Coherent cortical pruning and axonal integrity enhancement during brain development accessed by DTI tractography from parcellated cortex

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Target audience: Clinicians and MR physicists who are interested in understanding the underlying mechanisms of white matter integrity changes in normal developing brains and those with mental disorders.

Introduction: Cortical thinning during brain development is due to complicated cellular and molecular processes including synaptic pruning, apoptosis and cell shrinkage [e.g.1-3] during development. In parallel, association and commissural white matter (WM) tracts project from a group of selected and preserved neurons and connect certain cortical regions. And age-dependent axonal enhancement of these tracts during development, reflected by increase of fractional anisotropy (FA) derived from DTI, has also been found in the literature [e.g. 4-6]. These parallel processes are essential for the formation of the brain circuits which enable certain brain functions, especially those related to mental diseases. For example, excessive pruning and insufficient pruning have been suggested to be related to schizophrenia [e.g. 7] and autism [e.g. 8], respectively. However, the relationship of these two processes is poorly understood, as shown in cartoonography in Fig. 1. Our hypothesis is that these two processes are not independent, but highly interacted during the brain development for the selected axonal enhancement and ultimately formation of the brain circuits. In this study, 39 normal children and adolescents from 7 to 25 were recruited and DTI and T1-weighted images were acquired from them. We traced the axonal fibers directly from a parcellated cortical gyrus and investigated the relationship of the change of FA of these axons and change of the corresponding cortical thickness.

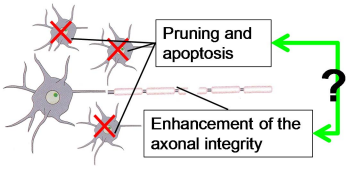

Fig. 1: The cartoonography demonstrates possible interaction of pruning and apoptosis reflected by cortical thickness decrease and enhancement of axonal integrity reflected by FA increase during brain development.

Methods: *Subjects and data acquisition:* DTI data of 39 normal children (21 Male and 18 Female; age 17.8±5.8; age range 7 to 25 years) were acquired from Philips 3T scanners of two institutions with identical imaging protocol. DTI data were acquired using a single-shot EPI with SENSE. The image parameters were: resolution=2x2x2 mm, 30 directions; b=1000 sec/mm^2, repetition=2. T1-weighted (MPRAGE) image with FOV=256/256/160mm and resolution 1x1x1mm was also acquired. *Identification of axons projected from a cortical gyrus:* The cortical labels were dilated by 7 voxels in order to touch the white matter and then transformed into DTI space as tracking seeds. FSL probtrackx was used for tractography. For visualization, an example of fibers traced from left precentral gyrus is show in Fig. 2. The fibers traced from all cortical gyri of all subjects were examined for reproducibility by inspecting the visualized fibers. *Measurements of cortical thickness and DTI metrics:* The mean cortical thickness was calculated for each gyral label by using representations of the GM-WM boundary and the pial surface then computing the distance in between these surfaces at each point across the cortical mantle. FA was calculated with axons projected from a cortical gyrus as a binary mask. *Measurements of age-dependent change slopes of cortical thickness and corresponding WM FA:* Change slopes of cortical thickness and corresponding WM FA were calculated from Pearson's correlations between these two parameters and age. In addition, Pearson's correlation of the change slopes of cortical thickness and corresponding FA of individual frontal gyrus was conducted to test coherence of the change patterns of these two parameters.

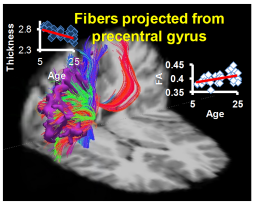

Fig. 2: Visualization of fibers projected from precentral gyrus, including part of body of corpus callosum, part of superior longitudinal fasciculus and some short association fibers. Scatter plots of thickness change and corresponding FA change of precentral gyrus are also shown.

Results

Heterogeneous change of regional cortical thickness during development: Left panels (Fig. 3a and 3c) of Fig. 3 show that cortical thicknesses of most frontal cortical gyri in both hemispheres decrease significantly during development. More importantly, these decrease patterns are heterogeneous, indicated by the colors painted on each frontal gyrus. Both the cortical thickness drop rates (Figs. 3a and 3c) and FA increase rates (Fig. 3b and 3d) of the frontal gyri are encoded sequentially by green, yellow and pink color, representing mild, median and sharp change, respectively. It is clear that dorsal prefrontal cortex has the sharpest cortical thickness decline while precentral gyrus and orbital frontal cortex have the slowest decline during brain development. *Heterogeneous change of FA of WM traced from parcellated cortical region during development:* Right panel of Fig. 3 (Fig. 3b and 3d) demonstrates the changes of FA of WM of the corresponding frontal cortical regions. Very similar FA increase patterns to those of cortical thickness decrease, shown by similar gyral colors, can be observed. *Coherent cortical thickness decrease and corresponding WM integrity increase during development:* By correlating the slopes of cortical thickness decrease and that of corresponding WM FA increase, we found that there is significant (p=0.0027) correlation between the two slopes, as shown in Fig. 4.

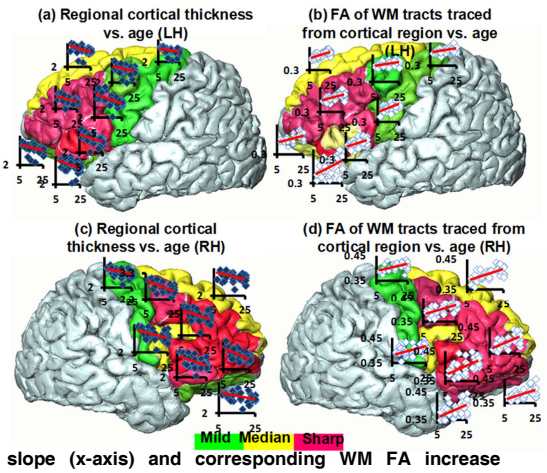

Fig. 3 (left): Coherent regional cortical thickness decrease and corresponding WM FA increase. Each cortical region is encoded by the change rate and categorized into mild (green), median (yellow) and sharp (pink) from smallest to largest. Scatter plots for regional cortical thickness vs. age (blue dots) and corresponding FA vs. age (white dots) are overlaid on the individual gyrus. LH/RH: left/right hemisphere.

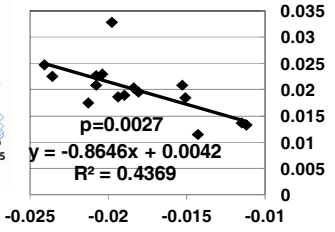

Fig. 4 (right): Statistical significant (p=0.0027) Pearson's correlation between the regional cortical thickness decrease slope (y-axis) and corresponding WM FA increase slope (x-axis). Each dot represents the slope measurements from each LH or RH frontal gyrus.

Conclusion and discussion

A strong and significant interaction between the cortical thickness decrease and corresponding WM FA increase takes place in the left and right frontal gyri during development, suggesting coherent cortical pruning and corresponding axonal integrity enhancement. The exact molecular and cellular mechanisms of these coherent changes of cortical thickness and corresponding WM integrity during development are not known. We speculate that there is some overlapping signaling pathways of axonal guidance and synaptic pruning or neuron apoptosis. Revealing coherence of cortical and white matter changes during development opens a new window for understanding underlying mechanism of white matter disruption in mental disorders such as autism and schizophrenia. Our results on age-dependent cortical thickness decreases and FA increases are consistent to the previous findings [1-2, 4-6]. Data from more child and adolescent subjects will be added.

References: [1] Shaw et al (2008) J Neurosci 28:3586. [2] Gotay et al (2004) PNAS 101:8174. [3] Morrison and Hof (1997) Science 278:412. [4] Lebel et al (2007) Neuroimage 40:1044. [5] Westlye et al (2010) Cereb Cortex 20: 2055. [6] Tammes et al (2010) Cerebral Cortex 20:534. [7] Keshavan et al (1994) J Psychiatr res 28: 239. [8] Barnea-Goraly et al (2004) Biol Psychiatry 55: 323.
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