Modulation of oscillatory changes in the genetic NMDAR hypofunction mutant PV-Cre/NR1f/f mice

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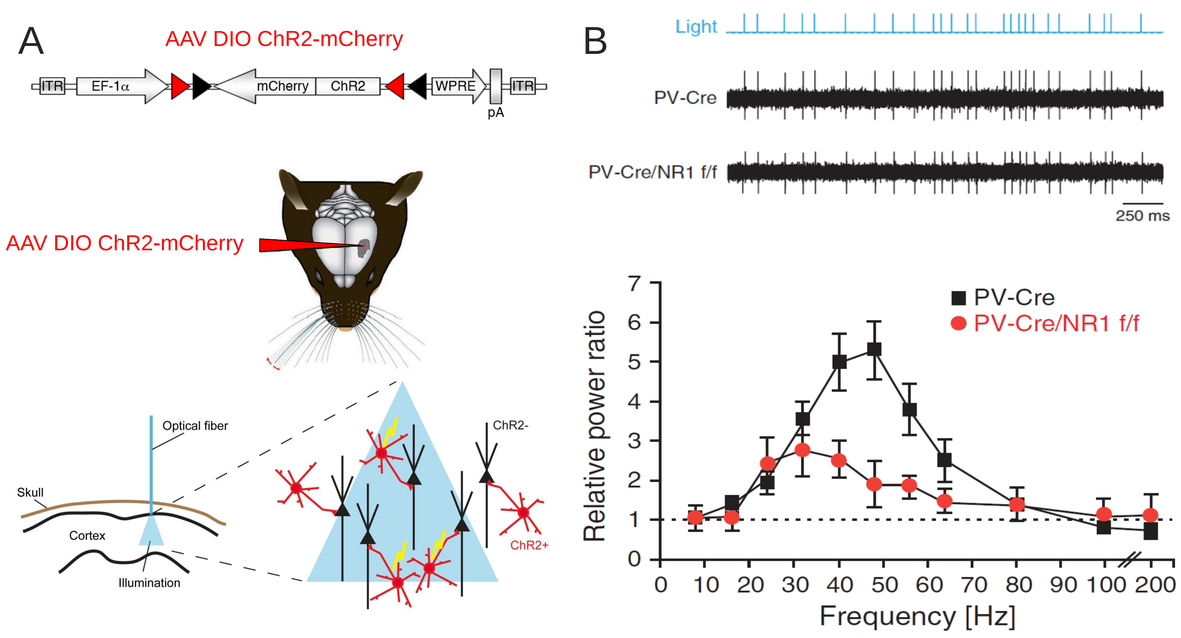
Summary

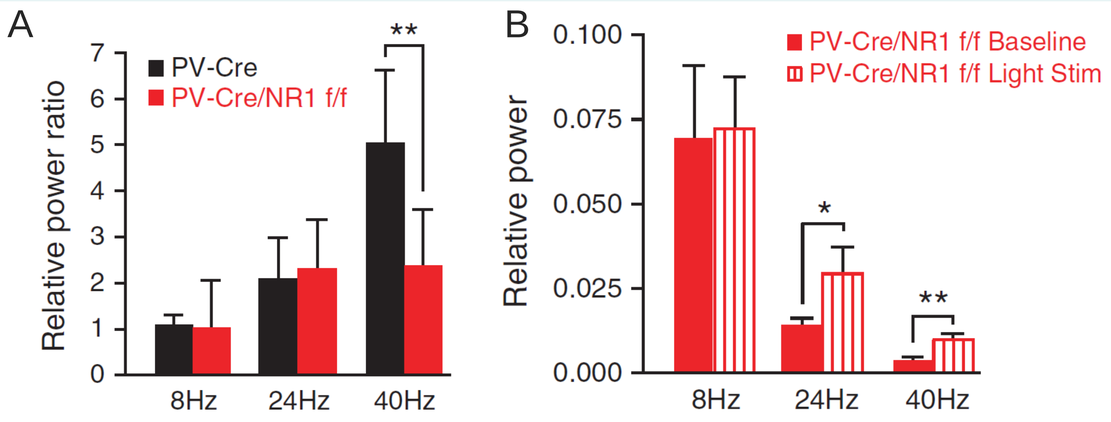
In the mouse model we generated with NMDAR selective deletion in mouse parvalbumin (PV) interneurons, by using *in vivo* optogenetic we found that animals that lacking N-methyl-D-aspartate glutamate receptors (NMDAR) in fast-spiking interneurons showed abnormalities in spontaneous brain oscillations and failed to respond to laser stimulation in generation of gamma oscillation. Behavioral analysis of the knockout animals showed there were deficits in working memory and fear conditioning but no difference in spatial reference memory. The atypical clozapine has been one of the most effective antipsychotic drug, and it improves some types of cognitive functions and execution. However, the precise antipsychotic or cognitive enhancing mechanisms of the drug are largely unknown. Therefore we want to explore if clozapine could restore the oscillatory abnormalities in these animals. In this study we recorded *in vivo* in the prefrontral cortex (PFC) with acute administration of clozapine in both knockout animals and controls. Our preliminary results showed there was no significant difference between two groups in the relative power of synchronized brain activity.



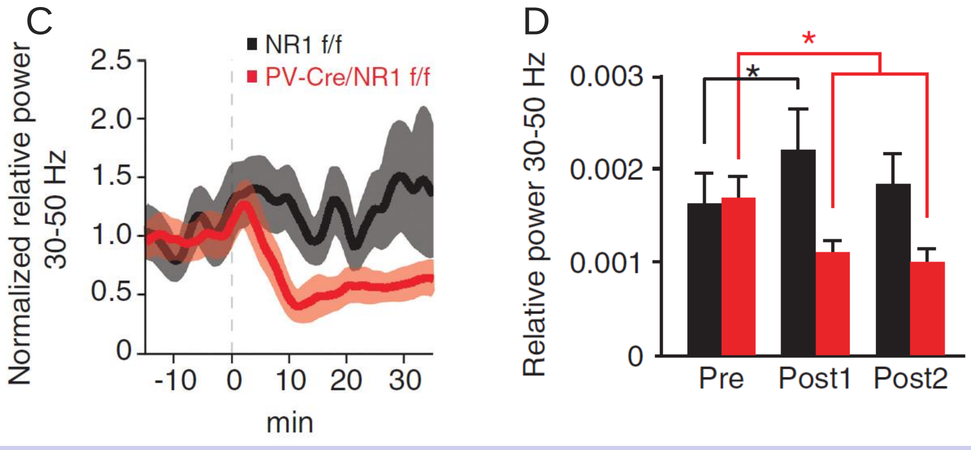
(A) Schematic illustration of cell-type specific stimulation by ChR2 in mouse cortex.

(B) Mean power ratio in each LFP frequency band in response to laser-driven ChR2 expressed in FS-PV neurons at varying frequencies in mouse barrel cortex.

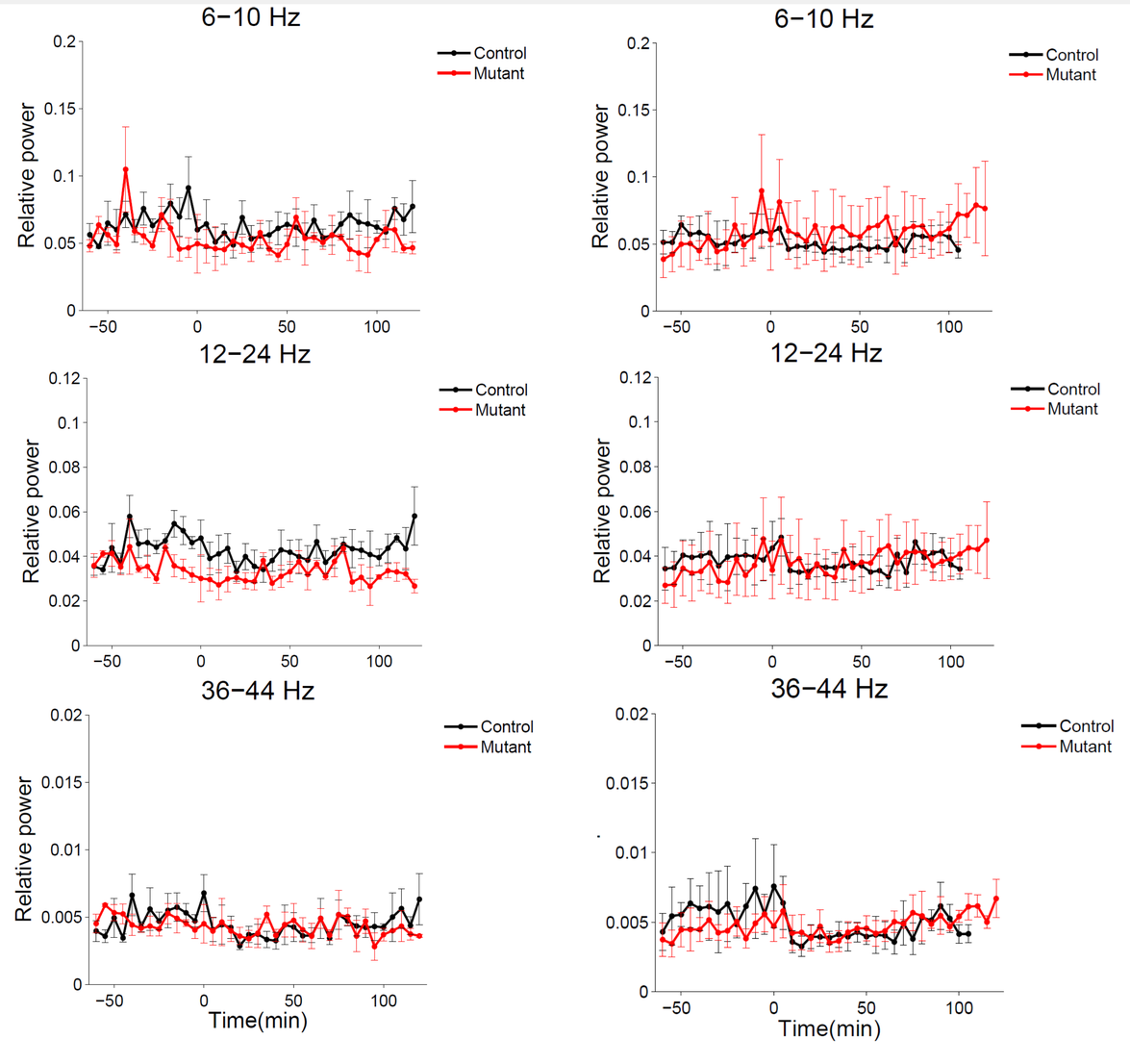
The NMDAR hypofunction hypothesis predicts that schizophrenia is associated with reduced neuro-transmission through NMDAR. Exposure to NMDAR antagonists (i.e. MK-801) creates oscillatory abnormalities in mice in the gamma band, changes correlating to abnormalities seen in schizophrenic patients. NMDAR preferentially drive activity of cortical inhibitory interneurons, giving NMDAR a greater role in regulating fast-spiking PV interneurons than excitatory neurons.



In vivo LFP recording in barrel cortex of aneathesized animals.
(A) Light activation of FS-PV neurons in the control and PV-Cre NR1f/f mice at 8, 24, 40 Hz on relative LFP power.
(B) Relative power at 8, 24, 40 in the PV-Cre NR1f/f mice during spontanous (solid bars) and light activated (striped bars) activities.



In vivo LFP recording in barrel cortex of freely behaving mice.
Average relative power in the 30-50 Hz gamma frequency range 15 min before administration of MK-801 (IP; 0.3mg/kg) (dashed line) to 35 min after. Acute MK-801 gives a significant increase in relative gamma power in control animals and significant reduction in PV-Cre NR1f/f mice.



In vivo acute clozapine (SC; 1.0mg/kg, left; and 3.0mg/kg, right) administration in aneathesized animals showed no significant difference in extracellular LFP in PFC between in PV-Cre NR1f/f mice and controls.

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