Fragile X Mental Retardation Protein Requirements in Activity-Dependent Critical Period Neural Circuit Refinement

Highlights

- Fragile X syndrome disease model shows critical-period-restricted circuit defects
- Critical period activity-dependent synaptic remodeling absolutely requires FMRP
- Critical period hyperexcitation phenocopies fragile X syndrome synaptic defects
- FMRP enables critical period sensory activity refinement of synaptic connectivity

Authors

Caleb A. Doll, Dominic J. Vita, Kendal Broadie

Correspondence

kendal.broadie@vanderbilt.edu

In Brief

Doll et al. discover that activity-dependent neural circuit refinement restricted to an early-use sensory critical period requires FMRP, lost in fragile X syndrome. Developmental hyperexcitation phenocopies synaptic connectivity defects. Sensory-, optogenetic-, and neurotransmission-dependent remodeling during the critical period all require FMRP.
Fragile X Mental Retardation Protein Requirements in Activity-Dependent Critical Period Neural Circuit Refinement

Caleb A. Doll,1 Dominic J. Vita,1 and Kendal Broadie1,2,3,4,5,*
1Department of Biological Sciences
2Department of Cell and Developmental Biology
3Department of Pharmacology
4Vanderbilt Kennedy Center for Research on Human Development
Vanderbilt University, Nashville, TN 37203, USA
*Lead Contact
*Correspondence: kendal.broadie@vanderbilt.edu
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SUMMARY

Activity-dependent synaptic remodeling occurs during early-use critical periods, when naive juveniles experience sensory input. Fragile X mental retardation protein (FMRP) sculpts synaptic refinement in an activity sensor mechanism based on sensory cues, with FMRP loss causing the most common heritable autism spectrum disorder (ASD), fragile X syndrome (FXS). In the well-mapped Drosophila olfactory circuitry, projection neurons (PNs) relay peripheral sensory information to the central brain mushroom body (MB) learning/memory center. FMRP-null PNs reduce synaptic branching and enlarge boutons, with ultrastructural and synaptic reconstitution MB connectivity defects. Critical period activity modulation via odorant stimuli, optogenetics, and transgenic tetanus toxin neurotransmission block show that elevated PN activity phenocopies FMRP-null defects, whereas PN silencing causes opposing changes. FMRP-null PNs lose activity-dependent synaptic modulation, with impairments restricted to the critical period. We conclude that FMRP is absolutely required for experience-dependent changes in synaptic connectivity during the developmental critical period of neural circuit optimization for sensory input.

INTRODUCTION

Fragile X syndrome (FXS) is the most common heritable autism spectrum disorder (ASD) [1]. Leading hypotheses of FXS pathogenesis emphasize faulty neural circuit refinement during early postnatal critical periods of neurodevelopment [3]. In addition to low intelligence quotient (IQ) and learning disabilities, FXS patients exhibit hypersensitivity to multiple sensory modalities [1] and up to 20% comorbidity for childhood epilepsy [3]. Fragile X mental retardation protein (FMRP) expression delineates early-use critical periods of neural circuit optimization in FXS disease models [4, 5]. FMRP is proposed to function within the activity sensor mechanism, mediating activity-dependent synaptic remodeling based on early sensory experience [6, 7]. Here, we test this hypothesis in the Drosophila FXS model [8], which closely replicates human disease state symptoms, including learning/memory deficits, hyperactivity, interrupted sleep, and impaired social interaction [9, 10]. This disease model has provided key mechanistic insights into FXS neuropathology through application of a sophisticated genetic toolkit within well-mapped circuitry to unlock FMRP activity-dependent roles in neural refinement.

Neural circuit remodeling occurs in critical periods of early sensory input brain development, when neurons are primed to alter synaptic architecture, connectivity, and function in response to initial experience [11]. The Drosophila brain olfactory learning and memory circuit provides an excellent model of experience-dependent refinement during a defined critical period immediately following eclosion, amenable to sensory conditioning paradigms [12–14] and targeted optogenetic manipulation [5, 15]. We have discovered neuron-type-specific requirements for FMRP in this circuit, with FMRP loss causing excessive activity in excitatory (E) neurons and reduced function in inhibitory (I) neurons, supporting the E/I imbalance theory of FXS and related ASD states [16, 17]. Importantly, E/I phenotypes are phenocopied by targeted optogenetic modulation of activity states during the critical period, suggesting tight temporal limits to activity- and FMRP-dependent mechanisms [5]. We have tested FMRP requirements within the antennal lobe medial projection neuron 2 (mPN2) [18] in regard to dendritic arbor development [15] and functional activity-dependent calcium signaling [19]. We now dissect sensory input-, activity-, and FMRP-dependent remodeling of mPN2 synaptic input to the Drosophila brain learning/memory center during the critical period.

In this study, we discover synaptic remodeling and activity-dependent refinement restricted to the early-use critical period in the central brain mushroom body (MB) calyx, where mPN2 has presynaptic input onto Kenyon cells (KCs) [20]. In dfmr1-null animals, we find synaptic dysmophria with both confocal and transmission electron microscopy imaging of synaptic microglomeruli, with reduced mPN2 branching, malformed...
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