Dopamine pathways mediating affective state transitions after sleep loss

Mingzheng Wu, Xin Zhang, Sihan Feng, Sara N. Freda, Pushpa Kumari, Vasin Dumrongprechachan, Yevgenia Kozorovitskiy
Department of Neurobiology, Northwestern University

Abstract

Pathophysiology of affective disorders—particularly circuit-level mechanisms underlying bidirectional, periodic affective state transitions—remains poorly understood. In patients, disruptions of sleep and circadian rhythm can trigger transitions to manic episodes, while depressive states are reversed. Here, we introduce a hybrid automated sleep deprivation platform to induce transitions of affective states in mice. Acute sleep loss causes mixed behavioral states featuring hyperactivity, elevated social and sexual behaviors, and diminished depressive-like behaviors, where transitions depend on dopamine. Using dopamine sensor photometry and projection-targeted chemogenetics, we reveal that elevated dopamine release in specific brain regions mediates distinct behavioral changes in affective state transitions. Acute sleep loss induces dopamine-dependent enhancement in dendritic spine density and uncaging-evoked dendritic spinogenesis in the medial prefrontal cortex, whereas optically mediated disassembly of enhanced plasticity reverses the antidepressant effects of sleep deprivation on learned helplessness. These findings demonstrate that brain-wide dopaminergic pathways control sleep loss-induced polymodal affective state transitions.

Hybrid SD paradigm combining elements of the traditional flowerpot and the rotating beam

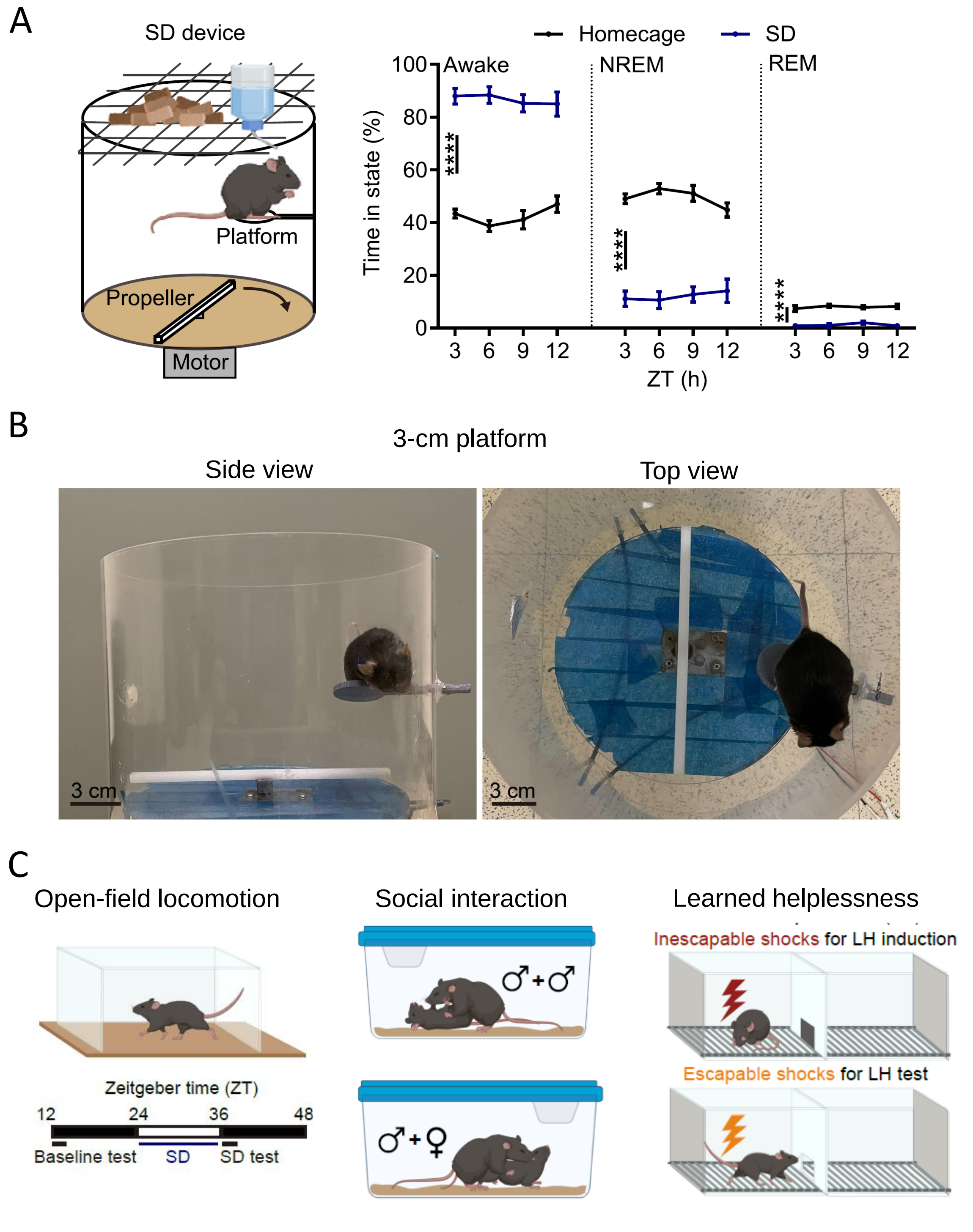


Figure 1. (A). Left, schematic of the hybrid sleep deprivation (SD) apparatus. Right, validation by EEG and EMG recording. n = 4-5 animals/group. Two-way ANOVA, homecage vs SD, Awake, p < 0.0001, NREM, p < 0.0001, REM, p < 0.0001. (B). Sideview and top view photos showing a mouse in a SD device with a 3-cm-diameter platform. Blue tape is on the outside of the floor of the chamber. Side walls are covered by opaque material during experiments. Food and water access are provided via the mesh on top (not shown). (C). Behavioral paradigms tested after acute SD

Acute sleep deprivation induces affective state transitions

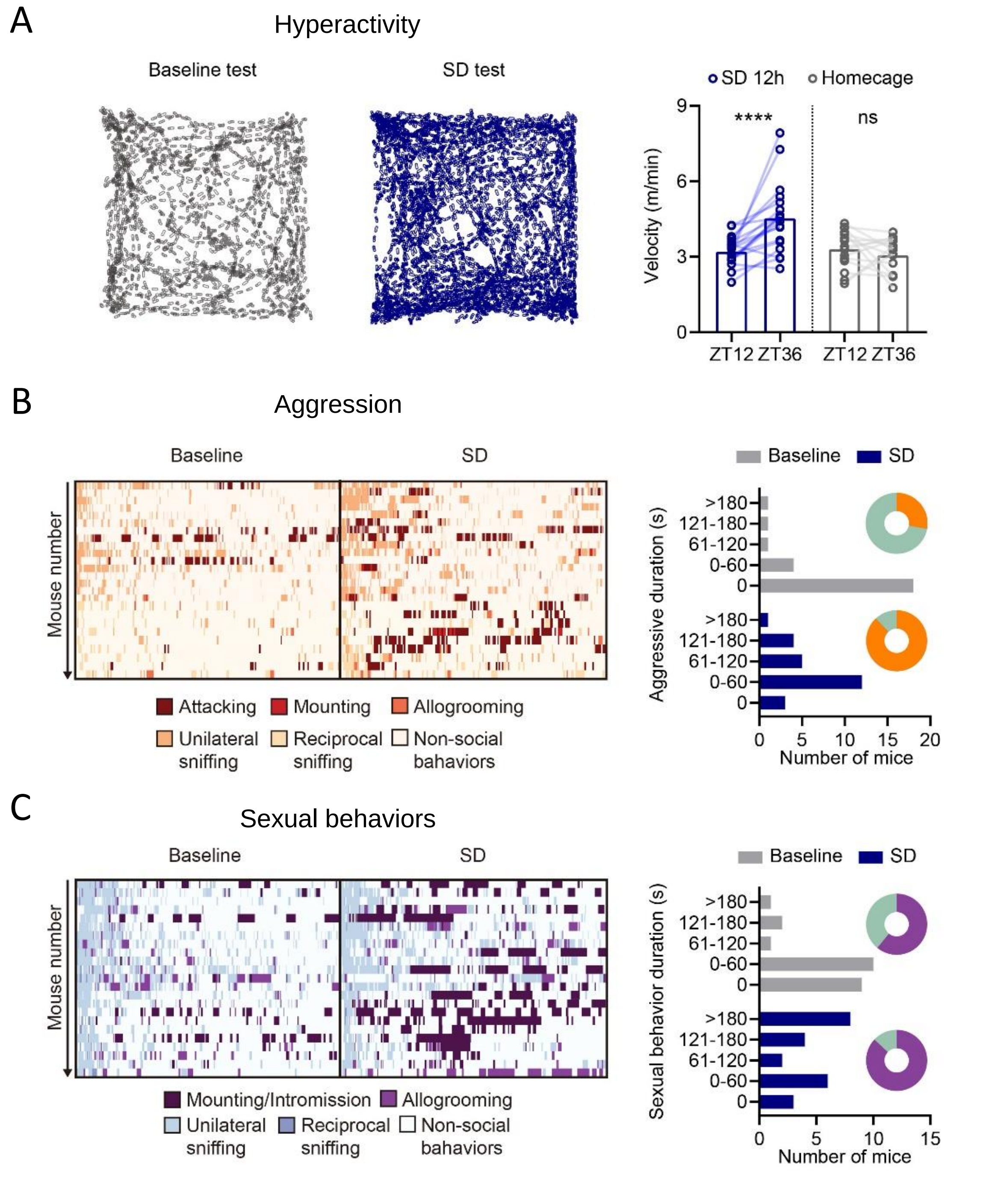


Figure 2. (A). Trajectories of locomotor activity and summary data showing the distance traveled in the open field locomotion test at ZT12 and ZT36 for SD and homecage control mice. (B). Plots showing behavioral motif classifications in individual resident mice and distribution of aggressive behavior before and after SD. (C). Plots show behavioral motif classifications of individual resident mice towards receptive females and distribution of sexual behavior timing before and after SD.

Acute sleep deprivation reverses depressive states

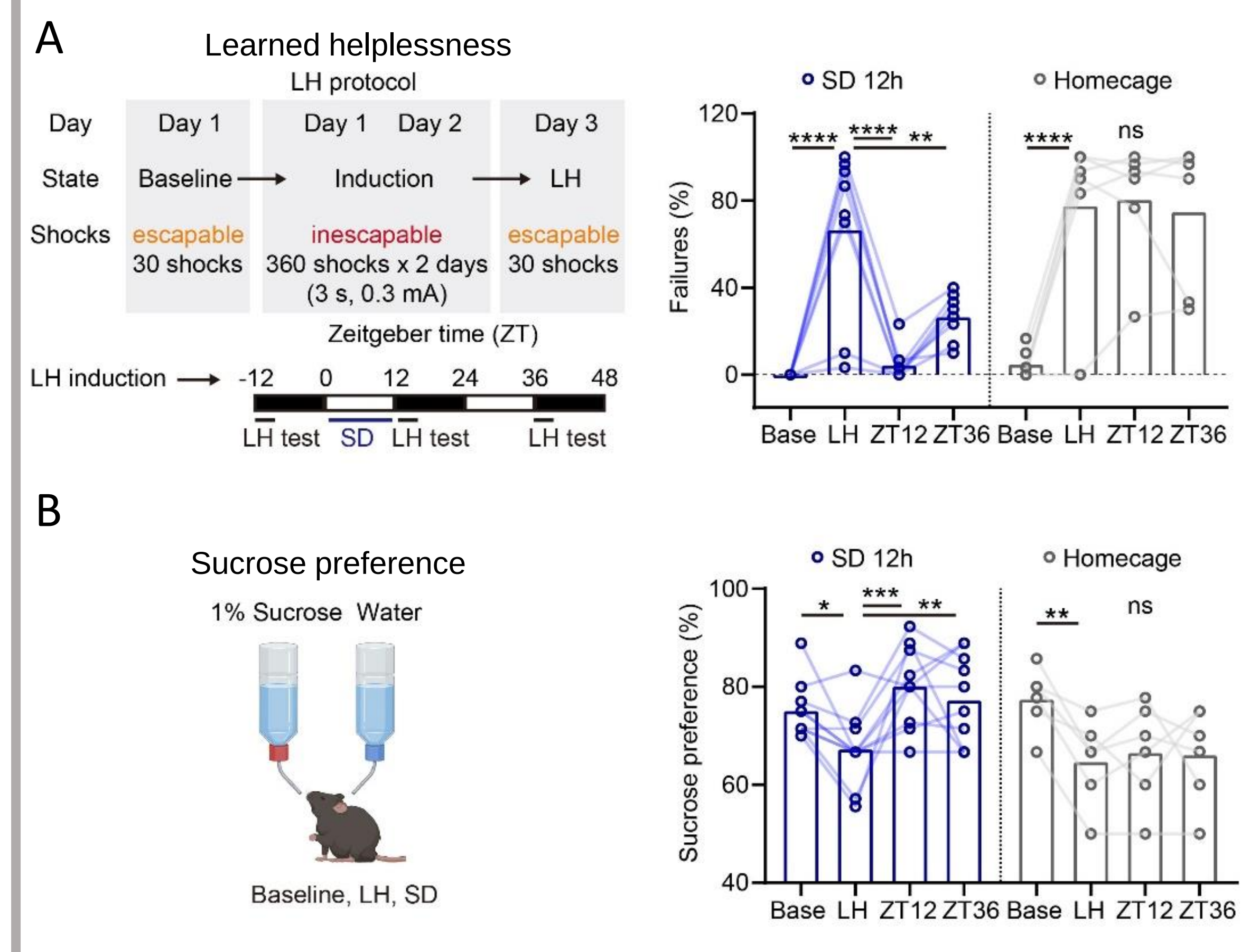


Figure 3. (A). Schematics show the timeline for learned helplessness (LH) induction and escape tests before and after SD. Summary data show the percentage of failures to escape an avoidable foot-shock across conditions. (B). Schematics show the conditions for sucrose preference test. Summary data show the percentage of sucrose preference by volume consumed across conditions.

Sleep perturbation amplifies spontaneous DA release in distributed brain regions

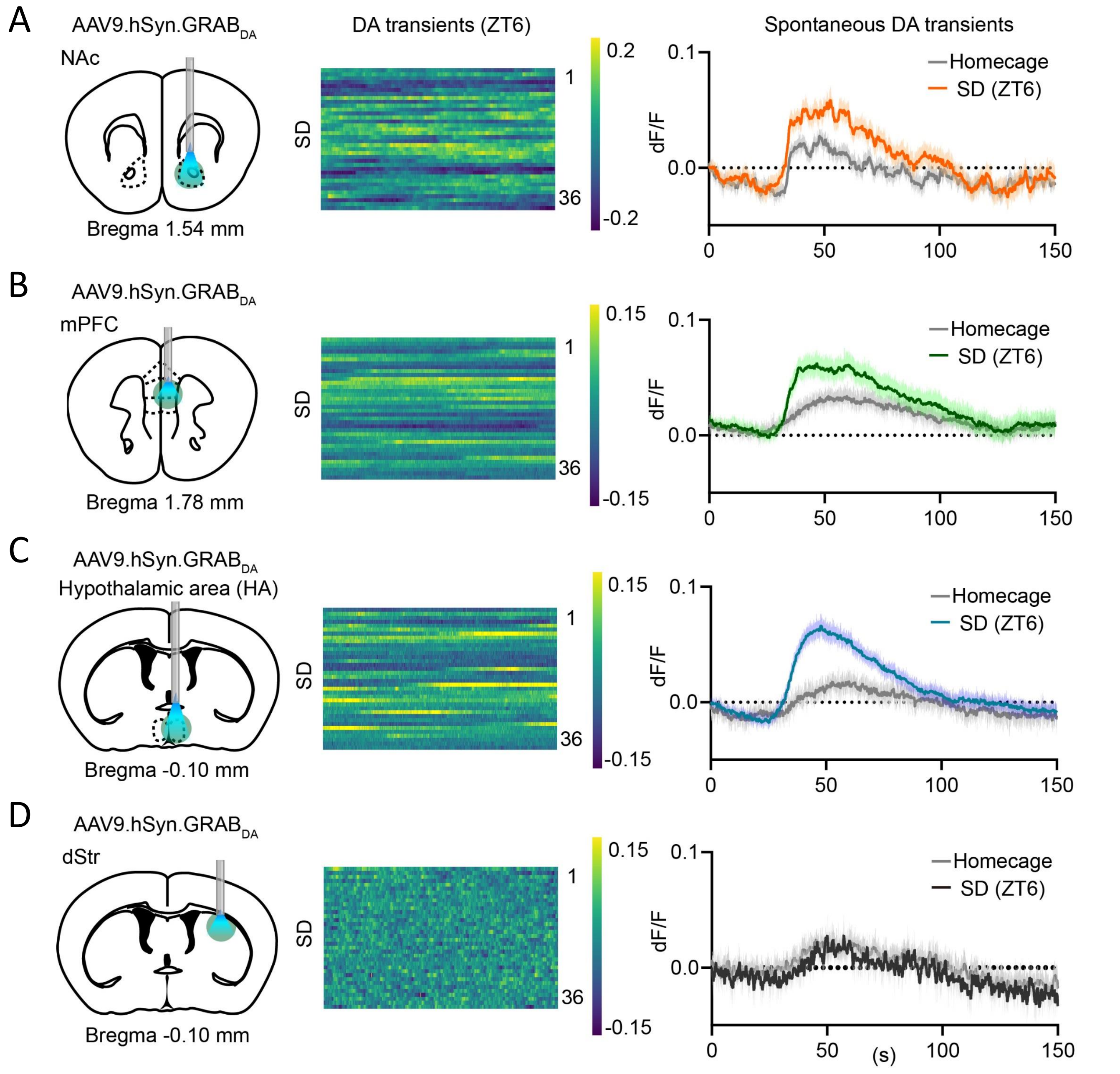


Figure 4. (A). Left, schematic showing viral transduction of AAV9.hSyn.GRABDA in the Nucleus Accumbens (NAc). Middle, heatmap plots showing spontaneous DA transients in the NAc at ZT6 during SD. Right, average trace of spontaneous DA transients in the NAc in the home cage and during SD from all animals. (B). Same as (A), but for DA transients in the mPFC. (C). Same as (A), but for DA transients in HA. (D). Same as (A), but for DA transients in the dStr.

Distinct modulation of state transitions by dopaminergic pathways

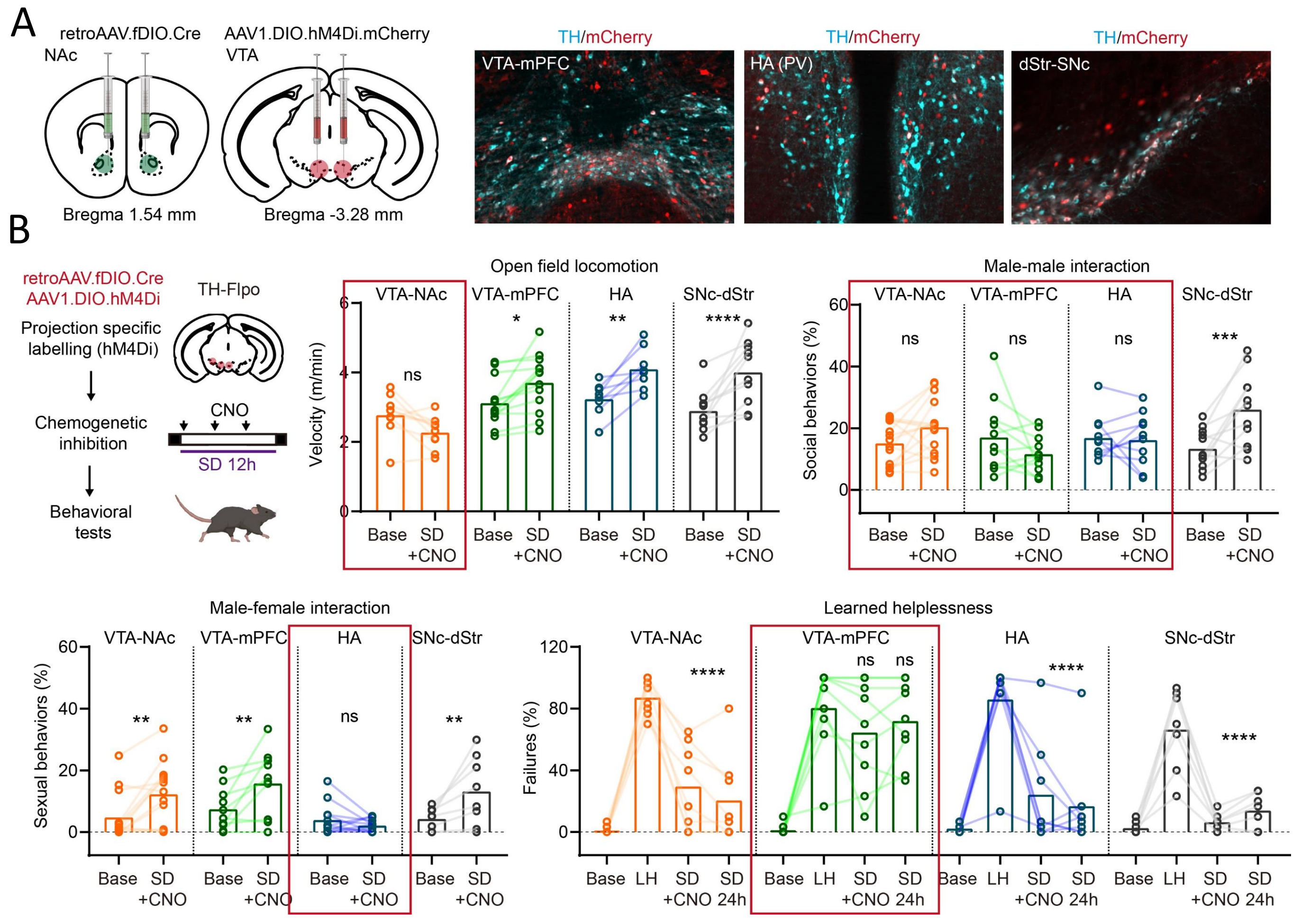


Figure 5. (A). Schematic shows projection-specific viral transduction strategies for targeting NAc-projecting, and histological images of mCherry+ cell bodies for DA neurons projecting to mPFC, HA, and dStr. (B). Schematic showing the timeline of CNO administration and behavioral tests. Summary data for distance traveled in the open field locomotion, social interactions in resident-intruder tests, summary data for sexual behaviors with receptive females, and the percentage of failures to escape across conditions for learned helplessness behaviors, in baseline and after SD with chemogenetic inhibition of different subgroups of hM4Di+ DA neurons.

Acute SD recovers LH resilience through DA-dependent cortical dendritic spinogenesis

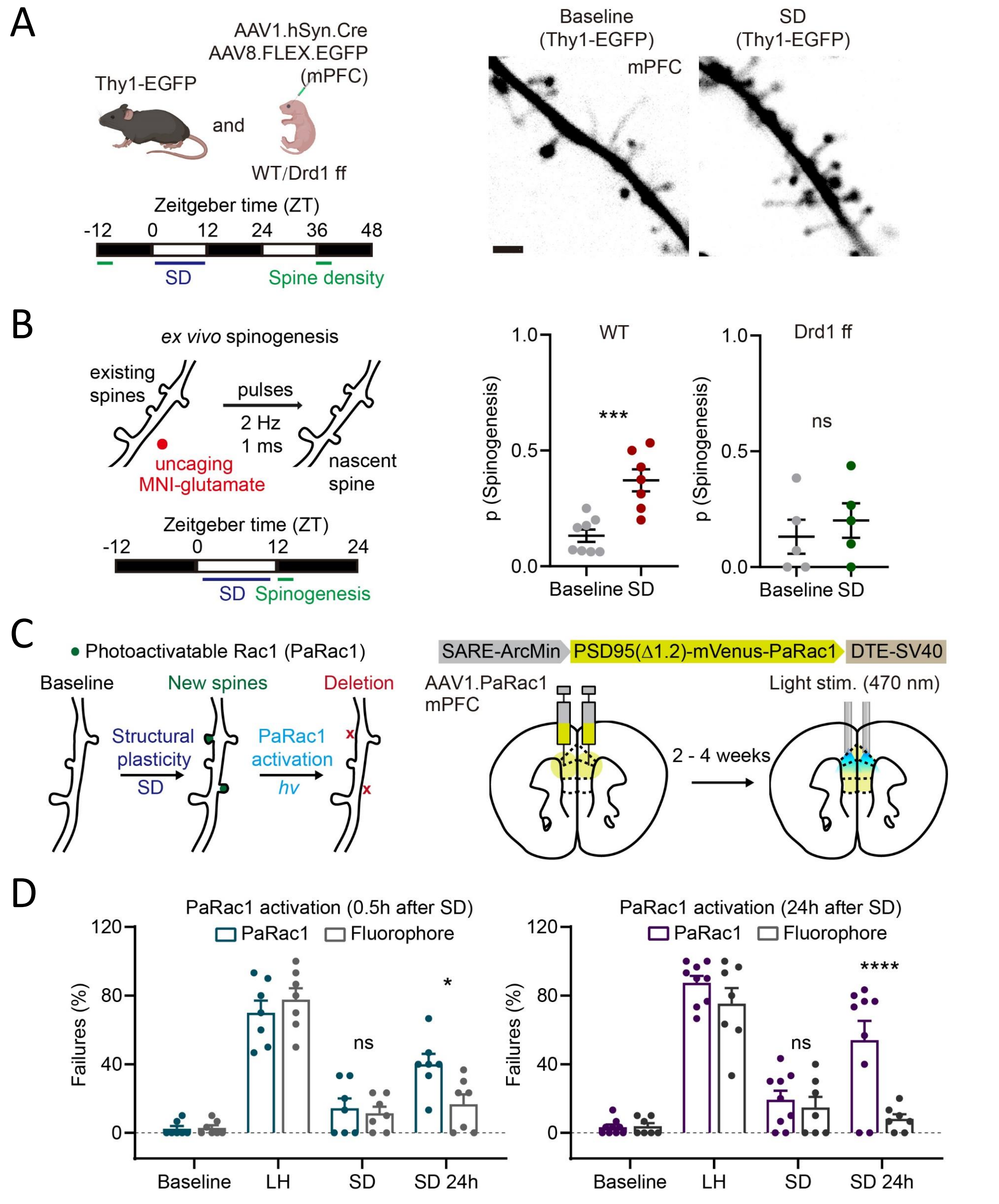
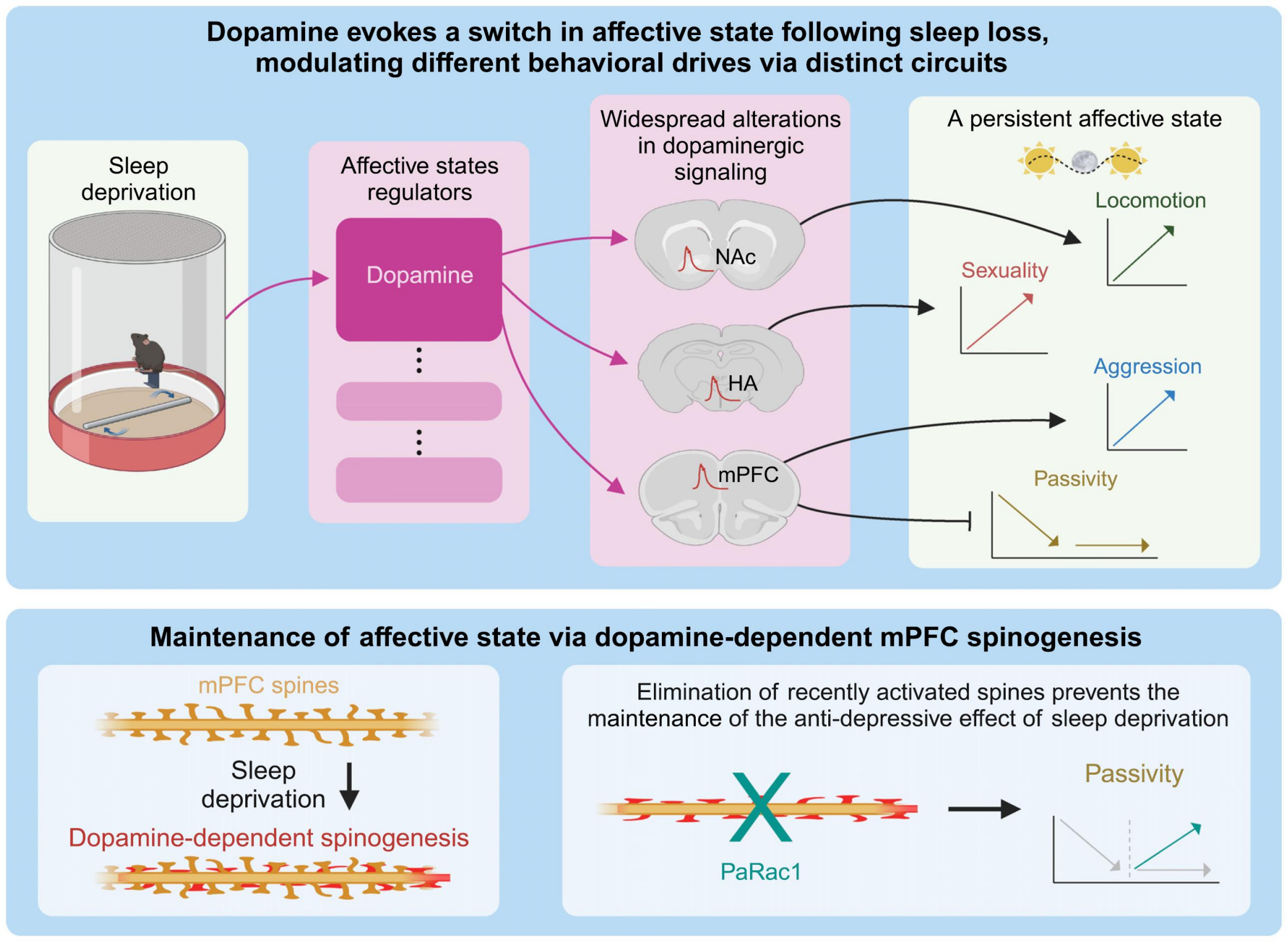


Figure 6. (A). Schematic showing neonatal viral transduction and 2PLSM images of distal dendrites of deep layer mPFC pyramidal neurons. (B). Schematic illustration of glutamate-evoked de novo spinogenesis, and summary data for the probability of spinogenesis on deep layer mPFC neurons. (C). Schematic showing the shrinkage of newly formed dendritic spines induced by the photoactivation of PaRac1 and the design of PaRac1 construct. (D). Summary data for the percentage of failures to escape across conditions in mice with PaRac1 photoactivation 0.5h and 24h after SD.

Conclusion



Dopamine evokes a switch in affective state following sleep loss, modulating different behavioral drives via distinct circuits

Maintenance of affective state via dopamine-dependent mPFC spinogenesis

Adapted from Bibi Sulaman, Tyler Kudlak, and Ada Eban-Rothschild
"Dopamine's reach: Unlocked by sleep loss"

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