

## BACKGROUND

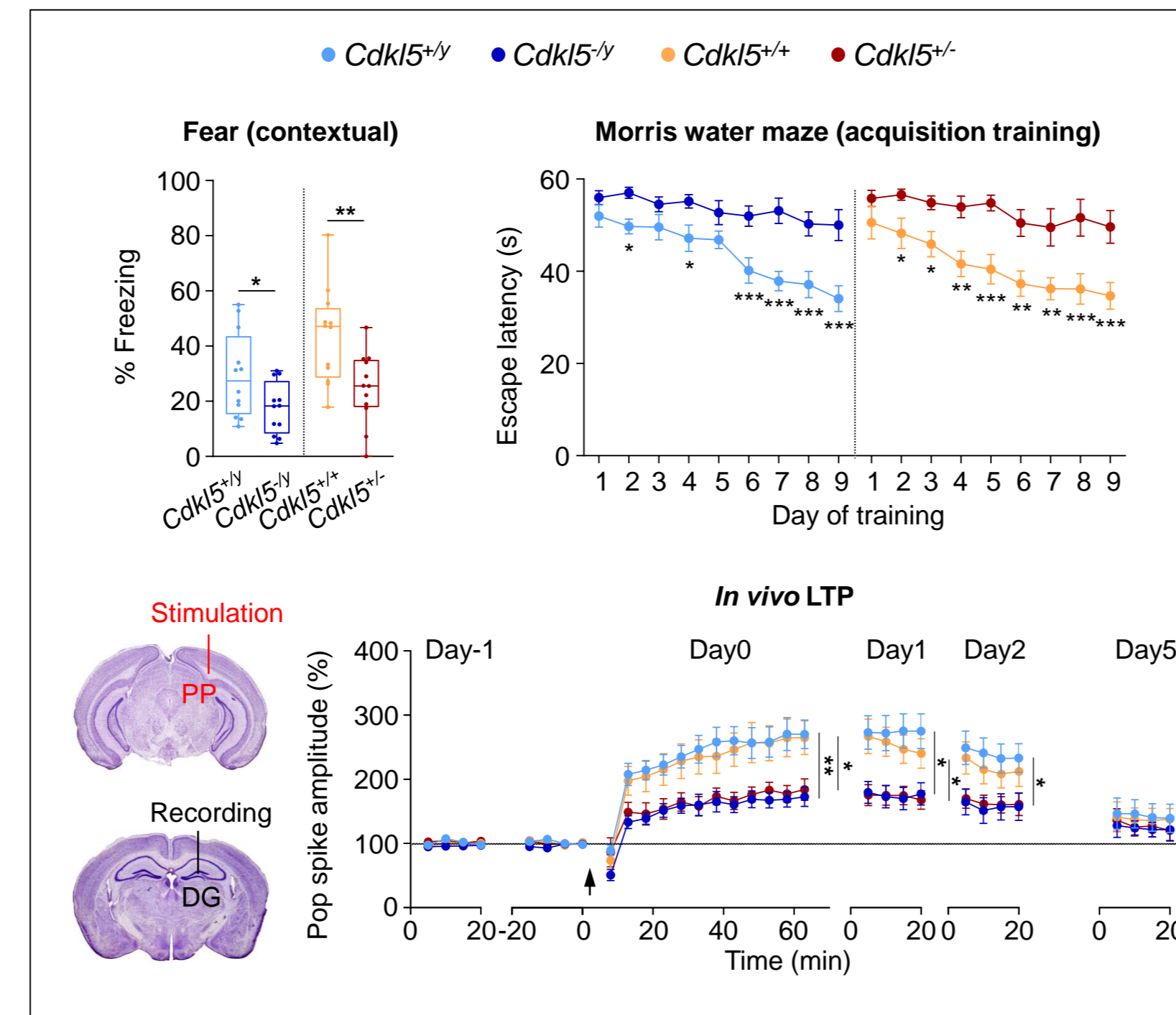
CDKL5 deficiency disorder (CDD) is a neurodevelopmental disease caused by mutation of the X-linked gene cyclin-dependent kinase-like 5 (*CDKL5*). CDD is characterized by severe intellectual disability, gross motor impairment, early-onset epilepsy, and autistic features. Mouse models of CDD recapitulate the cognitive deficits and other characteristics of this condition. Global KO/knock-in mutation of *CDKL5* or conditional *CDKL5* loss in forebrain excitatory neurons impairs hippocampus-dependent memory in mice. Although loss of *CDKL5* affects a number of molecular pathways, how *CDKL5* absence shapes the hippocampal neural circuit activity and, subsequently, affects the related memory function has not been elucidated.

## PURPOSE

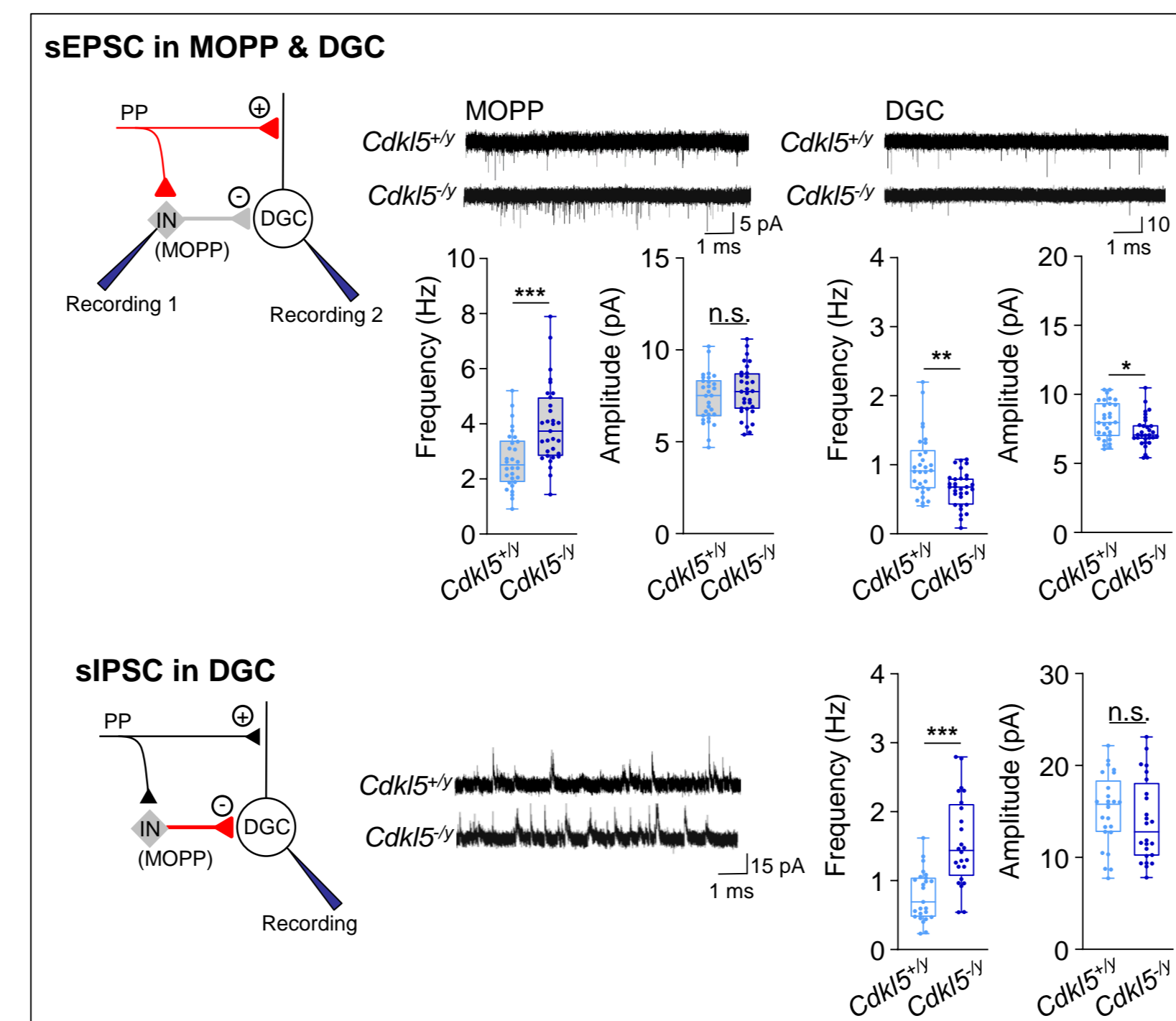
Here we assessed hippocampus-dependent memory, synaptic plasticity, and local circuit activity in a unique *CDKL5* knockout mouse model. In addition, we revealed the rescue effect of chronic fornical deep brain stimulation (DBS) on these deficits.

## METHODS

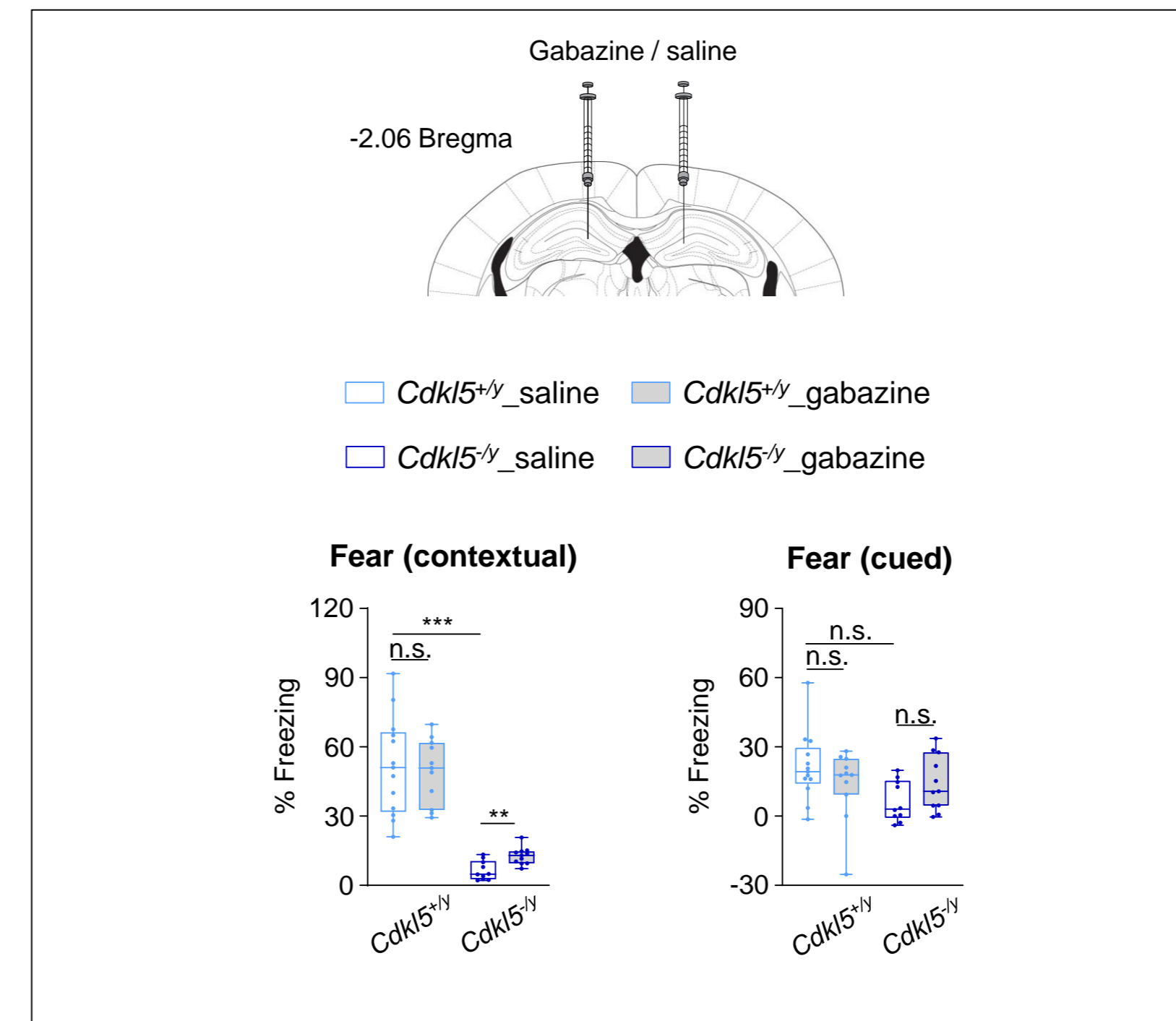
- Male *Cdkl5*<sup>-/-</sup> (4 months) and female *Cdkl5*<sup>+/-</sup> mice (6 months) (B6.129(FVB)-*Cdkl5*<sup>tm1.1Joz/J</sup>) with their wild type (*Cdkl5*<sup>+/-</sup>, *Cdkl5*<sup>+/+</sup>) littermates
- Behavioral tasks: fear conditioning and Morris water maze
- *In vivo* / *ex vivo* electrophysiology



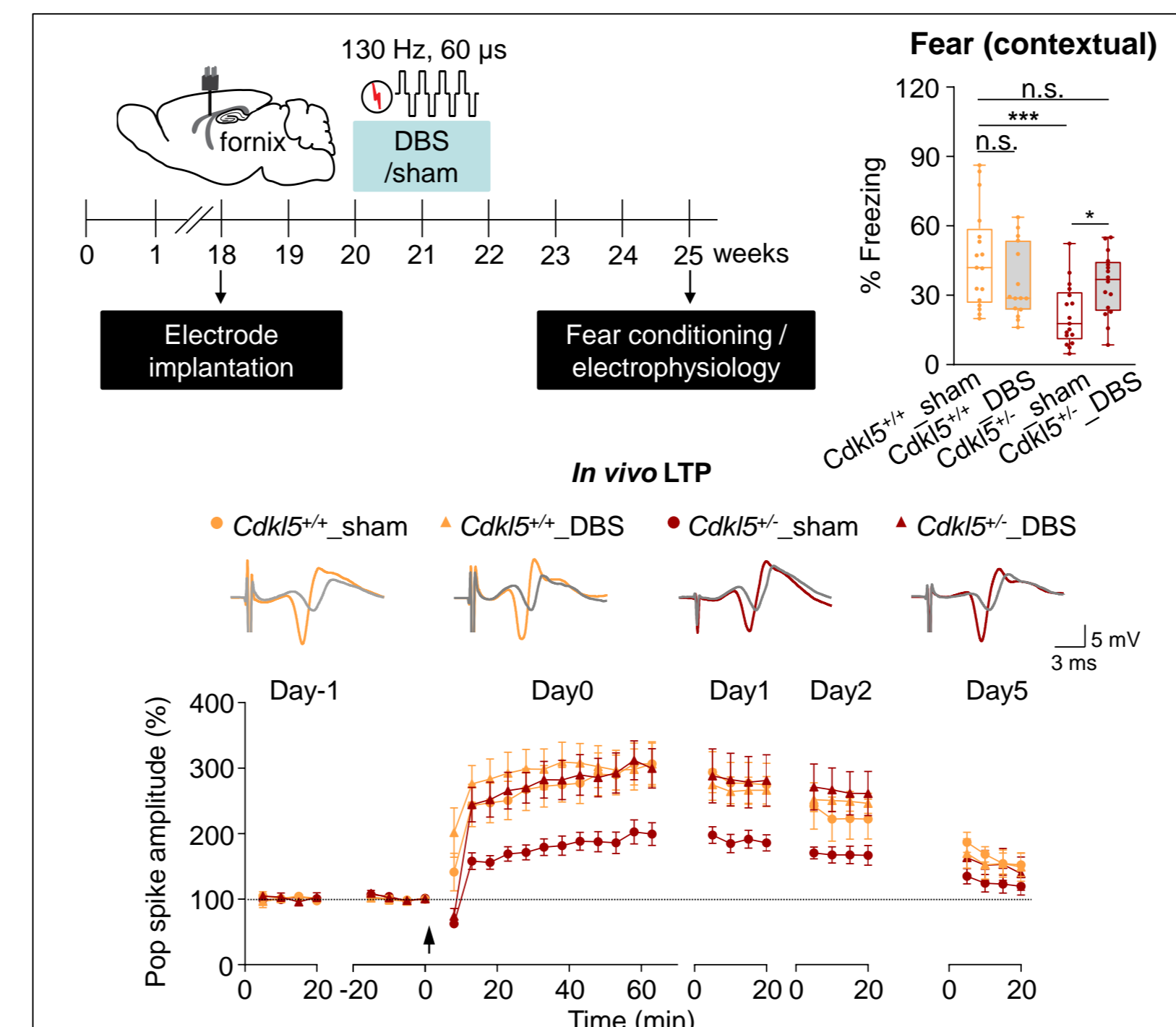
**Fig 1:** Loss of *CDKL5* impairs hippocampal memory and PP-DG synaptic plasticity *in vivo*



**Fig 2:** Loss of *CDKL5* shift the excitation / inhibition balance of dentate granule cell (DGC)



**Fig 3:** GABA<sub>A</sub>R antagonist improves hippocampal memory of male *CDKL5* knockout mouse

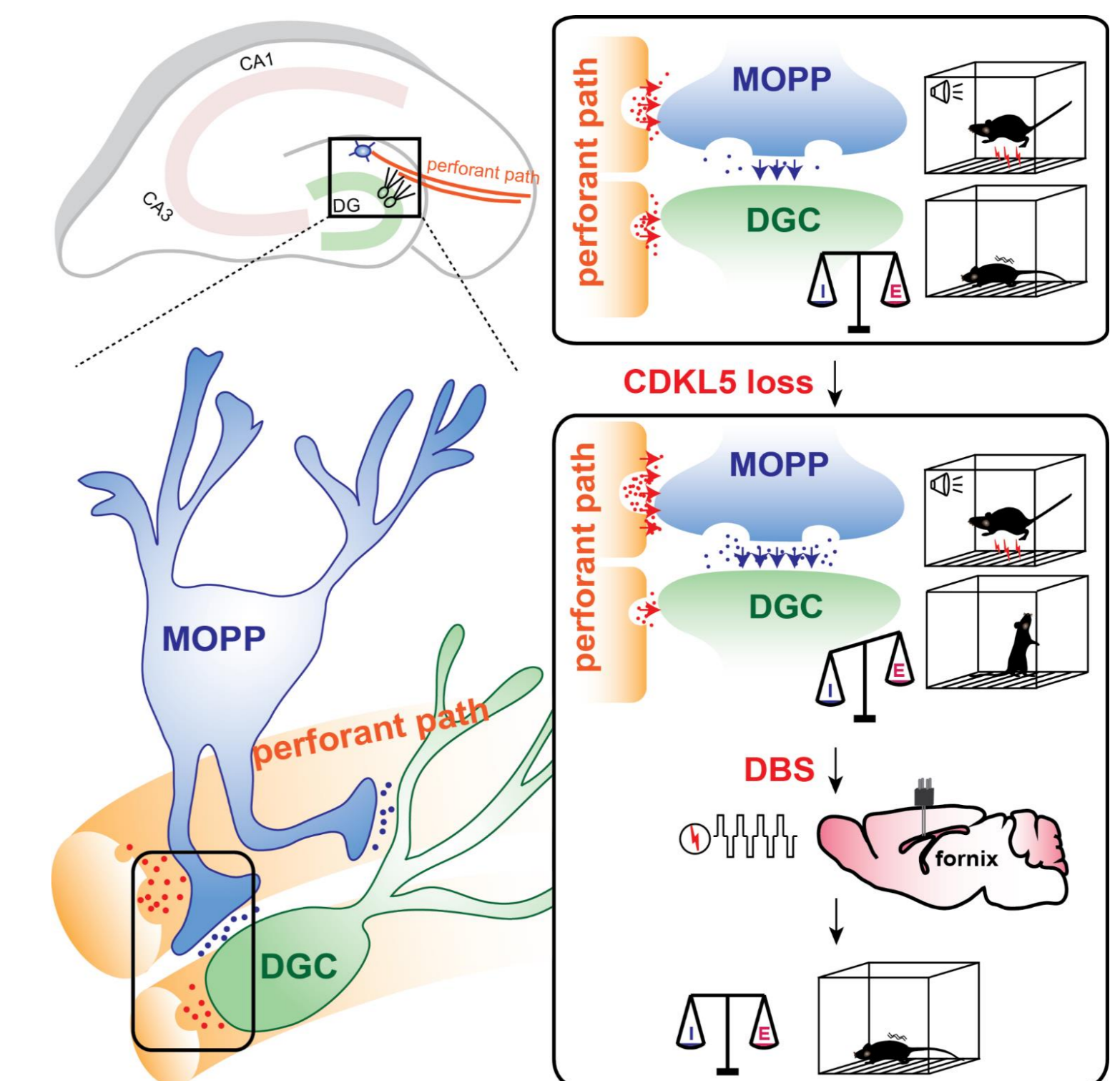


**Fig 4:** DBS rescues hippocampal memory and synaptic plasticity of female *CDKL5* knockout mouse

## RESULTS

- Loss of *CDKL5* impairs hippocampal memory and LTP in PP-DG pathway.
- Loss of *CDKL5* decreases excitatory, but increases inhibitory synaptic transmission in DGCs, skewed the E/I balance toward inhibition.
- Suppressing the overinhibition in the DG by gabazine improves hippocampal memory in *Cdkl5*<sup>-/-</sup> mice.
- Chronic fornical DBS rescues hippocampal memory, restores LTP, and relieves feedforward inhibition in *Cdkl5*<sup>+/-</sup> mice.

## CONCLUSION



## REFERENCES

1. Hao S, Tang B, Wu Z, Ure K, Sun Y, Tao H, Gao Y, Patel AJ, Curry DJ, Samaco RC, Zoghbi HY, Tang J. Fornical deep brain stimulation rescues hippocampal memory in Rett syndrome mice. *Nature*. 2015. [PMID: 26469053]
2. Hao S, Wang Q, Tang B, Wu Z, Yang T, Tang J. *CDKL5* deficiency augments inhibitory input into the dentate gyrus that can be reversed by deep brain stimulation. *J Neurosci*. 2021. [PMID: 34544833]