

Rescue of dentate gyrus/amygdala pathology and function in an inducible mouse model of FMR1-premutation

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A CGG-repeat expansion in the premutation (PM) range in the fragile X mental retardation gene (FMR1) is the genetic cause of fragile X-associated tremor/ataxia syndrome (FXTAS). FXTAS is a late-onset neurodegenerative disorder that manifests with intention tremor, ataxia, neuropsychiatric changes and deficits in memory and cognition. FXTAS behavioral features are accompanied by ubiquitin positive intranuclear inclusions that are a hallmark of the disorder.

PrP-rtTA/TRE-90CGG-eGFP is a Tet-ON bigenic mouse model of FXTAS that expresses a premutation (PM) range CGG-repeat expansion tract outside of the context of FMR1 under the control of doxycycline (DOX). Our previous work with this model has shown that motor as well as emotional alterations manifest in these transgenic mice after 12 weeks of DOX induction starting at post-natal day 28. In order to study emotional aspects of the PM without any interference from motor deficits, in this study we have adopted an early induction schedule starting from embryonic development. We have identified that an anxiety-like phenotype was already present albeit no motor changes. A rescue was possible after a period without transgene expression (washout phase) that was also reflected in the decreased inclusion load in the basolateral amygdala and dentate gyrus (DG) of the hippocampus. Moreover, electrophysiological read-outs have shown disruptions in the DG and lateral amygdala upon DOX administration and in line with the behavioral rescue and the reduction in the inclusion load, these also tend to normalize after the washout phase.

These findings suggest that emotional disturbances are present despite the lack of the motor deficits seen in FXTAS when adopting an early induction schedule. Furthermore, there is a possibility of a rescue of the pathology and function in the DG and amygdala upon cessation of the expanded CGG-track expression that translates into a phenotypical amelioration.