Quantitative analysis of the brain anatomy in cerebral palsy

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***Introduction*:** Cerebral palsy (CP) is the most common chronic motor disorder of childhood, with devastating health, psychological and economic consequences both at the individual and social levels. Despite the high prevalence, the outcomes and functional capabilities of CP patients cannot be reliably predicted. Our hypothesis is that neuroanatomic features present in CP patients hold important functional information, and clues to classification and prognostic determination. MRI, which often reveals anatomic abnormalities, even as early as the newborn stage, could offer a unique, non-invasive opportunity to predict neurological deficits and has the potential to enable the development of early intervention strategies for therapy[1,2]. The first step for the neuroanatomic characterization of CP patients is to provide a comprehensive quantitative analysis of brain anatomy. Therefore, our aim is to apply state-of-the-art technologies to analyze brain anatomy in CP patients based on two technical focal points: diffusion tensor imaging (DTI) to reveal detailed white matter (WM) anatomy; and an automated 3D whole brain segmentation based on our brain atlas and state-of-the-art non-linear normalization techniques (large-deformation diffeomorphic metric mapping, LDDMM) to a global and automated analysis of the whole brain.

***Methods*:** Thirteen CP patients (ages ranging from 4 to 13 years old, mean 7 years old) were included in this study. Images were acquired using a 1.5T scanner with b0=700s/mm^2. DTI images were calculated using the software DTIStudio[3]. Nonlinear transformations between each subject's data and a single subject atlas were obtained using the software DiffeoMap[4] using fractional anisotropy (FA) and b0 based (dual contrast) LDDMM. This atlas contains detailed parcellation of 176 white and gray matter structures[5]. By warping the atlas to each subject original space we measured parameters such as volume, FA, apparent coefficient diffusion (ADC), parallel and perpendicular diffusivities. The transformation-based segmentation was examined for accuracy by comparing the results with manual segmentation. To ensure the accuracy, we tested our method in patients with different types of large anatomic deformations. We extracted representative 2D slices and seven structures were manually delineated using ROIeditor[4]. Reliability analyses were performed to estimate kappa statistics. For demonstration purposes, we applied this atlas, enriched by normal development data (MRI/DTI database acquired under the "Human Brain Project", available for download at www.mristudio.org), processed with the same method, for the quantitative detection of abnormalities in these CP patients.

***Results and Discussion*:** Figure 1 is a demonstration of the normalization process and accuracy. Note that structures that are not accurately registered after the linear transformation (indicated by arrows) are well-registered after LDDMM, even in a CP brain with severe atrophy. The reliability of the segmentation measured by Kappa analysis was 0.82, which means "almost perfect" agreement based on Landis and Koch criteria. This result is similar to that obtained by the segmentation of normal adults and Alzheimer's subjects (kappa=0.81 and 0.82, respectively)[6]. With this technique, the quantitative evaluation can be extended to the entire brain, creating detailed reports that capture the individual anatomic features. For each patient, each region from more than 100 can be characterized in terms of volume, T2, FA, ADC, and eigenvalues, etc.; absolutely or as the deviation from a given group average. This concept is demonstrated in Fig. 2. Maps can be created for each patient (Fig. 3), allowing quantitative evaluation of the anatomical abnormalities at a glance. This regional quantitative analysis also provides valuable data for group comparisons, mutivariate analysis and functional correlation.

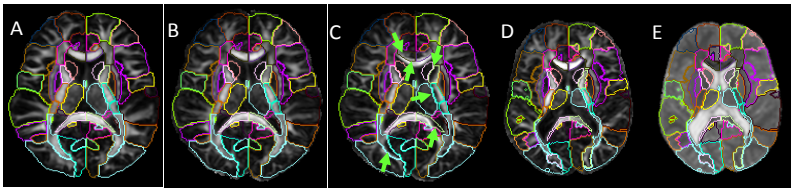
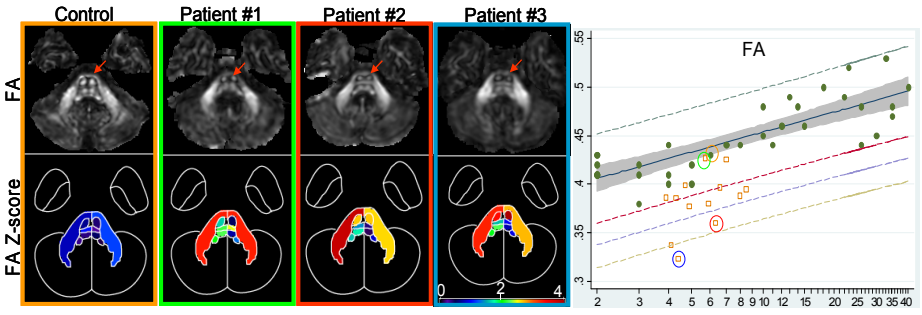


Figure 1: Demonstration of the normalization process and accuracy. (A) The atlas used as the normalization target image. (B) A normal adult subject image after LDDMM normalization. (C) The same subject warped to the atlas using the linear normalization. (D) and (E) The atlas warped by LDDMM and overlaid on FA and B0 images of a typical CP patient with large ventricles and WM atrophy. Note the high accuracy despite the severe anatomical deformation

Figure 2: FA maps of one control and three CP patients and the FA Z-score maps that show the degree of deviation from control values. The graph contains the actual data from the left corticospinal tract (arrows) in the enriched atlas (green dots) and the FA values from 13 CP patients (yellow squares). The linear regression of the FA vs. age in normal subjects, is shown by a blue line. Shaded area is 95% confidence interval of the curve and dashed lines are the prediction interval for z-scores of +/-2; -3 and -4. The color surrounding the images and circle colors in the scatter plots identify the subjects.



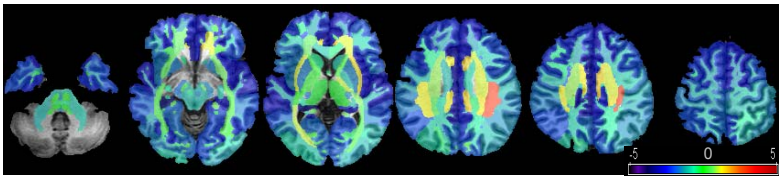


Figure 3: Volume Z-score map. Note the predominant atrophy of cortex and peripheral white matter over deep white matter in this subject

Conclusion: Based on DTI, atlas-based analysis and highly nonlinear normalization methods, we are able to provide a comprehensive quantitative analyses of brain anatomy on CP patients. The techniques developed and the potential results can provide a framework to determine the impact of various neuroanatomic features on motor and cognitive brain functions. This is the first step toward the evaluation of prognostic efficacy and design of specific therapy strategies.

***Bibliography*:** [1]Nagae LM, et al. *AJNR Am J Neuroradiol.* 2007 Aug; 28(7): 1213-1222; [2]Hoon Jr Ah, et al. *Dev Med Child Neurol.* 2009; 51(9):697-704; [3]Jiang, H. and Mori, S.; Johns Hopkins University, www.MriStudio.org; [4] Li, X.; Jiang, H. and Mori, S.; Johns Hopkins University, www.MriStudio.org; [5]Oishi K, et al. *Neuroimage.* 2008 Nov 15; 43(3): 447-457; [6]Oishi K, et al. *Neuroimage.* 2009 Jun; 46(2): 486-499.

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