Reduced Lateral Inhibition Impairs Olfactory Computations and Behaviors in a *Drosophila* Model of Fragile X Syndrome

**Graphical Abstract**

**Highlights**

- Lack of dFMRP leads to reduced olfactory attraction and aversion in fruit flies.
- Odor selectivity of antennal lobe projection neurons is impaired in *dfmr1*^-^ flies.
- GABAergic lateral inhibition within the antennal lobe is weaker in *dfmr1*^-^ flies.
- Deficient lateral inhibition impairs sensory computations and animal behavior.

**In Brief**

Franco et al. show that a *Drosophila* model of fragile X syndrome exhibits reduced GABAergic transmission, which leads to impaired lateral inhibition across the antennal lobe. These alterations in neuronal connectivity directly affect olfactory computations by reducing the specificity of odor responses and lead to behavioral defects.
Reduced Lateral Inhibition Impairs Olfactory Computations and Behaviors in a Drosophila Model of Fragile X Syndrome

Luis M. Franco,1,2,3 Zeynep Okray,2,3 Gerit A. Linneweber,2,3 Bassem A. Hassan,2,3,4,* and Emre Yaksi1,5,6,*

1 Neuroelectronics Research Flanders (NERF), KU Leuven, Kapeldreef 75, 3001 Leuven, Belgium
2 VIB Center for the Biology of Disease, KU Leuven, Herestraat 49, 3000 Leuven, Belgium
3 Center for Human Genetics, KU Leuven, Herestraat 49, 3000 Leuven, Belgium
4 Institut du Cerveau et de la Moelle Épinière (ICM) - Hôpital Pitié-Salpêtrière, UPMC, Sorbonne Universités, Inserm, CNRS, 47 Boulevard Hôpital, 75013 Paris, France
5 Kavli Institute for Systems Neuroscience and Centre for Neural Computation, NTNU, Olav Kyrres gate 9, 7030 Trondheim, Norway
6 Correspondence: bassem.hassan@icm-institute.org (B.A.H.), emre.yaksi@ntnu.no (E.Y.)

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SUMMARY

Fragile X syndrome (FXS) patients present neuronal alterations that lead to severe intellectual disability, but the underlying neuronal circuit mechanisms are poorly understood. An emerging hypothesis postulates that reduced GABAergic inhibition of excitatory neurons is a key component in the pathophysiology of FXS. Here, we directly test this idea in a FXS Drosophila model. We show that FXS flies exhibit strongly impaired olfactory behaviors. In line with this, olfactory representations are less odor specific due to broader response tuning of excitatory projection neurons. We find that impaired inhibitory interactions underlie reduced specificity in olfactory computations. Finally, we show that defective lateral inhibition across projection neurons is caused by weaker inhibition from GABAergic interneurons. We provide direct evidence that deficient inhibition impairs sensory computations and behavior in an in vivo model of FXS. Together with evidence of impaired inhibition in autism and Rett syndrome, these findings suggest a potentially general mechanism for intellectual disability.

INTRODUCTION

Fragile X syndrome (FXS) is a common inherited intellectual disability disorder. FXS patients exhibit neurological symptoms that include learning disabilities, social anxiety, attention deficits, hyperarousal, hypersensitivity, autism, and epilepsy [1]. Notwithstanding the complexity of neurophysiological and behavioral alterations, FXS is caused by the silencing, deletion, or loss-of-function mutation of a single gene, FMR1. As a result, FMRP (fragile X mental retardation protein), its protein product, is not expressed in the majority of cases or is non-functional in the rare cases with a point mutation [2–4]. FMRP is an mRNA-binding protein [5] that regulates several aspects of mRNA metabolism such as nuclear export, transport to synaptic terminals, activity-dependent ribosome stalling and gene expression [6–8]. Although much of FMRP activity is thought to be related to regulation of synaptic function [9–11], little is known about the potential defects in neuronal function caused by the absence of FMRP, in particular how these neurophysiological alterations lead to impairment in neuronal computations and behavior in patients with FXS.

Initial studies revealed that dendritic spine number is increased in the cortex of FXS patients [12, 13]. In fact, dendritic abnormalities are the most consistent anatomical correlates of intellectual disability [14]. Studies on animal models of FXS showed that FMRP regulates neuronal branching [15–17] as well as dendritic spine morphology and density [11, 18]. In addition to defects in synaptic structure and axonal branching, impairments in animal behavior have been observed [11, 16]. However, further studies showed that neuroanatomical and behavioral defects can be genetically uncoupled [17], suggesting that unknown impairments in neuronal circuit function may underlie behavioral deficits.

FMRP regulates translation of mRNAs at synapses, some of which encode proteins involved in synaptic plasticity [19, 20]. Importantly, the absence of FMRP leads to abnormally enhanced group 1 mGluR (metabotropic glutamate receptor) signaling, which results in exaggerated long-term depression [21], with a net loss of AMPA and NMDA receptors [22, 23]. Additionally, enhanced group 1 mGluR signaling contributes to the elongation of dendritic spines in rodent models of FXS [18, 24] and leads to increased intrinsic neuronal excitability through the downregulation of potassium channels controlling resting membrane potential and action potential afterhyperpolarization [25, 26]. Moreover, FMRP directly influences neuronal excitability by regulating expression of potassium channels [27, 28] and by interacting with potassium channels in a translation-independent manner [29]. Nevertheless, the recent failure of FXS clinical trials targeting group 1 mGluR signaling [30] has led the field to re-examine the group 1 mGluR hypothesis.

Loss of FMRP was shown to increase network-level hyperexcitability in the rodent cortex [31, 32], which has been associated with the symptoms observed in FXS patients, such as
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