Age associated changes in subcortical structures in preadolescent children

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Introduction:

There is evidence that abnormal brain development during childhood is a risk factor for various cognitive and psychiatric disorders. Although cortical development from childhood until early adulthood has been studied by several groups [1,2,3], there is very limited normative data available on subcortical structures of typically developing children, especially within the narrow preadolescent age range. We analyzed high resolution MRI images from 103 normally developing preadolescent children to study age associated differences in major subcortical structures.

Methods:

A normative sample of children between the ages of 6 and 10 years were recruited for this study. The study was approved by the IRB of the university and written consents were obtained from the parents. T1 weighted scans were acquired in a 3T Philips Achieva system using an MPRAGE pulse sequence (FOV=240×240mm^2, 1mm^3 isotropic voxel dimensions, 150 slices, TR=11ms, TE=3.3ms, inversion pulse delay =1100ms, flip angle=18^0, no averages and no SENSE acceleration). MRI scans were reviewed by a radiologist and subjects with an evidence of intraventricular hemorrhage, periventricular leukomalacia, and/or low-pressure ventriculomegaly were excluded from analysis. Volumetric segmentation of subcortical structures was performed with both the Freesurfer and FSL software packages (http://surfer.nmr.mgh.harvard.edu/ and http://www.fmrib.ox.ac.uk/fsl/, respectively), which compute accurate registration of brain images onto a stereotactic image and segment out subcortical structures precisely for each subject. Since the software suites use different algorithms for registration and segmentation, we used the resulting segmentation for further analysis if the outcome of the two algorithms were in good agreement. If the difference in volumes of a structure calculated by FSL and FreeSurfer was less than 10%, the data was used. When we inspected images for which FSL and Freesurfer segmentation produced significantly different results, we observed that the segmentation failed in children who had very small ventricles. This strategy lead to exclusion of 23 out of 126 images. The remaining 103 images were analyzed using FSL's FIRST software, which produces surface based models of subcortical structures and provides tools to analyze group differences in shapes and sizes of these structures [4].

We first analyzed the age-associated differences in volumes of subcortical structures using regression analysis in which intracranial volume (ICV) was entered as a nuisance variable (ICV was not significantly associated with child age r()=0.098, p=0.14). In this analysis only the volume of the thalami showed strong correlation with age (p=0.001 for left and p=0.06 for right thalamus). In the next step, we analyzed changes in the shape of each structure with age using FSL/FIRST subcortical shape analysis software. In order to study age-related differences in local shapes, the global scaling is removed so that variations in overall size of each structure are regressed out. We also repeated the analysis without removing the global scaling but using ICV as a covariate, instead. We had observed that ICV strongly correlated with the total volume of each structure, so it was a good surrogate to account for variations in total volume across subjects. Both approaches yielded similar results.

Results:

Fig.1 shows the thalamus, caudate and hippocampus from different views. Colors represent statistical significance of age-associated shape differences in each structure. Red represents areas with no statistically significant change in shape; green-blue represents strong correlation with age. Significant age related changes in thalamic development were observed. Further, the strongest associations with age were seen in the medial dorsal thalamus on the left side

Discussion and Conclusion:

Thalamus is a relay center between a variety of subcortical areas and the cerebral cortex. In our study, medial dorsal thalamus showed the largest association with age. This region of the thalamus receives inputs from the prefrontal cortex and the limbic system and relays them to the prefrontal association cortex. This circuitry plays a crucial role in attention, planning, organization, abstract thinking, multi-tasking and active memory. Kanemura et al [5] demonstrated that there was a relatively slow increase in prefrontal lobe size until age 8 and then this growth accelerated significantly until age 14. Our findings indicate that the thalamic nuclei, which have efferent and afferent connections to the prefrontal cortex, might follow a similar developmental trajectory. Between 6 and 10 years of age larger developmental changes were seen in the left thalamus as compared to the right thalamus. Dermon and Barbas [6] studied thalamocortical connections and showed that several subnuclei in the medial dorsal in the thalamus have connections to both ipsilateral and contralateral prefrontal cortices. The implications of this hemispheric difference in typically developing children in terms of cognitive development should be explored further.

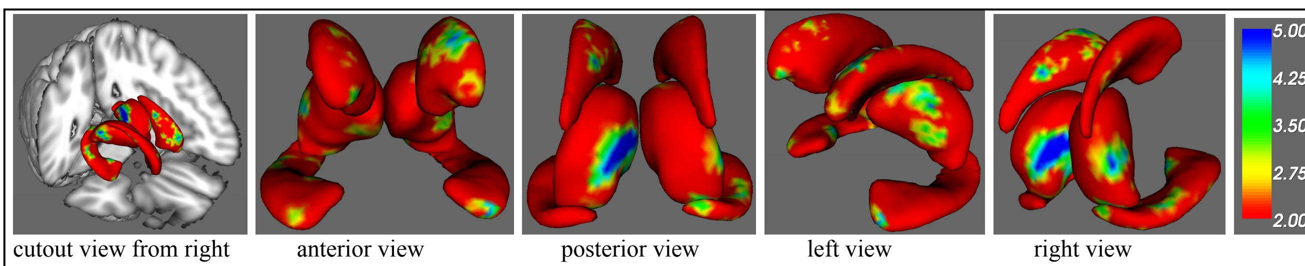

Fig.1. Age associated differences in the caudate, thalamus and hippocampus. Color represents t-scores of age-associated differences, as shown in the colorbar. For example, blue represents regions where significant differences with age were seen (t=5, p<0.001).

References: [1] *Gogtay et al PNAS 2004 101:8174-79*; [2] *Giedd et al JAACP 2009, 48:465-70*; [3] *Sowell et al J. Neuroscience, 2004, 24:8223-31*; [4] *Patenaude B., Ph.D Thesis. University of Oxford. 2007.* [5] *Kanemura et al Brain & Development 25:195–199, 2003*; [6] *Dermona and Barbas, J. Comparative Neurology, 344:508-531, 1994.*

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