Deciphering hyperexcitable networks associated with neurodevelopmental lesions, (DeCipher)

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Developmental malformations of the cortex (MCDs) are associated with a significant disease burden and often devastating epilepsies that are resistant to antiepileptic drugs. Neurodevelopmental disorders comprise a large spectrum of malformations and particular tumor entities that are rare in general brain tumor series. These neoplasms, with so-called *gangliogliomas* as most frequent type, are composed of often 'dysplastic' neuronal elements and generally slowly growing glial cells. Common features of developmental lesions and tumors are neurons that either do not reach their correct destination during cortical development or have substantially aberrant shape, particularly with respect to their size and/or structure of processes. Therefore, '*displaced'* as well as '*dysplastic'* neurons represent the edges of the pathology spectrum of aberrant neurons in MCDs. In recent years, our understanding of pathological intracellular signaling of these disorders has substantially emerged. However, these important advances have not led to substantially improved therapies. We suggest that this is due to our poor understanding of the mechanisms underlying increased excitability of neurons in these disorders. Preliminary data obtained by this consortium suggest a common mechanism underlying increased excitability in mouse and rat models of neurodevelopmental disorders: a profound imbalance between excitation and inhibition in the grey matter of the brain, which is functionally encoded by aberrant neurons and respective networks. Here, we will examine this concept in two relevant models of neurodevelopmental lesions associated with severe epilepsies: Firstly, a model of so-called doublecortex associated with mutations in the doublecortin (DCX) gene with the neuropathological hallmark of '*displaced'* neurons and secondly, a novel model of ganglioglioma, harboring prominent '*dysplastic'* neurons.
We will examine the neuronal basis of epileptic seizure generation in these models using recent methodologies that allow controlled stimulation (by so-called advanced photostimulation and optogenetic techniques) and analyses of the functional consequences (by in-vivo electrophysiology and imaging) in the brains of living experimental animals. These approaches will allow us to analyze in detail and in a highly controlled fashion potentially aberrant function of cellular sub-domains, i.e. synapses as functional intersections between neurons, down to the scale of individual compartments of processes, i.e. dendrites as main input structures of neurons, entire neuronal cells and networks of aberrant architecture. The technical approaches particularly allow an improved understanding of failure of interaction of neurons that constitute the MCD with the normal surrounding brain tissue, since we can manipulate and 'read' individual aspects of this aberrant interaction in-vivo. These approaches will shed light on the aberrant connectivity of '*displaced'* and '*dysplastic'* neurons that underlie the emergence of seizures. The results based on strong complementary expertise of the partners will foster the implementation of a conceptually novel approach directed towards better t herapies.