Understanding hyperexcitability of cortical malformations through network analyses

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Several biological processes are involved in the morphological development of the cortex during early gestation. Genetic and epigenetic factors can alter cortical development and result in morphological abnormalities collectively known as malformations of cortical development (MCD). One of these is focal cortical dysplasia (FCD), characterized by a delaminated cortex, blurring of the interface between gray and white matter, and variable architectural abnormalities. Their clinical importance lies in the fact that they can result in refractory and drug-resistant epilepsy, with greater incidence in the pediatric population. Their variability in morphology, location, and extension are major hurdles to an early and accurate diagnosis. Moreover, the relation between their aberrant morphology and their epileptogenic activity remains obscure. Here, we used an animal model of cortical dysplasia (Bernadete EA & Kriegstein, AR. 2002) to investigate the aberrant morphology with the functional network properties and their response to a hyperexcitable challenge.

We evaluate the morphology at a microstructure level, using diverse cortical antibodies, one of those anti-NeuN [1:400] to describe the morphology of the neurons by their shape (roundness) and area and the distribution of those along one cortical zone (M1). At functional level, using calcium imaging with a large field of view, we can record a wide number of live cells throughout the primary motor cortex in an early stage of development (p30), at their basal activity, and before and after an external stimulus (pilocarpine - an acetylcholine agonist). We inferred connectivity using the cross-correlation method in five 150-seconds windows. We evaluated five temporal windows (1-Before stimulus, 2-During stimulus, 3-5, After stimulus) describing global features by their degree of connectivity and position.

Our results show that the morphology of neurons are different in BCNU-treated cortices than controls; they showed larger and roundness neurons in two specific zones of the cortex (Fig.1-A,B) confirmed their aberrant morphology. At functional level, dysplastic cortices show greater correlation values, mainly before stimulation and the first window after it (Fig.1-CI). At the number of connections (k- degree) level, BCNU treated networks show higher k values especially around depth positions 0.4-0.8 in the before and during stimulus windows, then controls one increase their connectivity at the first window after (300s)(Fig.1-CII), whereas in the control we observe lower density and wider distribution throughout the cortex, which is more evident in the first and later temporal windows. Suggesting that dysplasia cortices present more connections only in

a focal region, while control cortices dissipate their connectivity across the cortex. In addition, internal connectivity shows differences in interactions at different depths between groups, with an increase in interactions in the last windows, where activity is found after the stimulus having more effect in the control connectivity (Fig.1-CIII).

We can conclude that the aberrant morphology in dysplastic cortices makes their communication stronger and dispersed along the cortex, features that may make them susceptible to hyperexcitability.

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References

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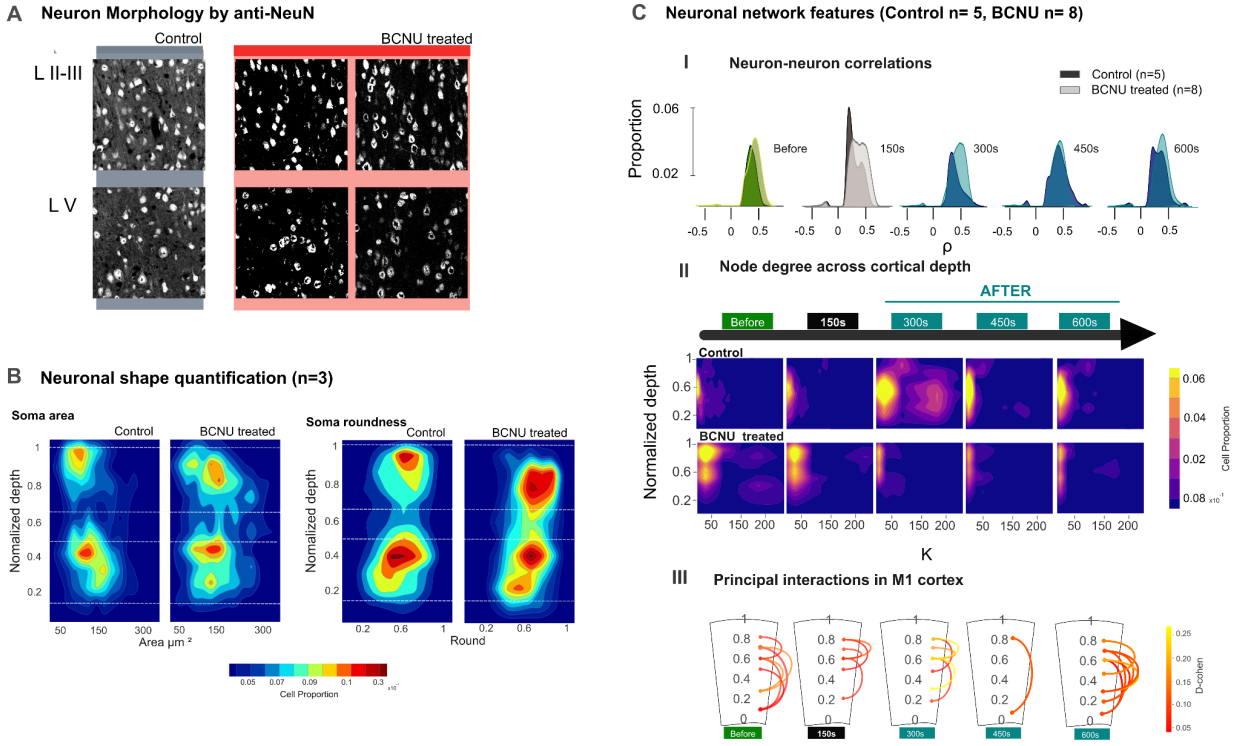

A) Neuron morphology examples of two layer zones (LII-III) and (LV) 250 µm. **B)** Neuronal shape quantification and their position relation, soma area and soma roundness. **C)** Network description at the different window time, by the correlation value (I), localization of the cell connectivity (II) and the principal interactions that are significative throught M1 cortex (III).

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