# Investigating the Neurobiological Effects of Chronic Cortisol in Human Embryonic Stem Cell-Derived Forebrain Neurons at Different Stages of Neuronal Development.

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Dysregulated hypothalamic-pituitary adrenal axis, in particular hypo- and hyper- function, has long been implicated in stress-related disorders like post-traumatic stress disorder (PTSD). However, only a small percentage of individuals are susceptible to PTSD following trauma exposure and it is unclear whether and how exposure to traumatic stress leads to alterations in cortical neurons that contribute to PTSD susceptibility in these patients. Therefore, the aim of this study was to investigate the chronic effects of the glucocorticoid cortisol (CORT), in human embryonic stem cell(hESC)-derived forebrain neural progenitors and neurons, to better understand neurobiological effects of CORT in an *in vitro* model. We generated forebrain neurons from hESCs of a healthy individual, and investigated the effects of chronic CORT exposure at three different neuronal developmental stages: neural progenitor cells, immature and differentiating neurons, and maturing neurons. In the initial stage, we observed changes in proliferation, survival, and apoptosis of neural progenitor cells, we also observed changes in neuronal morphology and survival of young immature differentiating neurons, and finally mature neurons showed modifications in spontaneous neuronal activity and synaptic transmission following chronic exposure to CORT. Whole-transcriptome sequencing revealed differentially expressed genes uniquely regulated in the different stages following chronic cortisol treatment. Together these results suggest distinct effects of CORT at different stages of neuronal development.

**Keywords**: Neurobiology, stress, neuronal development

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