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## 24h quantitative-EEG and *in-vivo* glutamate biosensor detects activity and circadian rhythm dependent biomarkers of pathogenesis in MECP2 KO mice

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**Background:** Mutations in the X-linked gene encoding methyl-CpG-binding protein 2 (MeCP2) cause most cases of Rett syndrome (RTT). Currently there is no cure or viable treatment for RTT. Abnormal EEGs are found in a 100% of the RTT cases and are associated with severe sleep dysfunction, the cause of which is not well understood. Mice that are deficient in MeCP2 show neuropathological and behavioural deficits similar to those reported for RTT.

**Objective:** To study the non-ictal EEG correlates in symptomatic MeCP2 KO mice and determine novel biomarkers of the progressive neurodegeneration

**Method:** We used 24h video-EEG/EMG with synchronous *in-vivo* cortical glutamate biosensors in the frontal cortex. We scored the EEG for activity states and did spectral analysis to evaluate correlations to the synchronous extracellular glutamate fluctuations underlying MeCP2 inactivation as compared to controls.

**Results:** Glutamate peaks and troughs tightly correlated with wake and sleep cycles respectively. However significant alterations in sleep structure, poor quality of slow wave sleep (SWS) and impaired activity dependent glutamate homeostasis was detected in KO mice that were also associated with a significant increase in glutamate loads per activity cycle. Colorimetric quantitation of absolute glutamate levels in the frontal cortices also showed significantly higher levels.

**Conclusions:** This study found that chronic sleep deprivation associated with glutamate toxicity may underlie the progressive neurodegeneration and fatality in the MeCP2 KO mice. Identification of these quantitative biomarkers will be valuable to evaluate the efficacy of novel interventions *in-vivo* to help guide the design of therapeutic approaches in the clinic.

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