Human Focal Cortical Dysplasia: A Brainbow Connectomics Approach

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Focal cortical dysplasia (FCD) is a common pathology finding in medically refractory seizure foci. Microscopically, it is characterized by disrupted cortical layering, dysmorphic neurons, and balloon cells. However, how these changes contribute to the initiation of seizures remains obscure. Two of the main limitations of our current pathological evaluations are: 1. Lack of structural data on the neuronal circuitry. For example, we do not know if the circuitry is altered when cortical lamination is abnormal. We also do not know if dysmorphic neurons receive or send out aberrant connections. 2. The scarcity of pathological studies on inhibitory interneuronal populations, which modulate the activity of pyramidal neurons and may play a critical role in epileptogenesis. Indeed, a class of inhibitory neurons — the parvalbumin-positive (PV+) interneurons, has been linked to seizures in animal models. However, how well these data extrapolate to human disease is not known. We propose a novel way to analyze the PV+ interneuron circuitry in humans to test the hypothesis that the inhibitory circuitry is altered in FCD. We sought to transfect human FCD surgical samples with Brainbow adeno-associated viral vectors. This approach would label the neurons in a wide variety of colors, enabling reconstruction of dendritic and axonal arbors. The advanced microscope at HCBI will greatly facilitate the imaging of these multicolor samples. This will mark the very first time for a type of human cortical neurons to be analyzed in a near-saturated manner, and the resulting data will provide the first structural evidence for alterations in the inhibitory circuitry in epilepsy.