The Rate of Reduction in Cerebral Cortical Diffusion Anisotropy Reflects the Rate of Brain Development

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Introduction Throughout the second half of human gestation, morphological differentiation of cortical neurons and glial cells cause water diffusion anisotropy within the developing cerebral cortex to decrease with age. Thus, in principle, changes in diffusion anisotropy with growth could be used to detect neurodevelopmental disorders that give rise to abnormal morphological development of the cerebral cortex. In order to facilitate this objective, the normal trajectory of fractional anisotropy (FA) changes with age has been documented in several species, ranging from mouse to human (1-11). Though it is commonly assumed that FA changes reflect the same underlying developmental processes across species, this assumption has not previously been tested. Herein, we compare the loss of cortical diffusion anisotropy reported by several research groups with results from a systematic comparative study of brain development (12). It is found that, when the loss of cortical FA is approximated as an exponential decay with age over a consistent span of brain development, the time constant reflecting the rate of FA change is proportional to independent estimates of the rate of brain development for a given species.

Methods Cortical FA values were obtained from 11 studies in mouse (1,2), rat (3-5), ferret (6,7), baboon (8), and human (9-11). For studies in which FA values were not reported in tabular format or otherwise available, estimates were based on values provided in graphical illustrations. For each study, FA values obtained over the age ranges given in Table 1 were fitted to the equation $FA = \exp\left(-PCdays/\tau_{FA}\right) + C$, in which *PCdays* is the reported age in days post-conception, τ_{FA} is the time constant reflecting changes in FA with *PCdays*, and *C* is the FA value observed within mature cortex. Log-transformed cortical FA values are shown versus *PCdays* for the 11 studies in Fig. 1.

To compare the FA values to independent measures of rates of brain development for the five species, developmental event scores reported by Finlay and co-workers (12) were used. According to the translating time model (http://bioinformatics.ualr.edu/ttime/); $PCdays = \exp(\mathrm{Y}) + 4.34$, in which Y is a species-specific score for each developmental event reflecting the age at which the event occurs (with appropriate corrections for cortical events as described (12)). To compare the species scores to FA changes, the difference in *PCdays* per unit event score was calculated for each species, and termed the Developmental Events Length (Fig 2, abscissa).

Results As illustrated in Fig. 2, the rate of change in FA with development is observed to be proportional to the Developmental Events Lengths derived by Finlay and co-workers (12).

Discussion In this comparison of cortical FA changes with development, data from several research groups in studies of five species are used to show that the rate of reduction in cortical diffusion anisotropy is proportional to rate in which developmental events occur, provided FA changes are modeled as an exponential decay. These findings suggest that changes in FA in the developing cerebral cortex reflect common underlying neurodevelopmental processes seen among independent studies of various species.

References 1. Baloch S. et al. Cereb Cortex **19**: 675 (2009) **2.** Larvaron P. et al. NMR Biomed **20**: 413 (2007) **3.** Sizonenko S.V. et al. Cereb Cortex **17**: 2609 (2007) **4.** Huang H. et al. J Neurosci **28**: 1427 (2008) **5.** Bockhorst K.H. et al. J Neurosci Res **86**: 1520 (2008) **6.** Kroenke C.D. et al. Cereb Cortex **19**: 2916 (2009) **7.** Barnette A.R. et al. Ped Res **66**: 80 (2009) **8.** Kroenke C.D. et al. J Neurosci **27**: 12506 (2007) **9.** deIpolyi A.R. et al. NeuroImage **27**: 579 (2005) **10.** Trivedi R. et al. Neurorad **51**: 567 (2009) **11.** McKinstry R.C. et al. Cereb Cortex **12**: 1237 (2002) **12.** Clancy B. Neuroscience **105**: 7 (2001)

Table 1

Species	Gestational Age Range (days)
Mouse	18-28
Rat	21-34
Ferret	40-72
Baboon	89-166
Human	163-269

Figure 1

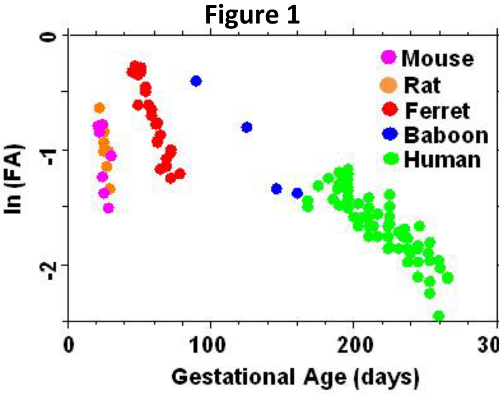

Figure 2