M27. EPIGENETIC ALTERATIONS OF THE GLIA CELL-DERIVED NEUROTROPHIC FACTOR AND RESPONSE TO ELECTROCONVULSIVE STIMULATION
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Background Electroconvulsive therapy (ECT) belongs to the most efficient treatments for major depression but its mechanisms remain elusive. Neurotrophic factors and their epigenetic status most likely play a role in the pathogenesis and treatment of depression. Thus, recent studies have focused on possible epigenetic biomarkers which could predict therapy response to different antidepressant treatments. Glial Cell Line-Derived Neurotrophic Factor (GDNF) expression has been shown to be restored during a successful antidepressant therapy in MDD patient’s serum. Furthermore, epigenetic marks in GDNF’s promoter affect the susceptibility and adaption towards chronic stressful life events in a rodent model. Interestingly, the neuroprotective effect of ECS in a Parkinson’s disease rat model has been shown to be crucially dependent on GDNF.

The aim of this study was to investigate if methylation of the GDNF promoter and GDNF expression is changed by electroconvulsive stimulation (ECS) and if possible changes are related to treatment response.

Methods We have previously shown that outbred rats from Charles River (Sulzfeld, Germany) exhibit increased anxiety-related behavior and response to chronic unpredictable mild stress (CUMS) compared to stress-resistant rats from Janvier Labs (Saint Berthevin, France). Therefore we chose to investigate changes due to ECS-treatment in rats bred by Janvier and response to therapy in rats bred by Charles River. Male wistar rats (9 weeks) were subjected to CUMS and randomly assigned to ECS or sham stimulation. ECS was applied via auricular or cortical stimulation and delivered once daily for 5 days. According to Christensen et al., positive treatment responders were anhedonic-like rats showing a >20%, non-responders rats showing a <20% and negative responders rats showing a decrease of >50% within-subject difference in Sucrose Preference Test. Methylation analysis of the negative regulatory region of the GDNF promoter was performed in blood, hippocampus and prefrontal cortex (PFC) with bisulfite sequencing technique. GDNF expression in the hippocampus and PFC of rats was determined via a sandwich ELISA.

Results Mixed linear modelling showed higher GDNF methylation and expression in the hippocampus after ECS in the stress-resistant Janvier rats (p<0.001). In Charles River rats, ECS led to lowered promoter methylation and lower expression of GDNF in the hippocampus but heightened GDNF promoter methylation and expression in the PFC of stimulated rats (both p<0.001). Hypermethylation of the GDNF promoter was also present in the blood of Charles River rats (p<0.001). Analysis of differences between responders and non-responders revealed that the observed differences were driven by response-type: Positive responders showed lower methylation and expression of GDNF in the hippocampus and higher methylation in the PFC and blood compared to non- and negative responders (all p≤0.001).

Discussion Our preliminary results show that GDNF promoter methylation and expression is changed by ECS. Furthermore, we could show that the observed changes are especially present in responders to ECS in a rat model of depression. At
the congress we will also present peripheral GDNF expression and methylation status of patients receiving ECT, to validate GDNF as a possible biomarker for responsiveness to ECT.

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