# Analysis of Hippocampal Shape in Children Using a Surface-to-Centerline Distance Method and Template-Based Surface and Volumetric Non-Rigid Registration Methods

**M. Lin[1], K. Head[2], C. Buss[2], T. Muftuler[1], E. P. Davis[1], C. A. Sandman[2], O. Nalcioglu[1], and M-Y. L. Su[1]**

[1]Tu & Yuen Center for Functional Onco-Imaging and Department of Radiological Sciences, University of California, Irvine, CA, United States, [2]Department of Psychiatry & Human Behavior, University of California, Irvine, CA, United States

***Background and purpose:***

The hippocampus is the most irregular sub-cortical structure in the brain, which makes shape analysis difficult. Several methods have been developed to compare the cross-sectional differences between groups, or longitudinal differences in the same subject group over time. There are two major approaches - one by mapping the distance from the surface contour to the centerline of the hippocampus onto a 2-D grid map, and the other by comparing the extent of transformation for each individual hippocampus to match to a standard template using non-rigid coregistration algorithms. The non-rigid transformation algorithms can be based on surface nodes, e.g. the robust point mapping (RPM) method, or using volumetric based registration (e.g. the Demons algorithm). We analyzed a dataset collected from children 6-9 years of age. The differences in shape based on age and sex were analyzed using three methods, the surface-to-centerline distance mapping and template-based registration using RPM and Demons, and the results of these different methods were compared.

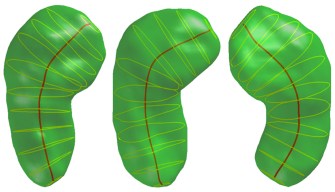

**Fig.1: Example of hippocampal centerline & cross-sections.**

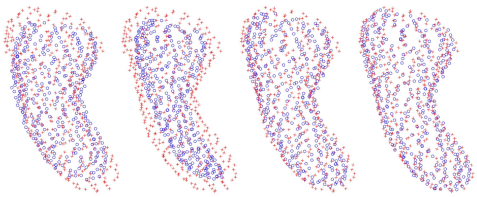

**Fig.2: The RPM surface point based registration at 0, 4, 20 and 40 iterations. The blue color shows the template.**

***Methods:***

Forty-eight T1 images from children between the ages of 6-9 years (22 males/26 females) were analyzed. The MRI scans were acquired using a Phillips Achieva 3.0T scanner. For age comparison, the subjects were divided into two groups based on the median age: 74-86 months (N=24) vs. 89-113 months (N=24). Pre-processing of the raw high resolution T1 images included correction for image intensity non-uniformities (Sled, Zijdenbos, & Evans, 1998) and linear stereotaxic transformation (Collins, Neelin, Peters, & Evans, 1994) into coordinates based on the Talairach atlas (Talairach & Tournoux, 1988).Volume analyses of the hippocampus were performed using the interactive software package DISPLAY developed at the Brain Imaging Center of the Montreal Neurological Institute and a standardized segmentation protocol was applied to outline the anatomical boundaries of the hippocampus (Pruessner et al., 2000). The operator was trained to reach a certain consistency level before proceeding to analyze these cases. The outlined hippocampi on the ICBM152 template were used for the shape analysis to control for differences in brain size. The outlined hippocampus was further separated into three segments, head, body, and tail, (Pruessner et al. 2000). The surface-to-centerline distance mapping method originally was developed by the UCLA group [1]. The centerline of the hippocampus was first extracted using a level-set based algorithm [2] and the whole hippocampus was divided into 150 sections, by uniformly segmenting each section perpendicular to the centerline with equal thickness. **Figure 1** shows 3 cases with different hippocampal shape, the centerline and the cross-sections used for distance analysis. The shapes at head, body, and tail are apparently different. On each cross-section, 100 surface points were uniformly assigned along the boundary. In total, there are 15,000 digitized grid-points on the hippocampal surface. The distance from each surface point to the centerline was calculated and recorded into a 150×100 matrix for age and sex comparison. Two non-rigid registration algorithms using the surface grid point based RPM and volume-based Demons were applied to register each hippocampus to the template. Since the UCLA method equally divides each hippocampus into 150 segments, the difference in the z-direction has been normalized. Therefore, a similar normalization along the z-direction was done as a pre-processing step before the non-rigid registration was applied. **Figure 2** illustrates the iteration steps of RPM in one case as an example. The template was shrunk in-ward first (seen at the 4th iteration) and then expanded to match the individual hippocampus. When completed, the transformations along x, y, and z directions were obtained at each of the 15,000 surface grid points. However, it is not meaningful to compare these x, y, or z displacements individually. The displacement was calculated as a magnitude, and the directionality (shrinking or expanding to match template) was determined using the centerline as the reference. Demons algorithm is volumetric based. The displacement is determined by Jacobian, where >1 indicates expansion and <1 indicates shrinkage. The p-value maps and displacement difference maps between children >88 months and <88 months, and between male and female, were analyzed using these three methods and compared.

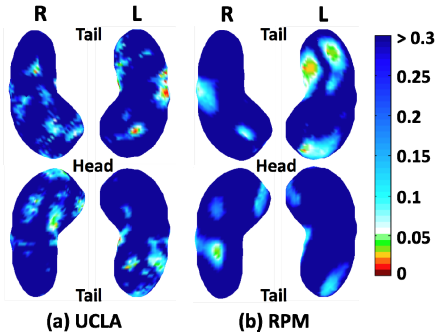


**Fig.3: Color-coded significance maps for age comparison. Green color represents the significant level at p < 0.05.**

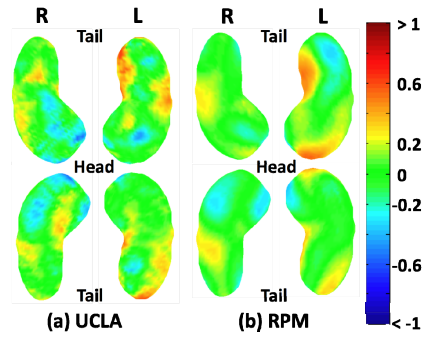


**Fig.4: Color-coded age-comparison difference maps. Warm color means shrinkage, and cold color means expansion in children > 88 months old compared to kids < 88 months old.**

***Results:***

The manual volumetric measurement results from the left hippocampus are listed in Table 1. These were relative volumes measured on the ICBM152 template. A high deviation was found, suggesting a high individual variability. There was no significant difference between the two age groups or between the two sex groups in the whole hippocampus, nor in the head, body, or tail segment. **Figure 3** shows the p-value maps between 2 age groups analyzed using the UCLA method, and the non-rigid RPM registration method. **Figure 4** shows the displacement maps. In **Figure 3** scattered regions showing a significant difference with $p < 0.05$ are noted, but in **Figure 4** it can be seen that some of these regions show warm color (i.e. children <88 months have greater distance from the centerline than children >88 months), and some show cold color (children <88 months have smaller distance from the centerline than children >88 months). The averaged difference is within one pixel, which is 1 mm. The comparison between the male and female groups also did not find significant differences within a big cluster of pixels. In **Figure 4**, it can be seen that the patterns in the difference maps analyzed using the UCLA method and the RPM method were similar. A warm color region was found in the tail of left hippocampus using both methods, and in **Table 1** the tail volume of children <88 months is slightly larger than that of children >88 months, but this difference was not statistically significant. The p-value maps and Jacobian maps analyzed using the Demons algorithm showed slightly different patterns, also no significant group differences.

**Table 1: Volume measure of left hippocampus (mean ± stdev)**

| | < 88 mo | > 88 mo | Female | Male |
|---|---|---|---|---|
| **Whole** | 3.99 ± 0.35 | 3.88 ± 0.38 | 3.94 ± 0.24 | 3.92 ± 0.48 |
| **Head** | 2.46 ± 0.24 | 2.47 ± 0.37 | 2.42 ± 0.26 | 2.51 ± 0.36 |
| **Body** | 0.98 ± 0.25 | 0.92 ± 0.22 | 0.99 ± 0.26 | 0.90 ± 0.20 |
| **Tail** | 0.55 ± 0.12 | 0.49 ± 0.13 | 0.54 ± 0.12 | 0.51 ± 0.14 |

***Discussion:***

The most useful application of hippocampal shape analysis is for assessment of atrophy in elderly patients with mild cognitive impairment and Alzheimer's disease. However, so far no method is considered robust and reliable for assessment of the atrophy progression pattern. In this study we used 3 algorithm-based methods to investigate the difference in the shape of the hippocampus in children, with carefully executed manual drawing results for comparison. The obtained results were consistent and indicated that the size and shape of the hippocampus within this age group does not show a strong age dependence or sex difference. The methods may be applied for assessing other factors that might influence brain/hippocampal development without concern about age and sex of subjects.

***Reference:*** [1] Thompson et al. Neuro Image 2004;22:1754-1766. [2] Telea et al. ACM Int Conf Proc 2003;40:185-194.

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