswanathan A, O’Sullivan M, Guichard J-P, Dichgans M, Bousser M-G, Chabriat H (2008): Cortical changes in cerebral small vessel diseases: A 3D MRI study of cortical morphology in CADASIL. *Brain* 131:2201–2208.
- Kelly CE, Chan L, Burnett AC, Lee KJ, Connelly A, Anderson PJ, Doyle LW, Cheong JLY, Thompson DK (2015): Brain structural and microstructural alterations associated with cerebral palsy and motor impairments in adolescents born extremely preterm and/or extremely low birthweight. *Dev Med Child Neurol* 57: 1168–1175.
- Kertzman C, Schwarz U, Zeffiro TA, Hallett M (1997): The role of posterior parietal cortex in visually guided reaching movements in humans. *Exp Brain Res* 114:170–183.
- Kolb B, Gibb R (2007): Brain plasticity and recovery from early cortical injury. *Dev Psychobiol* 49:107–118.
- Krögeloh-Mann I (2004): Imaging of early brain injury and cortical plasticity. *Exp Neurol* 190(Suppl):S84–S90.
- Krögeloh-Mann I, Horber V (2007): The role of magnetic resonance imaging in elucidating the pathogenesis of cerebral palsy: A systematic review. *Dev Med Child Neurol* 49:144–151.
- Krumlinde-Sundholm L, Holmefur M, Kottorp A, Eliasson AC (2007): The Assisting Hand Assessment: Current evidence of validity, reliability, and responsiveness to change. *Dev Med Child Neurol* 49:259–264.
- Lee TS, Mumford D, Romero R, Lamme VAF (1998): The role of the primary visual cortex in higher level vision. *Vision Res* 38: 2429–2454.
- Van Leemput K, Maes F, Vandermeulen D, Suetens P (1999): Automated model-based tissue classification of MR images of the brain. *IEEE Trans Med Imaging* 18:897–908.

- Leventer RJ, Guerrini R, Dobyns WB (2008): Malformations of cortical development and epilepsy. *Dialogues Clin Neurosci* 10:47–62.
- Li C, Huang R, Ding Z, Gatenby JC, Metaxas DN, Gore JC (2011): A level set method for image segmentation in the presence of intensity inhomogeneities with application to MRI. *IEEE Trans Image Process* 20:2007–2016.
- Lotze M, Montoya P, Erb M, Hülsmann E, Flor H, Klose U, Birbaumer N, Grodd W (1999): Activation of Cortical and Cerebellar Motor Areas during Executed and Imagined Hand Movements: An fMRI Study. *J Cogn Neurosci* 11:491–501.
- Luhmann HJ, Kilb W, Clusmann H (2014): Malformations of cortical development and neocortical focus. In: *Modern Concepts of Focal Epileptic Networks*. pp. 35–61.
- Lutz K, Koeneke S, Wüstenberg T, Jäncke L (2005): Asymmetry of cortical activation during maximum and convenient tapping speed. *Neurosci Lett* 373:61–66.
- Ma Y, Koyama MS, Milham MP, Castellanos FX, Quinn BT, Pardoe H, Wang X, Kuzniecky R, Devinsky O, Thesen T, Blackmon K (2015): Cortical thickness abnormalities associated with dyslexia, independent of remediation status. *NeuroImage Clin* 7:177–186.
- Makropoulos A, Ledig C, Aljabar P, Serag A, Hajnal JV, Edwards AD, Serena J, Counsell A, Rueckert D (2012): Automatic tissue and structural segmentation of neonatal brain MRI using expectation-maximization. In: *MICCAI Grand Challenge: Neonatal Brain Segmentation 2012 (NeoBrainS12)* 9.
- Martinussen M, Fischl B, Larsson HB, Skranes J, Kulseng S, Vangberg TR, Vik T, Brubakk A-M, Haraldseth O, Dale AM (2005): Cerebral cortex thickness in 15-year-old adolescents with low birth weight measured by an automated MRI-based method. *Brain* 128:2588–2596.
- Mechelli A, Humphreys GW, Mayall K, Olson A, Price CJ (2000): Differential effects of word length and visual contrast in the fusiform and lingual gyri during reading. *Proc Biol Sci* 267: 1909–1913.
- Moeskops P, Benders MJNL, Kersbergen KJ, Groenendaal F, de Vries LS, Viergever MA, Išgum I (2015): Development of cortical morphology evaluated with longitudinal MR brain images of preterm infants. *PLoS One* 10:e0131552.
- Mumford D, Shah J (1989): Optimal approximations by piecewise smooth functions and associated variational problems. *Commun Pure Appl Math* 42:577–685.
- Murgasova M, Dyet L, Edwards D, Rutherford M, Hajnal JV, Rueckert D (2006): Segmentation of brain MRI in young children. In: *Medical Image Computing and Computer-Assisted Intervention—MICCAI 2006*. Springer Berlin Heidelberg. pp 687–694.
- Narr KL, Bilder RM, Toga AW, Woods RP, Rex DE, Szaszko PR, Robinson D, Sevy S, Gunduz-Bruce H, Wang Y-P, DeLuca H, Thompson PM (2005): Mapping cortical thickness and gray matter concentration in first episode schizophrenia. *Cereb Cortex* 15:708–719.
- Nordahl CW, Dierker D, Mostafavi I, Schumann CM, Rivera SM, Amaral DG, Van Essen DC (2007): Cortical folding abnormalities in autism revealed by surface-based morphometry. *J Neurosci* 27:11725–11735.
- Northam GB, Liégeois F, Chong WK, Wyatt JS, Baldeweg T (2011): Total brain white matter is a major determinant of IQ in adolescents born preterm. *Ann Neurol* 69:702–711.
- Osher S, Sethian JA (1988): Fronts propagating with curvature-dependent speed: Algorithms based on Hamilton-Jacobi formulations. *J Comput Phys* 79:12–49.
- Oskoui M, Coutinho F, Dykeman J, Jetté N, Pringsheim T (2013): An update on the prevalence of cerebral palsy: A systematic review and meta-analysis. *Dev Med Child Neurol* 55:509–519.
- Pagnozzi AM, Dowson N, Bourgeat P, Bradley AP, Boyd RN, Rose S (2015): Expectation-maximization with image-weighted Markov random fields to handle severe pathology. In: *Digital Image Computing: Techniques and Applications (DICTA)*. Adelaide, SA. IEEE. pp 1–6.
- Papadelis C, Ahtam B, Nazarova M, Nimec D, Snyder B, Grant PE, Okada Y (2014): Cortical somatosensory reorganization in children with spastic cerebral palsy: A multimodal neuroimaging study. *Front Hum Neurosci* 8:725.
- Papoutsis M, de Zwart JA, Jansma JM, Pickering MJ, Bednar JA, Horwitz B (2009): From phonemes to articulatory codes: An fMRI study of the role of Broca's area in speech production. *Cereb Cortex* 19:2156–2165.
- Park HJ, Lee JD, Kim EY, Park B, Oh MK, Lee SC, Kim JJ (2009): Morphological alterations in the congenital blind based on the analysis of cortical thickness and surface area. *Neuroimage* 47: 98–106.
- Perona P, Malik J (1990): Scale-space and edge detection using anisotropic diffusion. *IEEE Trans Pattern Anal Mach Intell* 12: 629–639.
- Rimol LM, Nesvåg R, Hagler DJ, Bergmann O, Fennema-Notestine C, Hartberg CB, Haukvik UK, Lange E, Pung CJ, Server A, Melle I, Andreassen OA, Agartz I, Dale AM (2012): Cortical volume, surface area, and thickness in schizophrenia and bipolar disorder. *Biol Psychiatry* 71:552–560.
- Rivet-Hénault D, Dowson N, Greer PB, Fripp J, Dowling J (2015): Robust inverse-consistent affine CT-MR registration in MRI-assisted and MRI-alone prostate radiation therapy. *Med Image Anal* 23:56–69.
- Rodriguez-Carranza CE, Mukherjee P, Vigneron D, Barkovich J, Studholme C (2008): A framework for in-vivo quantification of regional brain folding in premature neonates. *Neuroimage* 41: 462–478.
- Rose S, Guzzetta A, Pannek K, Boyd R (2011): MRI structural connectivity, disruption of primary sensorimotor pathways, and hand function in cerebral palsy. *Brain Connect* 1:309–316.
- Sallet PC, Elkins H, Alves TM, Oliveira JR, Sassi E, de Castro CC, Busatto GF, Gattaz WF (2003): Reduced cortical folding in schizophrenia: An MRI morphometric study. *Am J Psychiatry* 160:1606–1613.
- Scarpazza C, Tognin S, Frisciata S, Sartori G, Mechelli A (2015): False positive rates in Voxel-based Morphometry studies of the human brain: Should we be worried? *Neurosci Biobehav Rev* 52:49–55.
- Schaer M, Cuadra MB, Tamarit L, Lazeyras F, Eliez S, Thiran J-P (2008): A surface-based approach to quantify local cortical gyrification. *IEEE Trans Med Imaging* 27:161–170.
- Sethian JA (1996): A fast marching level set method for monotonically advancing fronts. *Proc Natl Acad Sci USA* 93:1591–1595.
- Shaw P, Greenstein D, Lerch J, Clasen L, Lenroot R, Gogtay N, Evans A, Rapoport J, Giedd J (2006): Intellectual ability and cortical development in children and adolescents. *Nature* 440: 676–679.
- Shibasaki H, Sadato N, Lyshkow H, Yonekura Y, Honda M, Nagamine T, Suwazono S, Magata Y, Ikeda A, Miyazaki M, Fukuyama H, Asato R, Konishi J (1993): Both primary motor cortex and supplementary motor area play an important role in complex finger movement. *Brain* 116:1387–1398.

- Shollenbarger SG, Price J, Wieser J, Lisdahl K (2015): Impact of cannabis use on prefrontal and parietal cortex gyrification and surface area in adolescents and emerging adults. *Dev Cogn Neurosci* 16:46–53.
- Shroeder W, Martin K, Lorensen B (2006): The Visualization Toolkit, 4th ed. Kitware. Available at: <http://vtk.org>. [Accessed 11 May 2016]
- Soria-Pastor S, Gimenez M, Narberhaus A, Falcon C, Botet F, Bargallo N, Mercader JM, Junque C (2008): Patterns of cerebral white matter damage and cognitive impairment in adolescents born very preterm. *Int J Dev Neurosci* 26:647–654.
- Sowell ER, Thompson PM, Leonard CM, Welcome SE, Kan E, Toga AW (2004): Longitudinal mapping of cortical thickness and brain growth in normal children. *J Neurosci* 24:8223–8231.
- Sridharan D, Levitin DJ, Menon V (2008): A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks. *Proc Natl Acad Sci USA* 105:12569–12574.
- Sterling C, Taub E, Davis D, Rickards T, Gauthier LV, Griffin A, Uswatte G (2013): Structural neuroplastic change after constraint-induced movement therapy in children with cerebral palsy. *Pediatrics* 131:e1664–e1669.
- Sugiura N (2007): Further analysts of the data by akaike' s information criterion and the finite corrections. *Commun Stat - Theory Methods* 7:13–26.
- The R Development Core Team (2008): R: A language and environment for statistical computing. R Foundation for Statistical Computing. Vienna, Austria. Available at: <http://www.r-project.org>. [Accessed 27 April 2016]
- Thiel A, Herholz K, Koyuncu A, Ghaemi M, Kracht LW, Habedank B, Heiss WD (2001): Plasticity of language networks in patients with brain tumors: A positron emission tomography activation study. *Ann Neurol* 50:620–629.
- Thomas AG, Marrett S, Saad ZS, Ruff DA, Martin A, Bandettini PA (2009): Functional but not structural changes associated with learning: An exploration of longitudinal voxel-based morphometry (VBM). *Neuroimage* 48:117–125.
- Tustison NJ, Avants BB, Cook PA, Zheng Y, Egan A, Yushkevich PA, Gee JC (2010): N4ITK: Improved N3 bias correction. *IEEE Trans Med Imaging* 29:1310–1320.
- Ward NS (2005): Neural plasticity and recovery of function. *Prog Brain Res* 150:527–535.
- Wechsler D (1967): Wechsler Preschool and Primary Scale of Intelligence. New York: Psychological Corporation.
- Wells WM, Grimson WL, Kikinis R, Jolesz FA (1996): Adaptive segmentation of MRI data. *IEEE Trans Med Imaging* 15:429–442.
- White T, Andreasen NC, Nopoulos P, Magnotta V (2003): Gyrification abnormalities in childhood- and adolescent-onset schizophrenia. *Biol Psychiatry* 54:418–426.
- Wu CS, Pedersen LH, Miller JE, Sun Y, Streja E, Uldall P, Olsen J (2013): Risk of cerebral palsy and childhood epilepsy related to infections before or during pregnancy. *PLoS One* 8:e57552.
- Yezzi A (1998): Modified curvature motion for image smoothing and enhancement. *IEEE Trans Image Process* 7:345–352.
- Zhang Y, Brady M, Smith S (2001): Segmentation of brain MR images through a hidden Markov random field model and the expectation-maximization algorithm. *IEEE Trans Med Imaging* 20:45–57.
- Zhang Y, Inder TE, Neil JJ, Dierker DL, Alexopoulos D, Anderson PJ, Van Essen DC (2015): Cortical structural abnormalities in very preterm children at 7 years of age. *Neuroimage* 109:469–479.