Theme: Imaging Research in Basic and Clinical Science: Neuroscience, Cardiology and Oncology

Sex-dependent cortical morphometric and neurophysiological alterations in a genetic mouse model of tuberous sclerosis complex 2

Mariana Lapo Pais[1,2,3]*, José Sereno[2,3,4], Vanessa A. Tomé[2,5], Carla Fonseca[2,6], Inês Ribeiro[7,8], João Martins[2,3], Ana Fortuna[2,6], Antero Abrunhosa[2,3,5], Luísa Pinto[7,8], Miguel Castelo-Branco[2,3,9], Joana Gonçalves[2,3,9]

1 University of Coimbra, Faculty of Sciences and Technology, Portugal;
2 University of Coimbra, Coimbra Institute for Biomedical Imaging and Translational Research (CIBIT), Portugal;
3 University of Coimbra, Institute for Nuclear Sciences Applied to Health (ICNAS), Portugal;
4 University of Coimbra, CQC-IMS, Chemistry Department, 3004-535, Coimbra, Portugal;
5 ICNAS Pharma, University of Coimbra, 3000-548, Coimbra, Portugal;
6 University of Coimbra, Laboratory of Pharmacology, Faculty of Pharmacy, Coimbra, Portugal;
7 Life and Health Sciences Research Institute (ICVS), School of Medicine, University of Minho, Braga, Portugal;
8 ICVS/3B's - PT Government Associate Laboratory, Braga/Guimarães, Portugal;
9 University of Coimbra, Institute of Physiology, Faculty of Medicine, Coimbra, Portugal

*presenting author

Abstract:
Tuberous sclerosis complex (TSC) is a neurological disorder characterized by brain abnormalities, particularly cortical tubers, which often lead to severe epilepsy and autism spectrum disorder (ASD). While cortical lesions are a hallmark of TSC, the specific cortical alterations contributing to these symptoms remain largely unknown. Further, differences in clinical manifestations between males and females with TSC, highlight the need to investigate sex-specific mechanisms. To better understand cortical dysfunction in TSC, we used male and female Tsc2+/- mice to explore cortical changes, including neuron morphology, serotonergic signaling, tryptophan (Tryp) metabolism, excitatory/inhibitory (E/I) balance, and structural connectivity. At the molecular level, transgenic males had shorter and less complex cortical basal dendrites, while apical dendrites of transgenic females exhibited the opposite morphology suggesting inherent sexual dimorphisms in neuronal organization. We also found that Tsc2+/- females had lower cortical 5-HT1A receptor density and increased excitability. Moreover, for transgenic animals, we exposed that activation of those serotoninergic receptors was directly correlated with E/I imbalance towards excitability. Finally, the TSC2 mouse model displayed sex-dependent changes in the structural connectivity of the cortex-amygdala-hippocampus circuit: females showed a reduced number of axonal fibre pathways, while males exhibited a loss of tissue density. These findings provide evidence that sex-related alterations in cortical neurophysiology may partially explain the sexually dimorphic symptoms in TSC and related clinical manifestations.

Keywords: Excitation/Inhibition Balance; Neuron Morphology; Serotonergic System; Structural Connectivity; Tryptophan Metabolism; Tuberous Sclerosis Complex.