Neuroimaging Highlight

Editors: William Hu, Richard Farb

Functional Imaging of the Double Cortex

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Can. J. Neurol. Sci. 2004; 31: 254-256

A 24-year-old right-handed woman was investigated for medically intractable seizures. She was the product of a normal pregnancy and delivery, with no perinatal difficulties or infantile seizures. Early developmental milestones were delayed (walking, speech beginning at approximately 19 months) and she received special educational classes through early adulthood. Formal neuropsychological examination at age 24 demonstrated marked developmental delay of general cognitive functioning (mental age approximately five years) with no specific localization or lateralization evident. There was no history of maternal spontaneous abortions and no family history of epilepsy or other neurological disorders.

Her seizures began at age 16 and have been refractory to trials of all anti-epileptic medications and various combinations thereof. Seizures occur as often as fifteen times per day or as infrequently as once per week, preceded by a vague, poorly described aura, followed by speech arrest, unresponsiveness, and backward deviation of the head, progressing at times to falls. Video-EEG monitoring showed seizures to start with bilateral synchrony over both posterior hemispheres. Interictal epileptiform discharges were recorded synchronously or independently over both posterior quadrants without side predominance. Possible palliative surgical treatments for her epilepsy such as anterior callosotomy or neurostimulation have been discussed with the patient and her family, who have decided against surgical intervention to date.

The brain MRI showed the presence of diffuse subcortical laminar (band) heterotopia, or the "double cortex" syndrome (Figure 1). This is an X-linked neuronal migration disorder affecting mainly females with most patients heterozygous for a loss-of-function mutation in the *doublecortin* gene.[1,2] Males hemizygous for this mutation are typically much more severely affected with lissencephaly, although rare males with double cortex have been reported, some shown to have somatic mosaicism for a *doublecortin* mutation.[3,4] The process of X-inactivation is thought to account for the typical cortical abnormality in females: neuroblasts that inactivate the mutant X chromosome will migrate normally to the cortical surface and form the outer cortical layer, whereas neuroblasts that inactivate the normal X chromosome will have prematurely arrested migration along the radial path toward their programmed cortical targets, forming the inner cortical layer. The normal *doublecortin* gene product is a microtubule-associated protein presumably involved in the regulation of cell migration.[5,6] Pathological study of a female fetus with multiple cerebral malformations, including

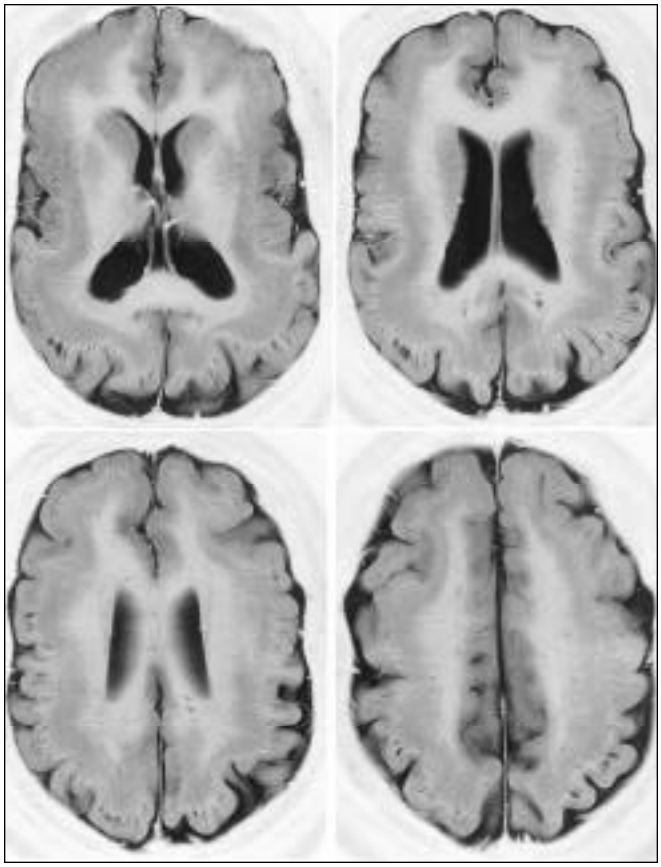

Figure 1: *Inversion recovery MRI shows diffuse subcortical band heterotopia separated from the overlying cortex by a thin layer of white matter.*

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RECEIVED MAY 27, 2003. ACCEPTED INFINALFORM NOVEMBER 7, 2003.

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https://doi.org/10.1017/S0317167100053907 Published online by Cambridge University Press

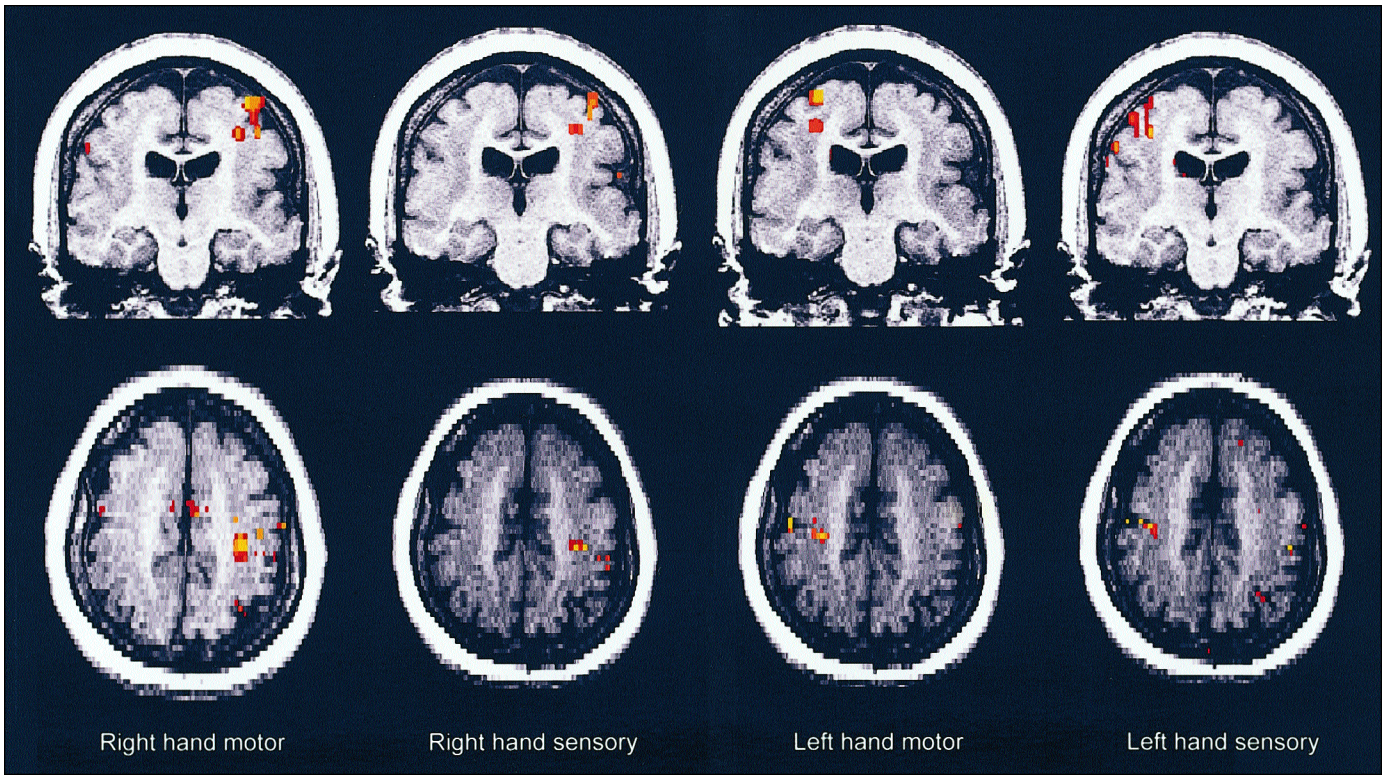

Figure 2: *Functional MRI shows spatially distinct simultaneous activation of focal cortical areas and subjacent heterotopic band regions during motor and sensory tasks. A block design was used with 15 sec "on" and "off" epochs alternating for four minutes. Images obtained using a 1.5-Tscanner; spiral 2D multi-slice fMRI pulse sequence (spiral trajectory through image space); six axial slices at 7 mm slice thickness; 2.3 mm^2 in-plane resolution; TR = 480 msec; TE = 40 msec; flip angle = 62^o; functional images registered on 3D spoiled gradient echo volumetric anatomical sequence. Data analysis using AFNI[14] (Robert Cox, PhD, Medical College of Wisconsin); calculation of coefficient of correlation (r-value) between time series data and a square wave reference waveform corresponding to the task sequence. Motor threshold set at r = .45 ($p < 1 \times 10^{-6}$), sensory threshold at r = .30 ($p < 0.0006$); colors represent interval scale in which brighter colors indicate greater significance.*

subcortical laminar heteroptopia, showed severe reduction in *doublecortin* immunoreactivity in the heterotopic grey matter, consistent with the X-inactivation hypothesis underlying formation of the double cortex.[7]

Whether the heterotopic band of neurons retains its functional connectivity is an interesting question that may be answered in part through functional imaging studies. Experimentally, a model of the human double cortex syndrome exists in the rat mutant, *tish*, where subcortical sensorimotor projections from the heterotopic cortex are similar to those from normal neocortex.[8] In humans, autonomous epileptogenicity has been localized to the heterotopic band, both by intracranial EEG[9] and magnetoencephalography,[10] which might suggest a significant disorganization of neuronal connectivity. Nevertheless, glucose uptake in the heterotopic band has been shown by positron emission tomography to be similar to normal cortex[11,12] and a functional MRI study in a 12-year-old boy with subcortical laminar heterotopia showed activation with a motor task (finger tapping) in both the heterotopic band and the overlying cortex of the contralateral frontal lobe.[13] In our patient, functional MRI with motor (sequential finger opposition) and sensory (brushing of the palm and fingers) paradigms demonstrated clear activation of the contralateral heterotopic grey matter and the overlying cortical areas for both motor and sensory function (Figure 2), showing that the cortex and its subjacent band form functionally related units. The band activations are adjacent to cortical areas of activation but remain spatially distinct, with a proximity consistent with premature arrest of the otherwise functional heterotopic neurons along the course of their radial migration during development.

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