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# Developmental changes in hippocampal shape among preadolescent children

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ABSTRACT

It is known that the largest developmental changes in the hippocampus take place during the prenatal period and during the first two years of postnatal life. Few studies have been conducted to address the normal developmental trajectory of the hippocampus during childhood. In this study shape analysis was applied to study the normal developing hippocampus in a group of 103 typically developing 6- to 10-year-old preadolescent children. The individual brain was normalized to a template, and then the hippocampus was manually segmented and further divided into the head, body, and tail sub-regions. Three different methods were applied for hippocampal shape analysis: radial distance mapping, surface-based template registration using the robust point matching (RPM) algorithm, and volume-based template registration using the Demons algorithm. All three methods show that the older children have bilateral expanded head segments compared to the younger children. The results analyzed based on radial distance to the centerline were consistent with those analyzed using template-based registration methods. In analyses stratified by sex, it was found that the age-associated anatomical changes were similar in boys and girls, but the age-association was strongest in girls. Total hippocampal volume and sub-regional volumes analyzed using manual segmentation did not show a significant age-association. Our results suggest that shape analysis is sensitive to detect sub-regional differences that are not revealed in volumetric analysis. The three methods presented in this study may be applied in future studies to investigate the normal developmental trajectory of the hippocampus in children. They may be further applied to detect early deviations from the normal developmental trajectory in young children for evaluating susceptibility for psychopathological disorders involving hippocampus.



## 1. Introduction

The hippocampus is a brain structure prominently involved in learning and memory. Many studies have evaluated hippocampal changes during the course of normal and pathological aging, fewer studies however, have addressed its normal developmental trajectory. The human hippocampus is identifiable between 6 and 7 gestational weeks (Humphrey, 1964) and by birth the basic neuroanatomical architecture of these regions is present (Arnold and Trojanowski, 1996a,b). Rapid hippocampal development continues over the first two postnatal years (Utsunomiya et al., 1999; Knickmeyer et al., 2008), which is reflected in gross anatomical changes. The changes after two years age have not been systematically investigated. Several studies reported developmental changes in the hippocampus from childhood to young adulthood. In general, age-associated increases in hippocampal size were observed

*Abbreviations:* AD, Alzheimer's disease; CT, computed tomography; FDR, false discovery rate; ICBM, International Consortium for Brain Mapping; IR-SPGR, inversion-recovery spoiled gradient recalled acquisition; LDDMM, Large Deformation Diffeomorphic Metric Mapping; MNI, Montreal Neurological Institute; MRI, magnetic resonance imaging; PET, Positron emission tomography; RDD, radial distance difference; RDM, radial distance mapping; ROI, region of interest; RPM, robust point matching; TE, echo time; TFE, turbo field echo; TI, inversion time; TR, repetition time.

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through young adulthood (Ostby et al., 2009) with some evidence for sex-specific developmental patterns (Giedd et al., 1996; Suzuki et al., 2005).

The hippocampus is the most irregularly shaped sub-cortical structure in the brain, and sub-regional changes are more likely to be detected using analyses that test for shape rather than volume differences. The only study that investigated longitudinal changes in hippocampal shape in 4- to 25-year-old subjects concluded that the structural development of the human hippocampus is remarkably heterogeneous (Gogtay et al., 2006). In standardized space, overall hippocampal volume did not change between 4 and 25 years age but there were significant changes in hippocampal shape.

In the present study we applied three shape analysis methods to investigate hippocampal shape in a group of 6- to 10-years old children. The methods that have been applied for shape analysis are based on analyzing the boundary of the segmented hippocampus (Qiu et al., 2008, 2009; Thompson et al., 2004). Two common approaches using structure-modeling and template-based registration have been reported. The structure-modeling approach analyzes the medial representation of each subject's individual hippocampus and compares the between-group differences (Styner and Gerig, 2001). The radial distance mapping method developed by Thompson et al. (2004) is the most widely applied structure-modeling method. It maps the distance of each surface boundary point to the centerline of the hippocampus as an index of "thickness". The template-based registration approach compares the extent of transformation for each individual hippocampus to match a standard template using registration algorithms. In the present study, two different registration algorithms, the robust point matching (RPM, Chui and Rangarajan, 2003) and the Demons (Thirion, 1998), were used.

The purpose of this study was to determine age-related patterns of hippocampal shape in a cohort of typically developing children using three different methods (radial distance mapping, RPM registration and Demons registration). Results achieved by different analytical methods were compared and in addition, the volumes of the manually outlined hippocampus (total as well as head, body and tail segments) were computed and compared to the results obtained using algorithm-based shape analysis methods. Besides the main analysis on the complete group of children, separate analyses stratified by sex were performed to investigate whether age-associated anatomical changes differed in boys and girls.

## 2. Materials and methods

### 2.1. Subjects and MRI protocol

This study was approved by the Institutional Review Board of the University of California, Irvine. The parents/guardians gave written informed consent and the children gave informed assent. The T1-weighted structural MRI scans were acquired from 103 children between the ages of 6–10 years, mean age: $7.3 \pm 0.9$ years (or, 74–119 months old, mean $87 \pm 11$ months old). The subjects consisted of 50 male and 53 female right-handed children. The age (in months) was used as a continuous variable in regression analysis.

All children were healthy and considered as typically developing. All of them had a stable neonatal course and did not have any known congenital, chromosomal, or genetic anomalies (e.g., trisomy 21) or neonatal illness (e.g., respiratory distress, mechanical ventilation over 48 h or sepsis). They had no ultrasound scanning evidence of intraventricular hemorrhage (IVH), periventricular leukomalacia, and/or low-pressure ventriculomegaly in the newborn period. At the time of enrollment, there were no emotional or physical conditions reported in a structured interview using the MacArthur Health and Behavior Questionnaire (Armstrong and Goldstein, 2003). In addition, the MR images were reviewed by a neuroradiologist and reported as normal without any structural abnormality.

Each child underwent an MRI scan conducted on a 3.0 Tesla Philips Achieva system. To minimize head motion, padding was placed around the head. Ear protection was given to all children. To further increase compliance and reduce motion, children were fitted with headphones and allowed to watch a movie of their choice while in the scanner. Following the scanner calibration and pilot scans, a high resolution T1 anatomical scan was acquired in the sagittal plane with 1 $mm^3$ isotropic voxel dimensions. A 3D Inversion-Recovery Spoiled Gradient Recalled Acquisition (IR-SPGR) sequence with the following parameters was applied: repetition rate (TR) = 11 ms, echo time (TE) = 3.3 ms, Inversion Time (TI) = 1100 ms, turbo field echo factor (TFE) = 192, Number of slices: 150, no SENSE acceleration, Flip angle = 18°. Acquisition time for this protocol was 7 min. Variations of these parameters were tested on volunteers to obtain an optimal set that provided the best gray-white matter contrast, sharpness and high resolution while ensuring that there were no discernible artifacts. The purpose was to keep the total acquisition time at a tolerable length for children.

### 2.2. Manual segmentation of the hippocampus

Pre-processing of the anatomic T1 images included correction for image intensity non-uniformities (Sled et al., 1998) and linear stereotaxic transformation (Collins et al., 1994) into coordinates based on the Talairach atlas (Talairach and 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 (MNI). All images were registered to the ICBM 152 model brain using the Affine transformation with 12 parameters (Mazziotta et al., 2001), and a standardized segmentation protocol was applied to outline the anatomical boundaries of the hippocampus (Pruessner et al., 2000). This procedure corrects for differences in head size (Collins et al., 1994). The outlined hippocampus was further separated into three segments: head, body, and tail (Pruessner et al., 2000). During late childhood (ages 6–10) the brain size reached approximately 85–95% of the adult brain. Therefore, the techniques and the template developed for the adult brain could be used for this population and the errors caused by using an adult brain template should be negligible.

All brains were segmented by the same operator (KH), who was trained to reach a certain consistency level with an experienced rater (with intraclass correlation coefficient > 0.90) before proceeding with segmentation analyses. The operator's intra-rater reliability was 0.95 (estimate based on 30 brains that were segmented repeatedly by the operator). The segmented hippocampus on the ICBM 152 template was used in the subsequent shape analysis. Inter subject variability in brain size/geometry was quite substantial. If this was not taken into consideration by normalizing to a template, the hippocampal shape analysis results would be profoundly affected by the size and shape of the brain.

### 2.3. Radial distance mapping (RDM) shape analysis method

Radial distance mapping or RDM (Thompson et al., 2004) considers the hippocampus as a 3D tube-like surface so the hippocampal shape change can be quantified by calculating the Euclidean distance between surface points and the centerline. To establish the consistent one-to-one correspondence of surface points among all subjects, a fixed grid structure is imposed on the surface of each individual subject's hippocampus. At each surface point of this grid structure, the distance from this point to the centerline of the hippocampus is calculated, and this radial distance is used as an index of "thickness" for evaluating shape variation between two groups.

First the centerline of the hippocampus was extracted using a level-set based algorithm (Telsa and Vilanova, 2003). In order to avoid the branching problem at the beginning and ending sides of the hippocampus, the starting and ending points of the centerline was manually selected based on anatomical features. Then the Bezier curve fitting is applied to fit the control points generated by the centerline extraction algorithm. The hippocampus was then divided into 150 cross-sections along the longitudinal direction. This was done by dividing the centerline into 150 equally spaced points, and an orthogonal plane at each point was defined. The intersection of the hippocampal surface with each orthogonal plane forms the level curve on that section. Fig. 1 shows 6 cases with different hippocampal shapes, as well as the centerline and the cross-sections used for radial distance mapping. The longitudinal length, and the shapes of head, body, and tail are apparently different. On each cross-section, 100 surface points were uniformly assigned along the boundary. The starting point was determined as the outer boundary on the Y–Z projection view shown in Fig. 1. For each subject, the hippocampus was represented by a matrix of $150 \times 100$ grid points. The radial distance was obtained by calculating the distance from each surface point to the centerline and recorded into a $150 \times 100$ matrix for group comparison. A template was then generated by averaging the radial distance at each digitized grid point from all 103 subjects.

### 2.4. Surface-based robust point matching (RPM) registration method

Robust point matching (RPM) (Chui et al., 2001; Chui and Rangarajan, 2003) converts feature-based registration to a non-rigid point matching problem, aiming to find an optimal transformation to match the deforming set to the reference set. The sizes of the two point sets do not need to be the same, and one-to-one correspondence between the points is not mandatory. Fuzzy correspondence (Wells, 1997), which allows a point in the deforming set $\{x_i,\ i = 1, 2, \ldots, I\}$ to correspond to more than one point in the reference set $\{y_j, j = 1, 2, \ldots, J\}$, is applied to estimate the correspondence of the two point sets during the iteration process. Given the fuzzy correspondence $M$ with $\sum_{i=1}^{I+1} m_{ij} = 1$ and $\sum_{j=1}^{J+1} m_{ij} = 1$ and the