Journal Club

Editor's Note: These short, critical reviews of recent papers in the *Journal*, written exclusively by graduate students or postdoctoral fellows, are intended to summarize the important findings of the paper and provide additional insight and commentary. For more information on the format and purpose of the Journal Club, please see http://www.jneurosci.org/misc/ifa_features.shtml.

Diffusion Tensor Imaging of Cortical Surface Development

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Review of Huang et al. (http://www.jneurosci.org/cgi/content/full/28/6/1427)

Diffusion tensor imaging (DTI) is a robust magnetic resonance imaging (MRI) method that expands the capabilities of structural MRI beyond volumetric and morphometric investigations toward the characterization of tissue microstructure. The three-dimensional diffusion of water in brain tissue can be imaged using DTI and quantified by DTI indices. Fractional anisotropy (FA) is a commonly reported DTI index that quantifies the magnitude of asymmetric diffusion, or anisotropy, in tissue. This value is high in tissues with directionally oriented structural characteristics, such as the myelinated axons in white matter. The magnitude of diffusion perpendicular to and along the axis of anisotropic tissue can be further characterized using DTI indices of perpendicular and parallel diffusivity, respectively. When used in combination with surface visualization, DTI measures provide a powerful tool to map structural characteristics across the entire cortex. Although DTI has gained substantial traction in human research, the application of DTI to animal studies is less common but growing.

In a recent publication of *The Journal of Neuroscience*, Huang et al. (2008) reported that FA could be used to quantitatively map spatiotemporal patterns of cortical development in the rat brain. Although well investigated at the cellular level, cortical development during the early postnatal period remains largely unmapped across all cortical regions in the whole brain because of the practical limitations of histological methods. To characterize whole-brain structural development, high-resolution DTI images of *ex vivo* rat brains were acquired at five time points during postnatal development [postnatal day 0 (P0), P3, P7, P11, and P19]. Using FA to index the degree of cortical columnar organization at single measurement points, the authors identified an age-dependent decrease in FA with regional specificity in the cortex [Huang et al. (2008), their Fig. 4 (http://www.jneurosci.org/cgi/content/full/28/6/1427/F4)]. In addition to single-point analysis, maps of FA values across the entire brain surface were generated at each developmental time point to visualize cortical maturation dynamics [Huang et al. (2008), their Fig. 3 (http://www.jneurosci.org/cgi/content/full/28/6/1427/F3)]. The observed patterns indicated that FA reduced during early cortical maturation in an anterior-to-posterior manner.

Although the results of this paper were generally sound, the methods used to determine measurement location could have led to inaccuracies. The authors recognized the importance of using a region-selection method that reduced point misplacement and aligned the data from different developmental time points by selecting FA map slices from the same anatomical locations. This slice selection was accomplished by proportional distance scaling along the anterior–posterior axis [Huang et al. (2008), their Fig. 1 (http://www.jneurosci.org/cgi/content/full/28/6/1427/F1)]. Cortical measurement points were then defined for these slices by conserving the angle from midline of an initial point set created using an atlas overlay on the P19 brain [Huang et al. (2008), their Fig. 2 (http://www.jneurosci.org/cgi/content/full/28/6/1427/F2)]. For each measurement point, the inner, middle, and outer layers of cortex were also defined. This alignment method greatly reduced the potential for user bias associated with region placement in developing brains but may not have accounted for measurement point misplacement resulting from anatomical changes in brain shape and local growth during development. A different or complementary registration approach, such as surface-based methods (Kroenke et al., 2007) or the use of a developmental rat brain atlas, may have provided more accurate measurement point placement and validation of the current technique. Measurement location for the FA map relied on the inward shrinkage of a cortical surface mesh by a

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constant number of two voxels. Given the variability in cortical thickness across different regions, perhaps mesh placement based on proportion of cortical thickness would have been more appropriate. The findings were nonetheless robust in describing a spreading reduction in FA across the outer layers of the cortex.

Another potential problem for interpretation was the choice of statistical measure used to characterize regional patterns of cortical maturation. Huang et al. (2008) tested the null hypothesis that the FA developmental time courses were comparable among cortices based on their subregion averages and found significant differences based on the Kruskal–Wallis statistic. Because 16 cortical measures were taken from a given rat, the six mean cortical FA measures derived from them were likely interdependent and therefore in violation of the independence assumption of the Kruskal–Wallis test. A preferable statistical approach may be to block on the rat factor and use the Friedman test, a nonparametric repeated-measures ANOVA of ranks (Friedman, 1937). Furthermore, interregional differences in FA maturation were identified by thresholding with a Bonferroni correction for seven comparisons [Huang et al. (2008), their Table 2 (http://www.jneurosci.org/cgi/content/full/28/6/1427/T2)]. However, if the authors would have used a more conservative Bonferroni correction for all 15 reported comparisons ($0.05/15 = 0.003$) rather than for the seven cortical regions compared, the cortical FA development would not have been significantly different among brain regions. Additional studies with a larger sample size ($n > 2$) at each time point will be necessary to determine the significance of regional differences in cortical FA maturation trajectories.

The results of this study indicate a general trend of FA reduction during postnatal maturation in outer cortical layers and further suggest the existence of four distinct regional maturation patterns (prelimbic and cingulate, insula, somatosensory and motor, and auditory and visual). Based on previous histological literature, the authors proposed that this change in FA is reflective of dendritic and axonal growth, interneuron infiltration, and the disappearance of radial glia. It is also possible that oligodendrocyte myelinogenesis and myelination of cortical axons contribute to the observed FA loss and that the variation in cytoarchitecture across cortical regions contributed to the heterogeneous FA profiles. The reported parallel and perpendicular diffusivity [Huang et al. (2008), their Fig. 5 (http://www.jneurosci.org/cgi/content/full/28/6/1427/F5)] may reflect different cellular correlates (Budde et al., 2007). Therefore, it would be interesting to know the structural substrates for selective loss of parallel diffusivity in this study.

The DTI analysis of postnatal cortical maturation presented by Huang et al. (2008) advances both the understanding of spatiotemporal dynamics in developing cortex and the contribution of DTI methods to basic neuroscience research. Despite the caveats in anatomical localization, statistics, and developmental interpretation that we identified in this paper, the future possibilities for work of this nature are promising and may include investigations of different regions, such as the hippocampus or cerebellum, which is known to undergo both radial and tangential development (Goldowitz and Hamre, 1998). The development of DTI quantification and visualization tools, such as described by Huang et al. (2008), and the extension of DTI to *in vivo* animal imaging have the potential to advance numerous areas of neuroscience research, including whole-brain development, disease models, and network plasticity.

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