Association between Mother's Depression and Children's Hippocampal Shape Analyzed Using Non-Rigid Registration

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Background and purpose:

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 in children. The human hippocampus is identifiable between 6-7 gestational weeks [1] and by birth the basic neuro-anatomical architecture of these regions is present [2-3]. Hippocampal development continues rapidly over the first two postnatal years [4-5], and becomes slower from childhood to young adulthood. Because fetal brain development proceeds at an extremely rapid pace, early life experiences have the potential to alter the trajectory of neurodevelopment, which may increase susceptibility for developmental and neuropsychiatric disorders. There is evidence that prenatal maternal stress, anxiety and depression may influence neurodevelopmental outcomes. We have collected an MRI dataset from a cohort of children 6-10 years old with well-characterized information from their mothers during and after pregnancy. In a previous study we have shown that the volume of the hippocampi in these children did not vary substantially with age, but the shape analysis was more sensitive to detect small subregional changes [6]. There are two major approaches for shape analysis- 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. In this study, we analyzed the association of hippocampal volume and shape with respect to mother's depression measured at different times during pregnancy and the post-partum depression. Shape analysis was performed using methods as previously reported in [6].

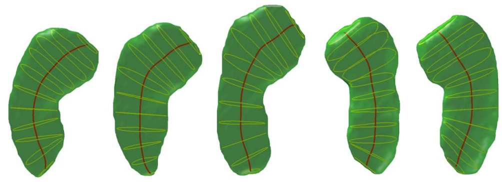

Fig.1: Example of 5 hippocampi showing various shapes. The centerline & cross-sections are used for normalization.

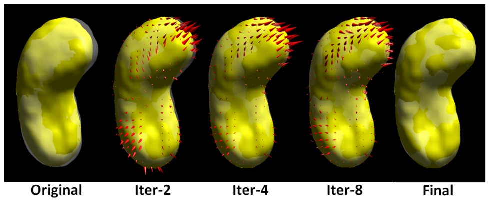

Fig.2: Example of non-registration using Demons algorithm. The solid volume is the moving source (template), the transparent volume is the target (subject). The subject has an expanded head.

Methods:

The structural MRI scans were acquired from 103 children between the ages of 6-10 years (74-119 months, mean 7.3±0.9 y/o), 50 males and 53 females. The hippocampus was manually outlined on the ICBM152 template using a protocol developed by the Montreal Neurologic Institute. Each hippocampus was further divided into head, body, and tail segments by the operator to measure these sub-regional volumes. As shown in **Fig. 1**, there is a high heterogeneity, and they need to be normalized for shape analysis. Based on the centerline the whole hippocampus was divided into 150 sections, and then the radial distance at each surface grid point was measured for analysis. For registration-based methods, a template was generated using the average of all subjects. 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. An example using Demons algorithm is shown in **Fig. 2**. Based on the deformation matrix, the radial distance difference (RDD) from the template at each surface point can be measured. RDD>0 means the subject has an expanded contour relative to the template, and RDD<0 means contracted contour compared to the template. Prenatal depression (at 15, 19, 25, 31, and 37 weeks during pregnancy) and post-partum depression were evaluated using the short form of the Center for Epidemiological Studies Depression (CESD) Inventory (Santor and Coyne 1997), and a higher score indicates a more severe impairment.

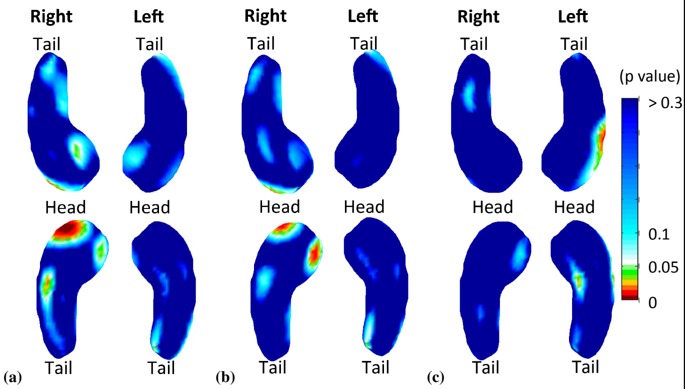

Fig.3: Color-coded significance maps for association with mother's CESD depression scores: (a) measured at 25 weeks; (b) averaged score during pregnancy; and (c) post-partum score. Green color represents the significant level at p < 0.05. The hippocampus was cut longitudinally and open to show top view and bottom view. It can be seen that the shape of the head segment in the right hippocampus was associated with mother's depression during pregnancy; and the association with the post-partum depression is seen in the body segment of the left hippocampus.

Results:

Fig. 3 shows the RDD significance map with respect to Mother's depression measured at 25 weeks(a), the averaged prenatal depression score (b), and the post-partum depression measured after delivery(c). It is interesting to find different areas involved: the head segment of the right hippocampus was associated with prenatal depression; and the body segment of the left hippocampus was associated with the post-partum depression. A region of interest (ROI) of 7.1 mm^2 was placed over the significant area, and the RDD value for each subject was extracted for further analysis, as shown in **Fig. 4**. The RDD was negatively correlated with maternal depression, indicating that when the mother has a more severe depression the child is more likely to have contracted hippocampus relative to the template. The results in males and females were similar. The association p-values of the sub-regional volumes and the ROI-RDD with 25-weeks depression score are listed in **Table 1**. None of the volumetric measurements is significantly correlated with the depression score. Similarly, no volume parameter was associated with the averaged prenatal or the post-partum depression score.

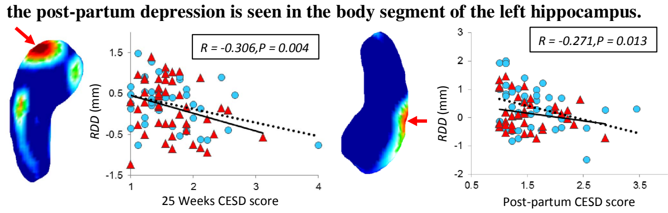

Fig.4: The analysis by placing a 7.1 mm^2 ROI on the significant region (arrows). The association of children's radial distance difference (RDD) with mother's prenatal CSED score measured at 25 weeks(left) and the post-partum CESD score(right) are shown. More severe depression is associated with greater contracted hippocampus. Results are similar in males (blue circles) and females (red triangles).

Table 1: The association p-values of the volumetric and shape ROI parameters with the 25-weeks CESD depression score in the whole group and in the respective male and female groups.

	All subjects	Males	Females
Right Whole vol	0.390	0.519	0.566
Right Head vol	0.793	0.360	0.412
Right Body vol	0.621	0.613	0.236
Right Tail vol	0.590	0.334	0.704
Shape ROI RDD	**0.004**	**0.031**	**0.052**
Left Whole vol	0.421	0.629	0.527
Left Head vol	0.518	0.269	0.859
Left Body vol	0.787	0.636	0.908
Left Tail vol	0.356	0.442	0.624

Discussion:

A growing number of prospective studies demonstrate that prenatal psychological distress is associated with cognitive impairments of the offspring during infancy, childhood, and adolescence. Also many studies have demonstrated the strong influence of parental care and environment on the development of children. In this exploratory study we demonstrated that the shape analysis, not volumetric analysis, can reveal different areas in the hippocampus that are associated with mother's depression during and after pregnancy, respectively. These results suggest that shape analysis may provide a sensitive tool for detecting subtle subregional changes that are not noticeable in volumes.

References: [1] Humphrey. Trans Am Neurol Assoc 1964; 89:207-209. [2, 3] Arnold & Trojanowski. J Comp Neurol 1996; 367:274-292(PartI); 367:293-307(II). [4] Utsunomiya et al. AJNR 1999; 20:717-723. [5] Knickmeyer et al. J Neurosci 2008; 28:12176-12182. [6] Lin et al. Int J Dev Neurosci. 2013; 31(7):473-481.