Regional Variation in Human Thalamic Maturation Revealed by Diffusion Tensor Imaging of Premature Newborns

A. R. deIpolyi[1], P. Mukherjee[2,3], S. Veeraraghavan[2], J. I. Berman[2,3], R. G. Henry[2,3], D. B. Vigneron[2,3], A. J. Barkovich[2,4]

[1]Neuroscience Graduate Program, University of California, San Francisco, San Francisco, CA, United States, [2]Department of Radiology, University of California, San Francisco, San Francisco, CA, United States, [3]Program in Bioengineering, University of California, San Francisco, San Francisco, CA, United States, [4]Departments of Neurology and Pediatrics, University of California, San Francisco, San Francisco, CA, United States

Introduction: Diffusion tensor imaging (DTI) is sensitive to microstructural changes in gray and white matter during human brain development. Although often considered a gray matter structure, the thalamus also contains much white matter. Prior DTI studies have shown that its mean diffusivity decreases and its diffusion anisotropy increases with age during human brain maturation [1-3]. During development, the various thalamic nuclei become interconnected with different regions of the cortex. A recent DTI investigation of preterm development has provided evidence of hierarchical maturation of cortical areas, with earlier development of primary sensorimotor cortex than higher-order association areas [4]. In the present study, we hypothesized that DTI may also show regional variation in human thalamic maturation, as each thalamic nucleus develops in synchrony with the cortical area to which it has reciprocal connectivity. We focused on three of the largest thalamic nuclei: the mediodorsal nucleus (MD), which has diffuse projections to the frontal cortex; the ventrolateral complex (VC), which connects with the primary sensory and motor areas of the perirolandic cortex; and the pulvinar nucleus, which projects to the parieto-occipital cortex. Since the pulvinar is an especially large nucleus with many subdivisions, we examined the medial pulvinar (MP) separately from the lateral pulvinar (LP), for a total of 4 thalamic regions. Furthermore, we hypothesized that a first-order relay nuclear complex such as VC will develop earlier than higher-order nuclei such as MD or the pulvinar nucleus, in keeping with the hierarchical maturation observed with DTI in the preterm cerebral cortex.

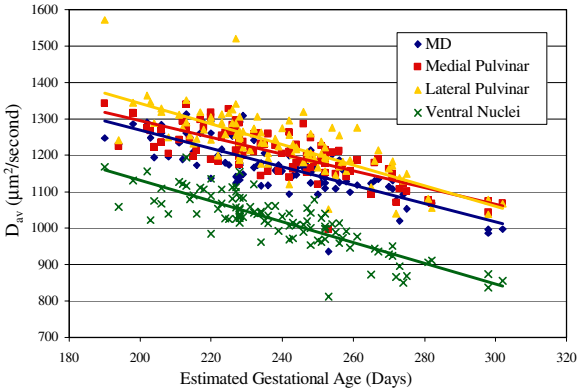
Methods: Using an MR-compatible incubator with a high-sensitivity neonatal head-coil, we performed diffusion tensor MRI at 1.5T in 66 premature newborns born at 24-34 weeks estimated gestational age (EGA) and imaged at 27-43 weeks EGA, with 2 serial exams in 34 of the infants and 3 serial scans in one of the infants, for a total of 102 exams. The voxel resolution of the whole-brain axial DTI images was 1.4 x 1.4 x 3.0 mm, using a single-shot EPI sequence with 6 gradient directions, b=0 and 600s/mm^2, TE=99.5ms, TR=7s, and 3 repetitions [4]. We placed all 4 thalamic regions of interest on T2-weighted images on a single axial slice in which the VC was readily identified by its T2-weighted hypointensity. The LP was identified as the region just posterolateral to the VC; the MP was identified just medial to the LP; the MD was identified as the region anteromedial to the VC. The regions of interest were all 6 voxels in size, and were placed in both the left and right thalamus. We calculated the mean diffusivity (D_{av}), fractional anisotropy (FA), and eigenvalues (λ_1, λ_2, λ_3) in all regions, then averaged the values from each side for each nucleus.

Results: We found that for all 4 thalamic regions, D_{av} correlated negatively with EGA at the time of scan (MD: R^2=0.61, p<0.0001; MP: R^2=0.59, p<0.0001; LP: R^2=0.57, p<0.0001; VC: R^2=0.70, p<0.0001). FA in all regions except the MP correlated positively but more weakly with EGA at the time of scan (MD: R^2=0.32, p<0.0001; MP: R^2=0.008, p=0.45; LP: R^2=0.18, p<0.001; VC: R^2=0.07, p=0.006). Like D_{av}, all 3 eigenvalues decreased with age in all 4 thalamic regions. Interestingly, we observed systematic differences in the DTI parameters across all 4 studied thalamic regions. For D_{av}, a one-way ANOVA with region as a factor and EGA at the time of scan as a covariate revealed main effects of both region (p=0.01) and age (p<0.0001) on diffusivity. Fisher's protected least significant difference (PLSD) post-hoc tests revealed that the D_{av} of each region differed significantly from all others, with the VC consistently exhibiting the lowest D_{av} and LP showing the highest D_{av} at any given EGA (see Figure and Table). A one-way ANOVA for FA with region as a factor and EGA at the time of scan as a covariate revealed a main effect of EGA (p<0.0001) and a significant interaction between region and EGA (p=0.008). Fisher's PLSD post-hoc tests revealed that the FA of each thalamic region differed significantly from all others, with VC having the highest FA at any given EGA. Analyses of the 3 eigenvalues revealed patterns similar to D_{av}, in that they all decreased with EGA and the VC had consistently lower eigenvalues than all other regions at any given EGA, most markedly for λ_2 and λ_3.

Discussion: Consistent with previous reports, we found that mean diffusivity decreases and anisotropy increases in the developing thalamus [1-3]. Furthermore, we demonstrate that DTI reveals regional variation of human thalamic maturation in premature newborns. In particular, we provide support for our hypothesis that the thalamus also exhibits the hierarchical pattern of maturation previously shown by DTI of the preterm neocortex [4], with lower D_{av} and higher FA at any given age in first-order relay nuclei such as the VC compared to higher-order nuclei such as MD or the pulvinar nucleus. This implies earlier development of VC. We also demonstrate that systematic differences in development can exist even within a large, functionally heterogeneous thalamic nucleus by comparing the medial and lateral parts of the pulvinar nucleus. To our knowledge, this is the first report of regional variation in thalamic maturation using DTI, and this investigation emphasizes the sensitivity of DTI to the microstructural changes of human brain development.

References:
1. Mukherjee et al. Radiology 2001; 221:349-58.
2. Mukherjee et al. AJNR 2002; 23:1445-56.
3. Snook et al. Neuroimage 2005; 26:1164-73.
4. deIpolyi et al. Neuroimage 2005; 27:579-86.

Diffusivity in Different Thalamic Regions



	D_{av} in μm^2/s Mean (SD)	FA Mean (SD)
MD	1170.2 (73.1)	0.159 (0.032)
MP	1207.2 (68.4)	0.140 (0.035)
LP	1235.1 (87.3)	0.187 (0.041)
VC	1022.7 (78.9)	0.233 (0.041)