DNMT1-mediated regulation of PV interneuron activity modulates cortical circuits through oligodendroglial remodeling and perineuronal net maintenance

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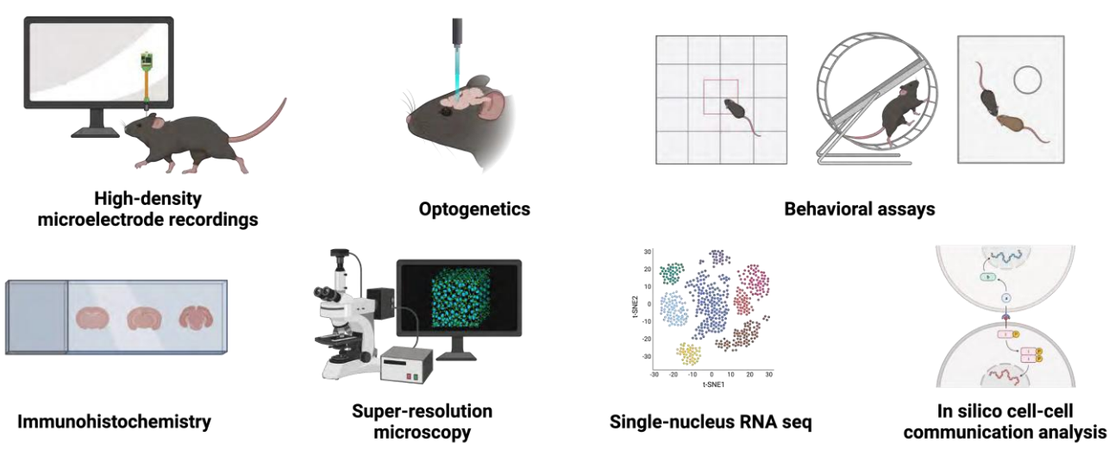
Introduction

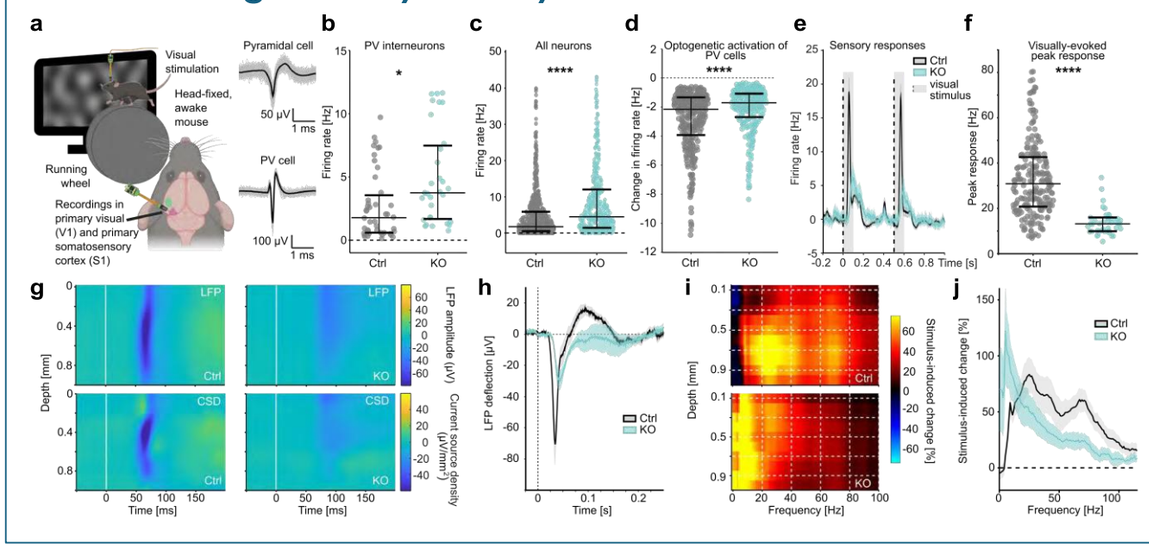
Parvalbumin-positive (PV) interneurons play essential roles in cortical computation, generating gamma oscillations and maintaining network excitability, and their dysfunction is implicated in schizophrenia, epilepsy, and other neuropsychiatric disorders. Epigenetic mechanisms, such as DNA methylation catalyzed by DNA methyltransferases (DNMTs) have emerged as critical regulators of synaptic function and neuronal plasticity, coupling persistent transcriptional control to activity-dependent processes. Our group has previously demonstrated that DNMT1 modulates clathrin-mediated endocytosis and synaptic vesicle replenishment in PV interneurons through repressive DNA methylation of endocytosis-related genes, thereby influencing GABAergic transmission and inhibitory output. Yet, how this epigenetic control propagates to circuit-level dynamics and influences the surrounding extracellular niche remained unexplored. Perineuronal nets (PNNs), specialized extracellular matrix structures that preferentially surround PV interneurons and stabilize their function, are often disrupted in psychiatric and neurological conditions. Here, we investigate how DNMT1 deletion in PV interneurons triggers non-cell-autonomous transcriptional remodeling in neighboring cell populations, and examine the consequences for PNN integrity, circuit dynamics, and behavior.

Methods

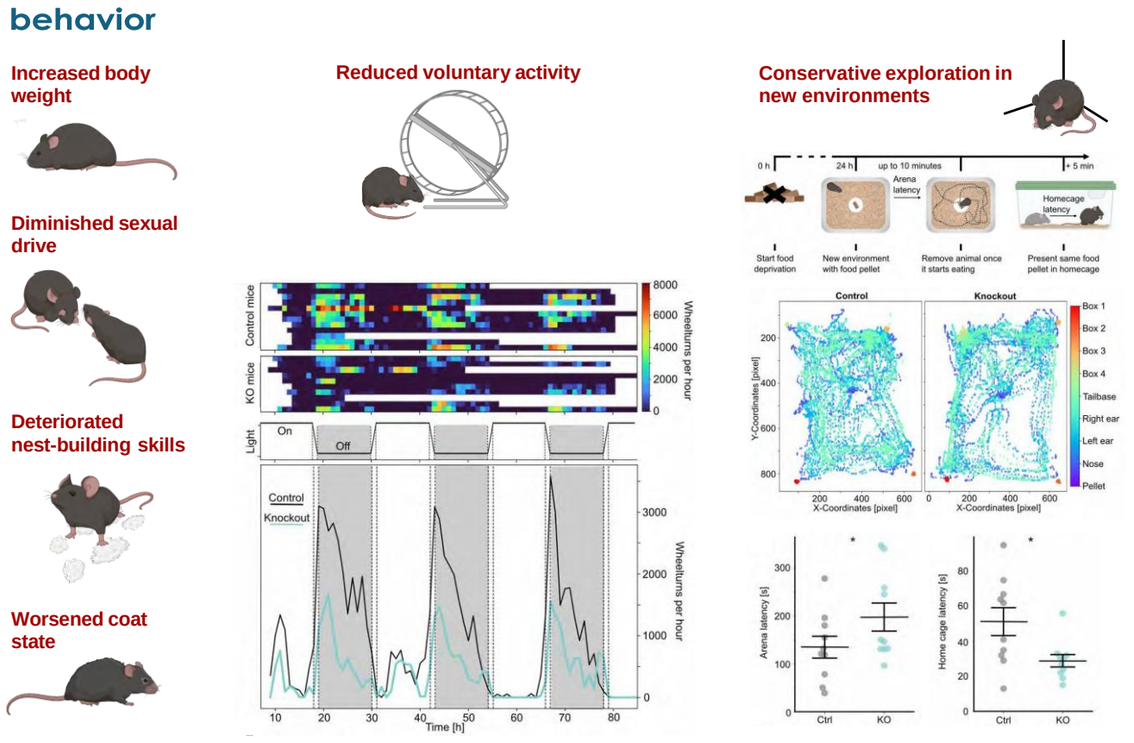


Findings

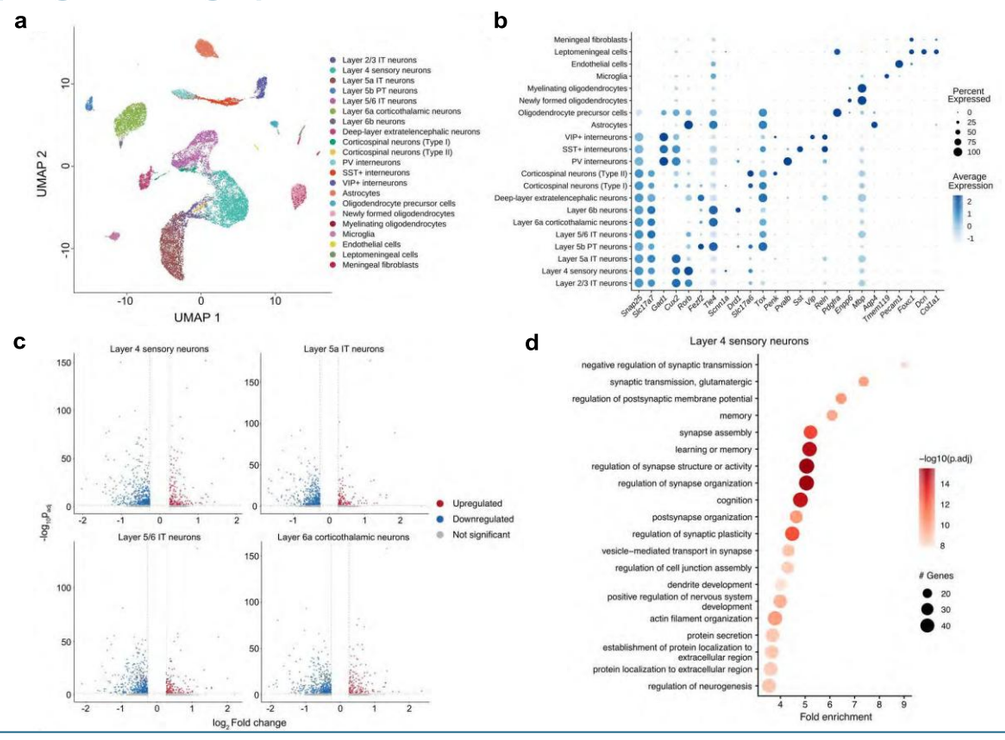
1. *Dnmt1* deletion in PV interneurons increases overall network activity and disturbs gamma synchrony



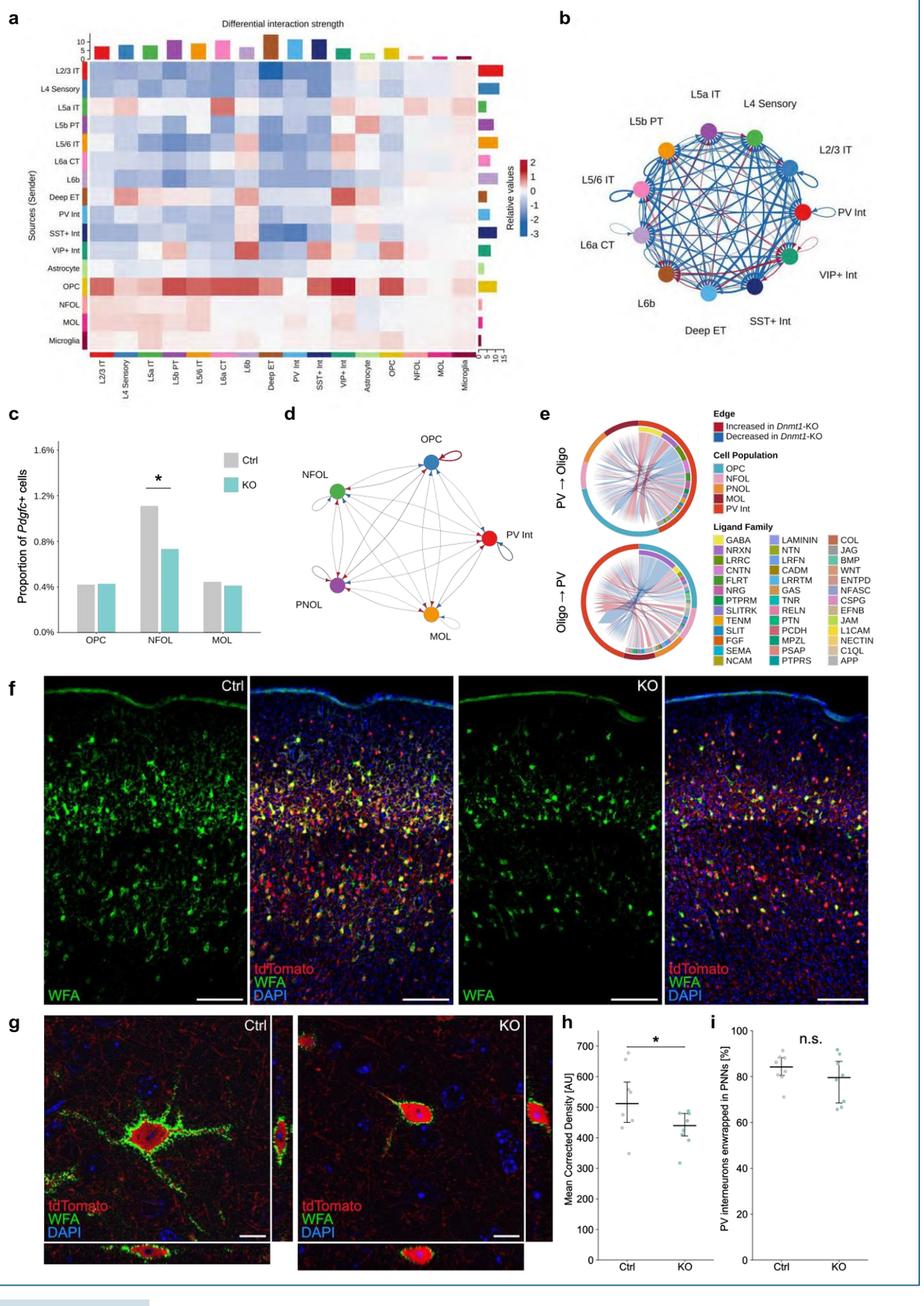
2. Mice with DNMT1-deficient PV interneurons display depression-like behavior



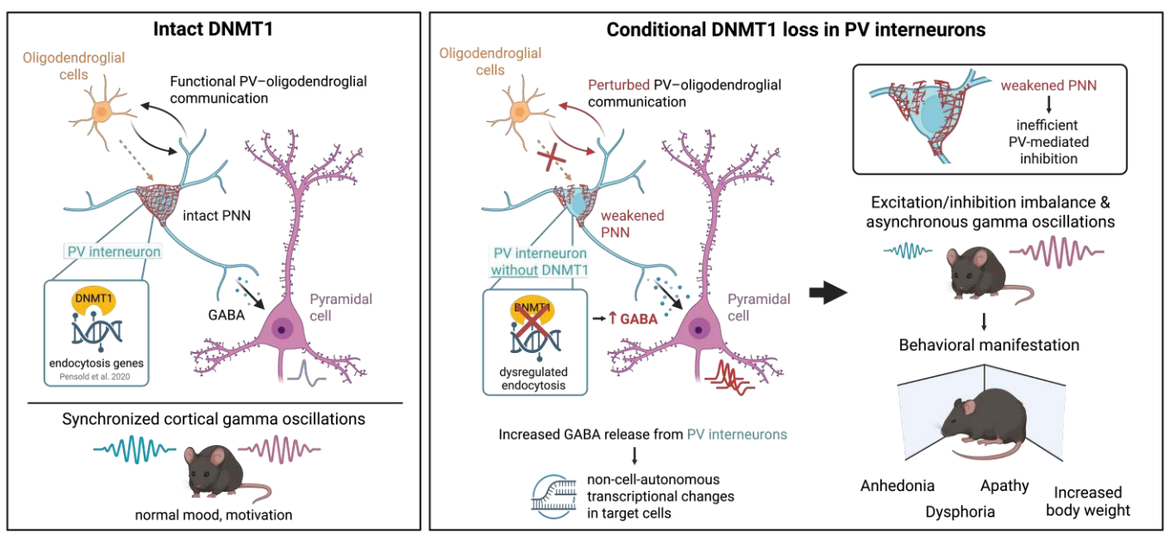
3. Single-nucleus RNA sequencing reveals cortex-wide transcriptional reprogramming upon *Dnmt1*-deletion in PV interneurons



4. PV–oligodendroglial communication is perturbed upon loss of DNMT1 in PV interneurons, leading to weakened perineuronal nets



Summary



Affiliations & References

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Pensold, D. et al. (2020) 'DNA Methylation-Mediated modulation of endocytosis as potential mechanism for synaptic function regulation in murine inhibitory cortical interneurons,' *Cerebral Cortex*, 30(7), pp. 3921–3937. https://doi.org/10.1093/cercor/bhaa009.

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Funded by DFG Deutsche Forschungsgemeinschaft German Research Foundation
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