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Conditional mutations of *Fmr1* demonstrate an acute requirement for mouse phenotypes.

Fragile X syndrome is considered to be a disorder involving impaired neural development; yet direct evidence to support this is limited. As efforts to develop effective treatment of individuals with Fragile X syndrome are developed, it is important to understand whether defective development contributes to the disease, and to what extent it might reduce the potential of drug or other therapies.

We have generated mouse models that allow expression of FMRP to be manipulated in a time-dependent manner to determine the effects of FMRP expression on phenotype during the lifespan. One model allows the *Fmr1* gene to be expressed until it is turned off at a specific time point using drug (tamoxifen) inducible Cre recombinase to ablate the promoter and first exon of the gene (a conditional knockout or cKO). The other model (cON) allows the *Fmr1* gene to be turned on at a defined time after growth and development without FMRP (conditional ON or cON). Our results indicate that restoration of FMRP in adult (4-6 week old) mice rescued nearly all phenotypes. These included abnormal dendritic spines, a deficiency on the accelerating rotarod, circadian rhythm anomalies and altered expression levels of the FMRP target PSD-95 in the hippocampus. The adult ablation of FMRP likewise caused mice to develop abnormal phenotypes when compared to untreated control animals.

Our findings demonstrate that the abnormal phenotypes found in mutant mice are dependent on the presence or absence of FMRP, but do not depend on the state of expression of the protein during development.