Not All Brain Regions Are Created Equal: Insights From Longitudinal Imaging of Early Postnatal Mouse Brain Development.

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Target Audience and Purpose: Scientists studying brain development, especially those using mutant and transgenic mice as a model of human neurodevelopmental disorders, as well as all those using Mn-enhanced MRI (MEMRI), will benefit from this work. Lacking among the currently available set of MRI techniques has been an imaging approach that allows for 3D noninvasive, longitudinal studies of brain development in individual mice. The goal of this project was to develop and optimize a robust MEMRI imaging approach and to create a comprehensive database of normal mouse brain development to serve as a reference for future studies of normal brain development, and neurodevelopmental defects in mutant and transgenic mouse models.

Methods: Two groups of mice (N=6/group) were imaged on odd or even days between postnatal days (P)1 and 11. Data was collected on a 7T Biospec imaging system (Bruker BioSpin MRI), using actively shielded gradients (BGA9-S, 750mT/m gradient strength; Bruker) and a 25-mm (ID) quadrature, transmit / receive Litzcage coil (Doty Scientific). Three-dimensional (3D) T1-weighted gradient echo images (echo / repetition times, TE / TR = 3.6 ms / 50 ms; flip angle = 40°; matrix size = 256 x 256 x 135; number of averages = 2; total acquisition time = 2h 18min; isotropic resolution = 100 µm) were acquired 24h after maternal injection of $MnCl_2$ (80 mg/kg), using a self-gated sequence to minimize motion-artifacts (Fig. 1a)[1]. Novel registration approaches[2] for developmental data as well as metrics derived from deformation based morphometry (DBM)[3-5] were used for analysis of growth of different brain structures (Fig. 1b,c), patterns of growth (Fig. 1d,e), and for analysis of developmental changes in MEMRI signal intensity (Fig. 1f).

Results: Analysis of the growth patterns (Fig. 1b-e) showed that brain regions not only grow at different rates, but that the patterns of growth vary between regions. In some regions growth is better modeled using linear fit (blue, Fig. 1e), while in others quadratic (green) or even cubic (red) is a better fit. In addition to the volumetric changes, different regions also achieve their maximum MEMRI signal intensity at different developmental time points (Fig. 1f).

Discussion and Conclusion: Our imaging approach provided a unique set of 3D, quantifiable, anatomical data on brain development in individual animals for analysis of growth rates, and volume and shape changes of different brain regions. We showed that different brain regions grow differently, and that these volumetric changes are accompanied by region-specific changes in MEMRI signal intensity. The types of analyses employed in this study have potential to further our understanding of the role of different genes in the process of brain development, using developmental data acquired from a variety of mutant and transgenic mice.

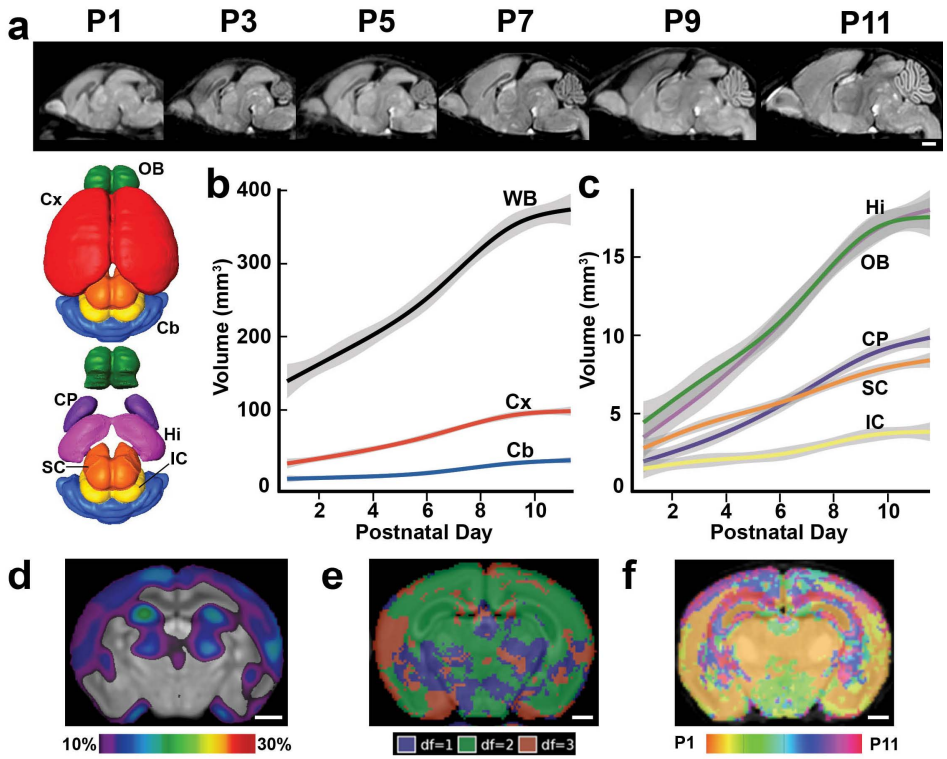

Fig. 1 (a) Mid-sagittal sections of average images (N=6) of neonates imaged at odd postnatal stages. Average images are characterized by better anatomical detail. (b) Plots showing change in volume of selected brain structures including: (b) whole brain (WB), cortex (Cx) and cerebellum (Cb); and (c) olfactory bulbs (OB), hippocampus (Hi), caudate-putamen (CP), superior (SC) and inferior colliculus (IC). (d) Growth map (P4.5-5.5) overlaid on corresponding P5 average anatomical image. The map shows daily growth rate (in % per day, color scale in insert), computed on a voxel-by-voxel basis, between half a day prior and half a day after from the developmental stage of interest. (e) Brain development patterns were investigated by fitting three different growth models (linear, quadratic, cubic) at every voxel, using natural splines with increasing degrees of freedom. The parametric map (e) summarizes these differences by color-coding each voxel depending on its best fit. (f) Results of voxelwise analysis of changes in MEMRI signal intensity. Brain voxels were color-coded to identify the developmental time point at which maximum signal intensity was reached in each voxel.

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References: [1] Nieman BJ et al. (2009), [2] Szulc KU et al. (2011). *Proc ISMRM* 19:238**;** [3] Lerch JP et al. (2011). *MR Neuroimaging* 711(3):353-7; [4] Dorr AE et al. (2008). *Neuroimage* 42:60-69; [5] Genovese CR et al. (2002). *Neuroimage* 15:870-78;