Changes in Connectivity Associated with Neuronal Migration Disorder as Assessed by Diffusion Tractography

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Target audience

Neuroradiologists and neuroscientists interested in neuronal migration disorders.

Purpose

Disruption of neuronal migration to the cerebral cortex is associated with a wide range of developmental disorders. Animal experiments aimed at modeling these neuronal migration disorders have provided important insights as to the genetic modulation of this phenotype, as well as to their anatomical, physiological, connectional, and behavioral consequences. Recent evidence suggests that knocking down the function of the candidate dyslexia susceptibility gene homolog *Kiaa* in rats by *in utero* electroporation with small hairpin RNA (shRNA) results in disruptions of neuronal migration. The goal of this study is to use non-invasive diffusion weighted imaging and tractography to develop a quantifiable and verifiable biomarker of neuronal migration disorder.

Methods

Rat brains were embryonically transfected with plasmids containing either *Kiaa* shRNA (**shRNA** condition, n = 3), KIAA expression construct (over expression; **OX** condition, n = 7), or *Kiaa* shRNA scrambled (control, **Mutant** condition, n = 10). Brains were perfused and fixed in 4% paraformaldehyde solution containing 1 mM gadolinium (Gd-DTPA) MRI contrast agent. For MR image acquisition, the brains were placed in Fomblin. Brains were scanned on a 4.7T Bruker Biospec MR system with a 3D diffusion-weighted spin-echo echo-planar imaging sequence (TR/TE 1,000/45.47 ms) with a spatial resolution 200 × 200 × 200 μm. Sixty diffusion-weighted and one non diffusion-weighted (b = 0) measurements were acquired, with b = 4,000 sec/mm^2. The total acquisition time was approximately 2 hours for each imaging session.

Tractography pathways were reconstructed using a high-angular resolution diffusion imaging (HARDI) technique with an angle threshold of 35°. Diffusion Toolkit and TrackVis (http://trackvis.org) were used to reconstruct and visualize tractography pathways. The color-coding of tractography pathways is based on a standard RGB code, applied to the vector between the end-points of each fiber.

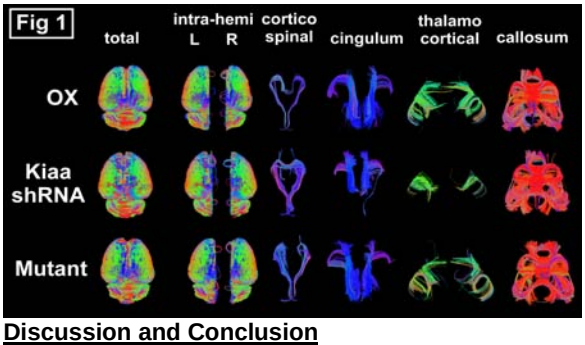
Whole brain total pathways, anterior/middle/posterior intra-hemisphere pathways in both left and right hemispheres, cortico-spinal, cingulum, thalamo-cortical, anterior/middle/posterior callosal pathways were identified. We measured the number, length, and volume of tractogrpahy pathways, as well as the fractional anisotropy (FA) and apparent diffusion coefficient (ADC) along the tractography. FA and ADC values were calculated from orientation vectors by fitting the data to the usual tensor model.

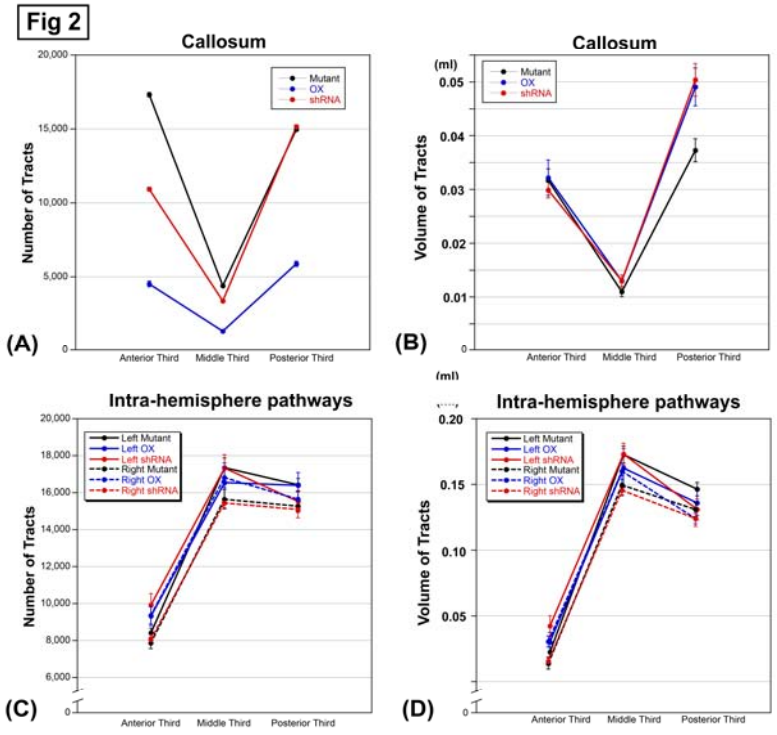
Results

ANOVA demonstrated that there was a statistically significant effect of group on the length of total ($F_{2,17} = 3.66$, $p = 0.048$), left ($F_{2,17} = 12.56$, $p = 0.0004$) and right ($F_{2,17} = 5.23$, $p = 0.017$) intra-hemisphere pathways, as well as on the number of right intra-hemisphere pathways ($F_{2,17} = 4.73$, $p = 0.0233$). Post-hoc analyses showed that the length of total, right, and left intra-hemisphere pathways were significantly shorter in the **OX** condition than in the **Mutant** condition. The number of right intra-hemisphere pathways was significantly greater in the **OX** condition than in the **shRNA** condition.

We further identified anterior, middle, and posterior callosal pathways, as well as anterior, middle, and posterior intra-hemisphere pathways in the left and right hemispheres.

Repeated measures ANOVA demonstrated that mean number and volume of identified callosum and intra-hemisphere pathways significantly differed across groups (**Fig. 2**).





Discussion and Conclusion

Our results suggest that the number and volume of identified tractography pathways were significant predictors of neuronal migration disorders in callosum and intra-hemispheric pathways. The length of tractogrpahy pathways was also a significant predictor of the disorders in the total and intra-hemispheric pathways. These experiments clearly support the notion that there are profound changes in the nature of connectivity associated with disruption of neuronal migration.