STRUCTURE AND FUNCTION OF CORTICAL DYSPLASIAS

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Focal cortical dysplasia (FCD) is one of the most frequent causes of refractory focal epilepsy. Their variability in morphology, location, and extension are major hurdles to early and accurate diagnosis and prognosis. Moreover, it is still unclear which mechanisms drive epileptogenicity in these lesions. Here, we used an animal model of cortical dysplasia (Benardete, Epilepsia 2002; 43, 970-982) to investigate the functional network properties and their response to a hyperexcitable challenge.

Main

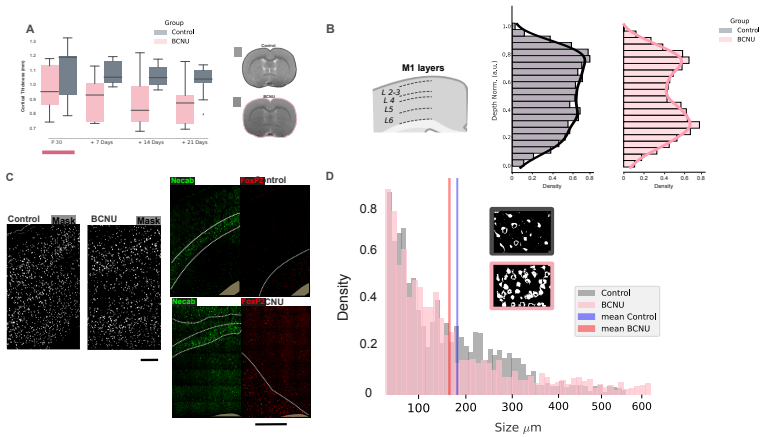
To characterize at the structure and functional level the cortical dysplasia induced by carmustine in an early stage of development

Methods

We studied the offspring of pregnant Wistar rats that were injected with either saline solution (Control n=21) or carmustine (BCNU n=26) (20 mg/kg i.p.) at 14 days of gestation. Ten animals per group were submitted to anatomical T2-weighted MRI at 30, 37, 44, and 51 postnatal days using a 7 T preclinical scanner (resolution = 67x67x80, 80 μm^3) to derive cortical thickness at the level of primary motor cortex (M1) in a coronal slice. To confirm cortical cellular disorganization, we performed layer-specific immunofluorescence examinations of M1 in coronal sections of 3 control and 6 BCNU cryopreserved specimens at p30 (Foxp2 for layer V, Necab for layer IV, and NeuN for neurons). Finally, another group of Control (n=8) and BCNU (n=10) animals were used for in vitro calcium imaging to assess the activity and organization of intracortical circuits at p30.

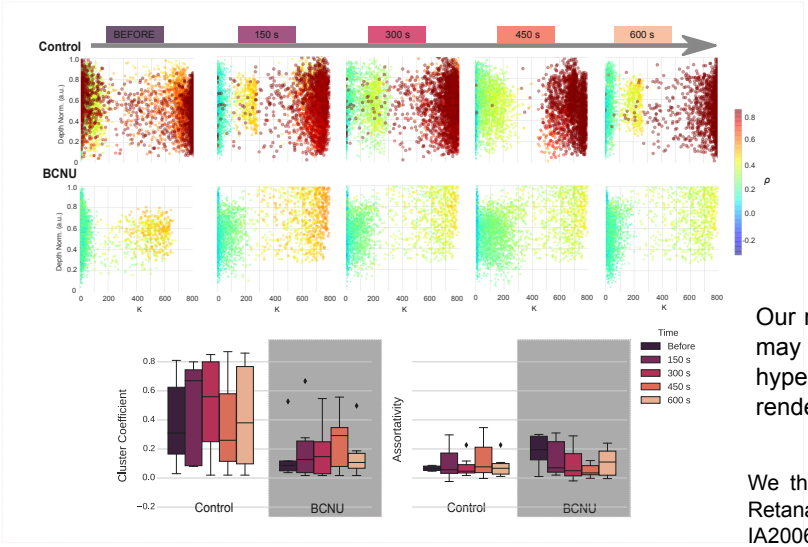
Results

STRUCTURE- MACRO AND MICRO-CHARACTERISTICS



Morphological characteristics of cortical dysplasias by BCNU at macro and micro scales. A) Longitudinal evaluation of cortical thickness in M1 cortex at postnatal day 30 and 7,14,21 days later. The control group is represented by the gray boxes and the injured group by the pinks. **B)** The probability distribution of neuronal profiles along the cortex at arbitrary depth values (Depth a.u.). Control = 3, gray; BCNU =5, pink. **C)** Representative immunofluorescences of each group, before the antibodies evaluated, anti-NeuN espective binary mask corresponding to the segmentation analysis (scale bar, 250 μm). The right panel shows the labels to specific antibodies cortical layers, in green, anti-Necab1, or layer IV and in red anti-Foxp2 or layer VI, (scale bar, 300 μm). **D)** Histogram of soma size of total segmented neurons in the region of interest.

FUNCTION - NETWORK COMUNICATION AND EVOLUTION



Evaluation of cell communication along temporal windows at global and local level. Distribution of correlation values along the M1 cortex, and their evolution in each temporal window in both groups, Control (n=8) and BCNU (n=10). The color scale represents the density of values per neuronal pair**. C)** Evolution of connectivity degree (K) values weighted to the correlation value ρ, in their distribution along the M1 cortex and in each time window. The color scale and size of the circles represent the ρ values in each scatter plot, temporal. **D)** Values of local metrics, such as cluster coefficient and assortativity in each temporal window and group

Conclusion

Our results suggest that the disarranged structure of dysplasias may affect intracortical connectivity after an external hyperexcitable stimulus, which reduces their connections and renders them less dynamic.

Acknowledgments

We thank Nydia Hernández-Ríos, Ericka de Los Ríos and Juan Ortiz-Retana for technical assistance. Funding: UNAM-DGAPA (IN204720, IA200621).