A quantitative diffusion tensor magnetic resonance histology atlas of rat brain development

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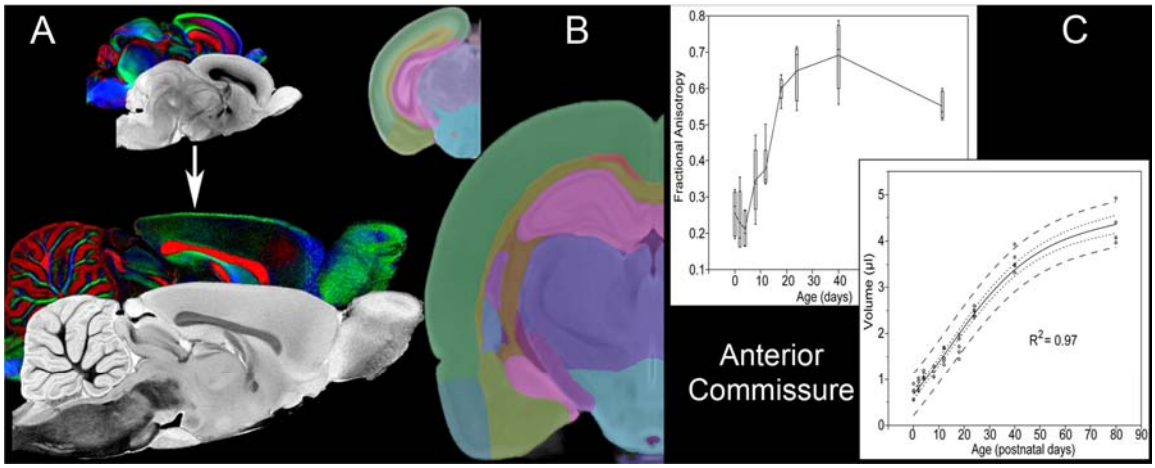
Target audience
This study is intended for researchers studying small animal models of neurodevelopmental disease.

Purpose
Interest has grown in the role of postnatal brain development in the etiology of several neurologic diseases including schizophrenia, attention deficit hyperactivity disorder, and autism spectrum disorders[1,2]. In addition, the developing brain is exposed to a large range of environmental and pharmacologic toxicants that have as yet unknown affects on neurodevelopment. The rat is a powerful model system for studying neurodevelopment and neurotoxicology. However, the complex spatiotemporal changes that occur during rat neurodevelopment remain to be elucidated. This work establishes the first diffusion tensor magnetic resonance histology (MRH) atlas of the developing rat brain. The atlas establishes a timeline of normal morphometric and diffusion tensor changes throughout neurodevelopment and represents a quantitative database of rat neurodevelopment for characterizing rat models of human neurologic disease.

Methods
We performed ex-vivo brain imaging on 5 rats at each of 9 time points between birth and adulthood (postnatal day [p]0, p2, p4, p8, p12, p18, p24, p40, and p80) for a total of 45 subjects. All animals were normal males from liters of 10-12 (average=11) and had a body weight within one standard deviation of mean weight for age. Animals were perfusion fixed with formalin and a gadolinium-based MRI contrast agent (gadoteridol) to enhance MR signal. The imaging protocol included 3D gradient recalled echo (GRE) images at 25-μm isotropic resolution (TR=50 ms, TE=8.3 ms, α=60°, NEX=2) and diffusion tensor imaging (DTI) at 50-μm isotropic resolution (TR=100 ms, TE=16.2 ms, NEX=1, directions=6, b=1500 mm^2/s). At each time point, image data were spatially normalized using non-linear image registration and manually segmented into 26 developmentally defined brain regions. We analyzed regional changes in DTI parameters and volume throughout postnatal development in each of the 26 manually defined brain segments.

Results
The rat neurodevelopmental atlas is multidimensional, consisting of the 3 spatial dimensions, the 4th dimension of time (neurodevelopment), and a 5th dimension of image contrast**.** Each time point comprises 8 distinct MR contrasts, 6 of which are quantitative DTI metrics. (A) mid-sagittal slices of the GRE and directionally-encoded fractional anisotropy color map for both the p0 and p80 timepoint show the time span encompassed by the atlas. (B) coronal slices of the GRE image for p0 and p80 timepoints with color overlays that highlight the 26 brain segments that have been delineated at each time point. (C) the quantitative microstructural information (i.e. fractional anisotropy, upper-left) and morphometric (i.e. volume, bottom-right) data that the atlas provides for each brain segment throughout postnatal neurodevelopment (anterior commissure data shown here).



Discussion
The work presented here is the first MRH atlas of rat brain development. We highlight the quantitative nature of our atlas because we believe this is one of the most important advantages of MRH-based atlasing. We have demonstrated the use of the atlas as a database for quantitative morphometry and DTI tissue microstructural metrics throughout normal postnatal neurodevelopment.

Conclusions
This atlas provides researchers the foundation for using MRI to identify subtle deviations from normal neurodevelopment in rat models of neurologic disease.

References
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