

Mesolimbic dopamine modulates social motivation in an effort-based social decision-making task

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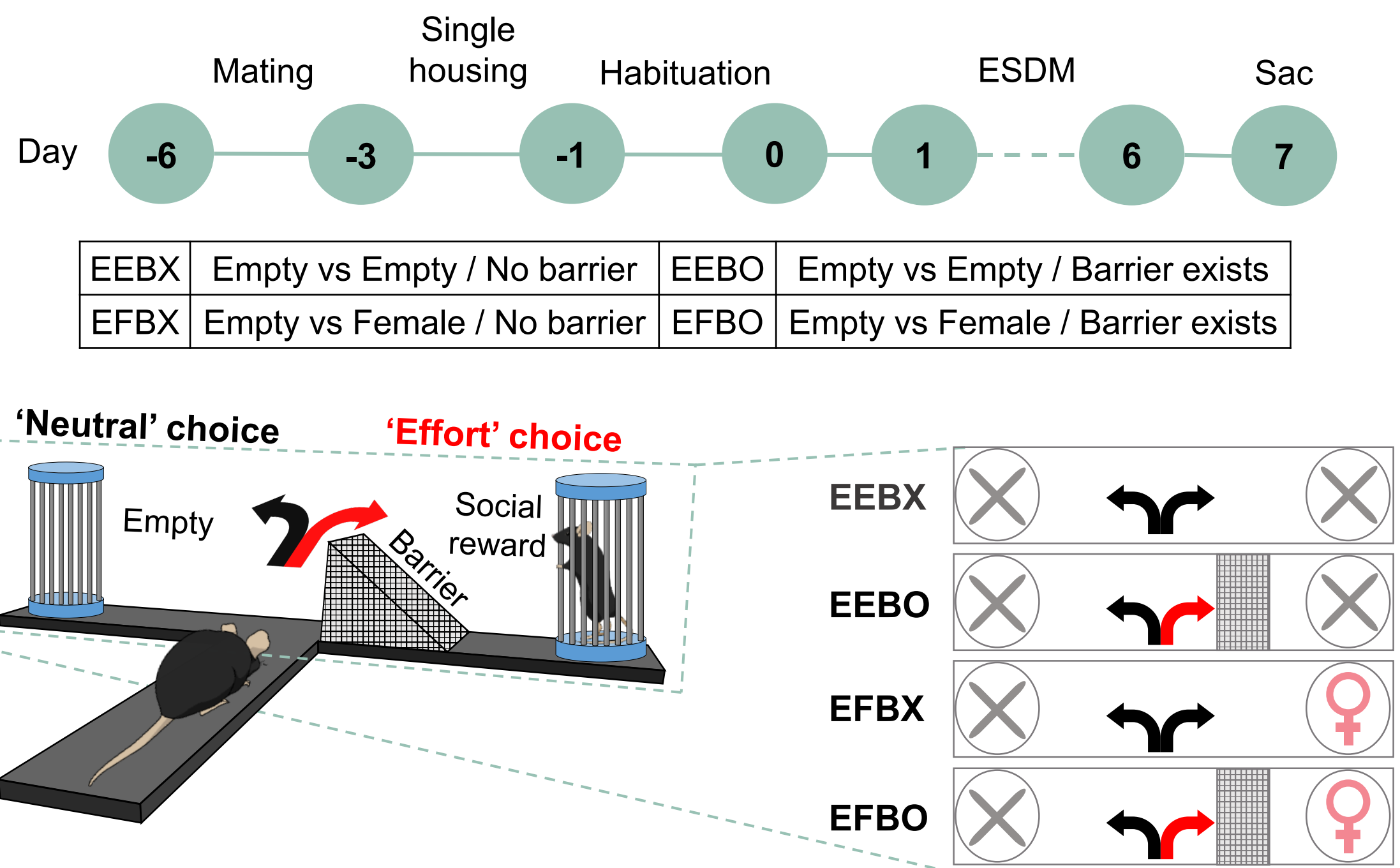
Abstract

Motivation is crucial for animals' goal-directed behavior, aiding them in persevering through challenges. In social animals, social interaction serves as a potent motivator to surmount obstacles. Nevertheless, the precise mechanism underpinning social motivation remains unclear. We designed an effort-based social decision-making (ESDM) task focusing on 'Effort' choices. Male mice consistently chose to approach females, even when it required necessitating a barrier (EFBO), especially on the last day of the task. We delved into dopamine receptor gene expression in the nucleus accumbens (NAc), a pivotal region for dopamine reception. Interestingly, *Drd1a* gene expression was notably elevated in the EFBO group. Furthermore, direct infusion of a D1R antagonist into the NAc, resulted in reduced 'Effort' choice levels. We also monitored real-time in vivo dopamine signals in the NAc during the task, noting that dopamine signals associated with 'Effort' choices were strengthened on the last day. Given the central role of the ventral tegmental area (VTA) in dopamine release, we conducted optogenetic manipulations of the VTA→NAc circuit. We found that it caused significant changes in 'Effort' choice levels. Finally, we discovered that heightened dopamine levels induce histone H3 dopaminylation at the *Drd1a* gene promoter region, thereby reinforcing ESDM behavior. These findings suggest that D1-cells within the mesolimbic dopaminergic system may play a crucial role in effort-based decision-making for social reward.

Keywords: Social behavior, Decision-making, Motivation, Nucleus accumbens, Dopamine

Method

Effort-based social decision-making (ESDM) task



EFBO group male mice made more 'Effort' choices for female social interaction reward

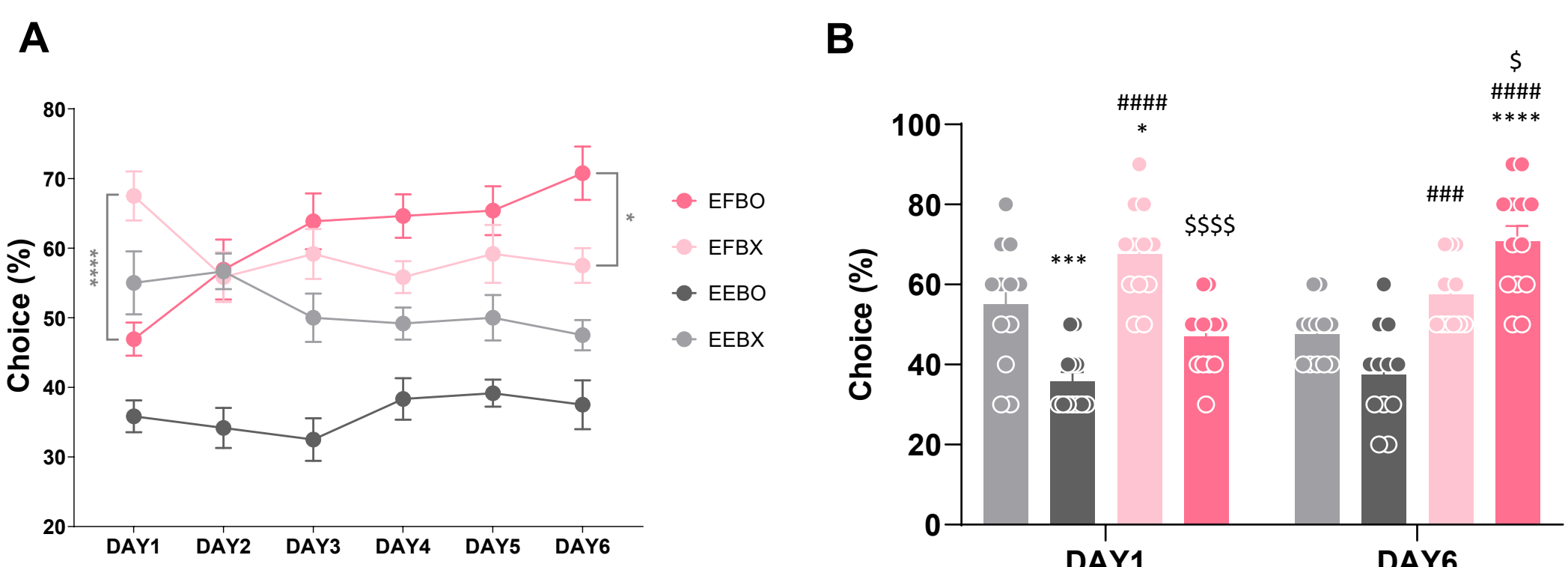


Fig 1. (A) Learning curves of 'Neutral' or 'Effort' choice level for empty or female enclosure during the entire task (Two-way ANOVA with Tukey's multiple comparisons test, *P<0.05, ****P<0.0001; data expressed as mean ±SEM). (B) Quantification of choice level illustrating that EFBO group mice chose 'Effort' choice significantly more than others on the last day of the task (Two-way ANOVA with Tukey's multiple comparisons test, *P<0.05, ***P<0.0005, ****P<0.0001 compared with the EEBX group; ###P<0.0005 ####P<0.0001 compared with the EEBO group; §P<0.05, §§§P<0.0001 compared with the EFBX group; data expressed as mean ±SEM).

Nucleus accumbens *Drd1a* gene expression was increased exclusively in the EFBO group

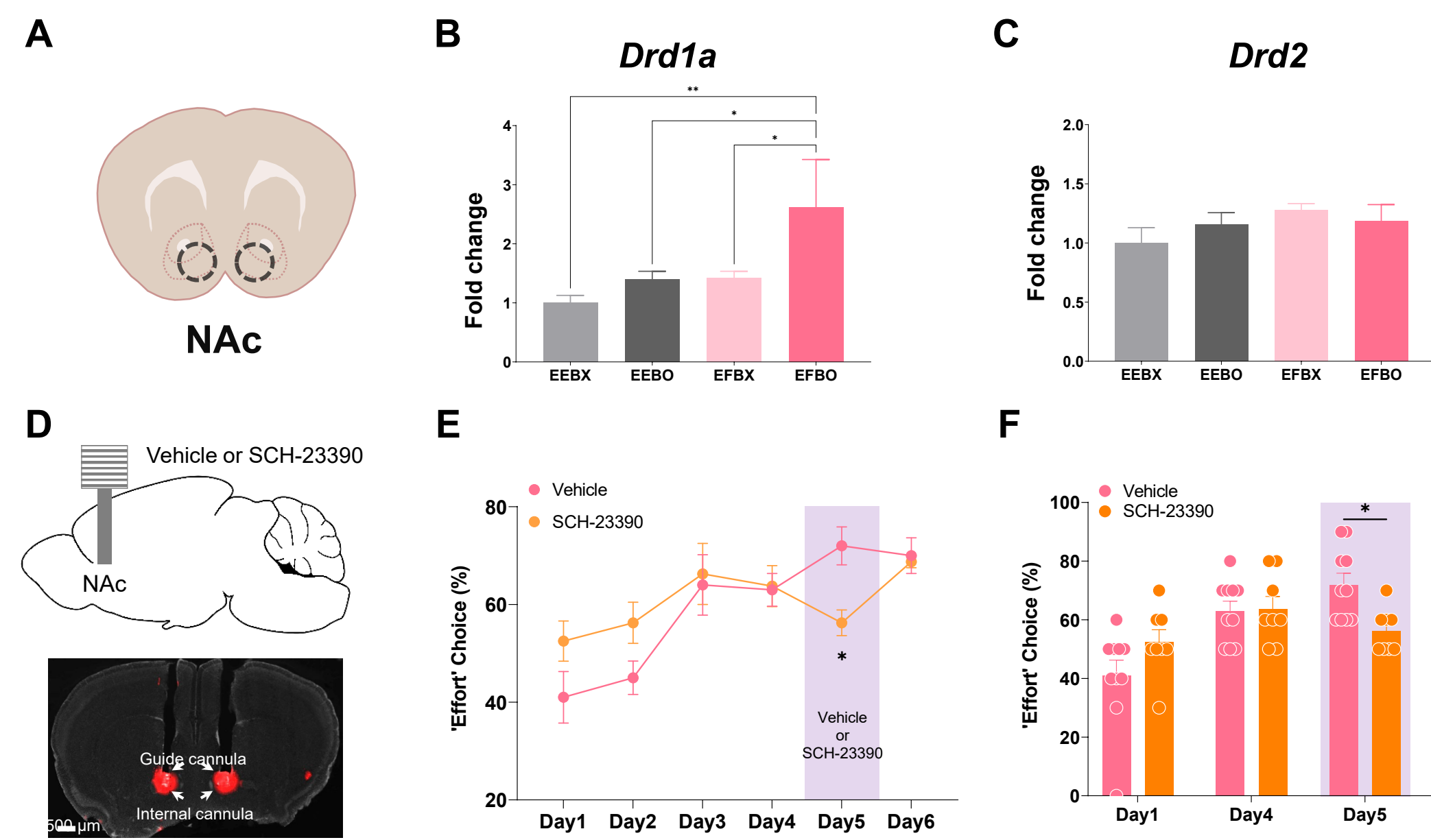


Fig 2. (A) Schematic showing NAc punch region for quantitative PCR work. (B) *Drd1a* gene expression after 6 days of ESDM task (One-way ANOVA Fisher's LSD multiple comparisons test *P<0.05, **P<0.005; data expressed as mean ±SEM). (D) Schematic showing cannula implantation for micro-infusion of the vehicle or D1R antagonist (SCH-23390) into the NAc. (E) Learning curves of 'Effort' choices for whole days (Two-way ANOVA Bonferroni's multiple comparisons test *P<0.05; data expressed as mean ±SEM). (F) D1R antagonist reduced 'Effort' choices on the day 5 of the ESDM task (Unpaired t-test **P<0.005; data expressed as mean ±SEM).

In vivo dopamine signals were enhanced by social motivation

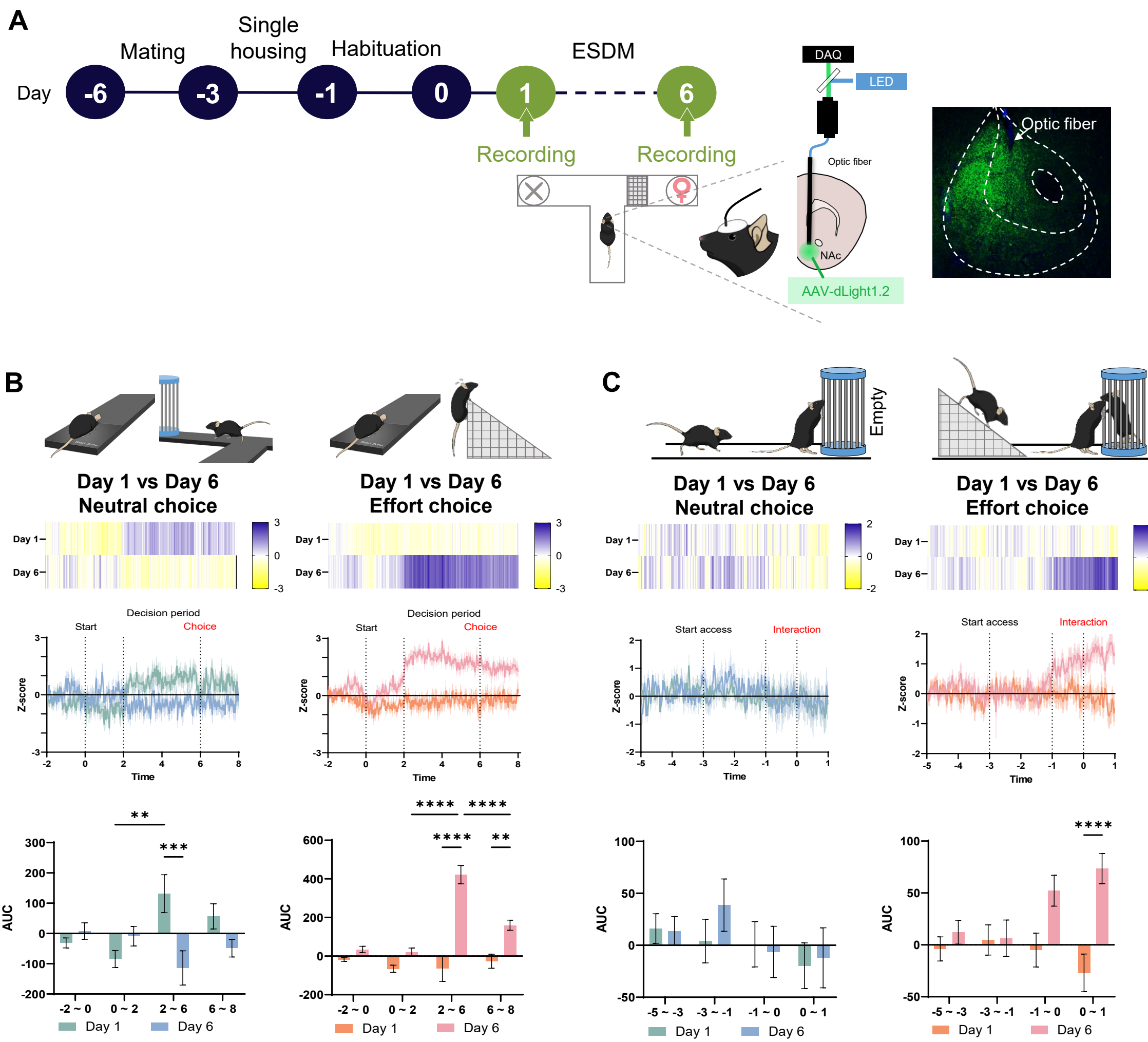


Fig 3. (A) Schematic showing experimental schedule and behavioral concepts for in vivo dopamine fiber photometry of ESDM task. (B-C) Changes in averaged dopamine signals (top) and quantification of area under curves (AUC) per time windows (bottom) during (B) decision-making and (C) interaction based on 'Neutral' or 'Effort' choices of mice on the day 1 or day 6.

'Effort' choice level was modulated by activation or inhibition of the VTA→NAc dopaminergic pathway

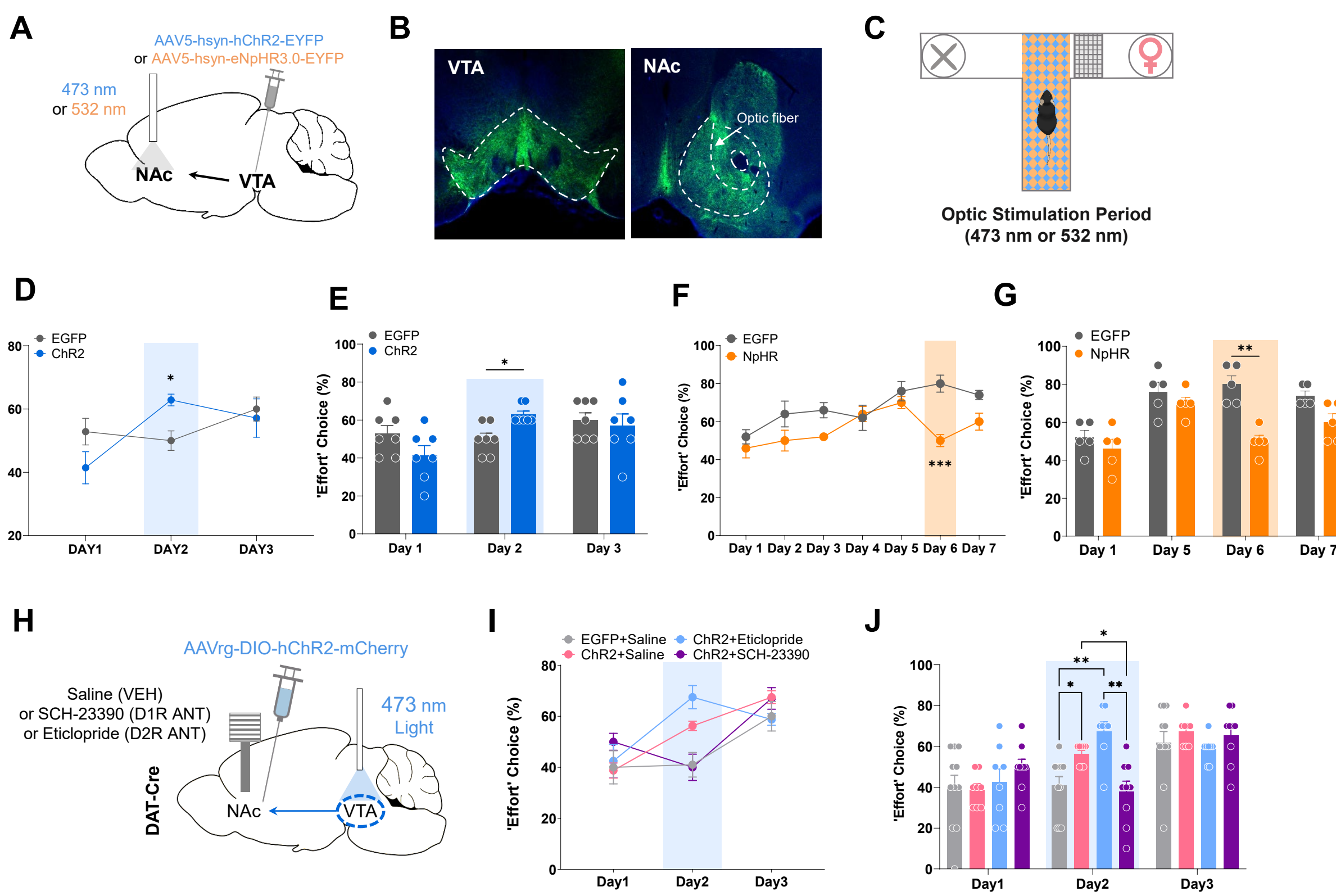


Fig 4. (A) Schematic showing viral injection and fiber implantation for optogenetic activation/inhibition of the VTA→NAc pathway. (B) The fluorescence images showing viral injection site and optic fiber implant site. (C) Light stimulation was given during the time before making a choice. (D) Learning curves of 'Effort' choices for the initial days. (E) Photoactivation of VTA→NAc pathway promoted 'Effort' choices on the day 2 of the ESDM task. (F) Learning curves of 'Effort' choices for whole days. (G) Photoinhibition of VTA→NAc pathway reduced 'Effort' choices on the day 6 of the ESDM task. (H) Schematic showing retrograde viral injection and cannula implantation into the NAc and fiber implantation into the VTA to the dopamine transporter gene-dependent Cre expression (DAT-Cre) mice for micro-infusion of the vehicle or D1R antagonist (SCH-23390) or D2R antagonist (Eticlopride) with optogenetic activation of the VTA→NAc dopaminergic pathway. (I) Learning curves of 'Effort' choices for the initial days. (J) Photoactivation of VTA→NAc pathway promoted 'Effort' choices on the day 2 of the ESDM task, but dampened when D1 receptors were blocked.

Enhanced dopamine itself function as an epigenetic modulator at the *Drd1a* promoter region, thereby reinforcing social motivation

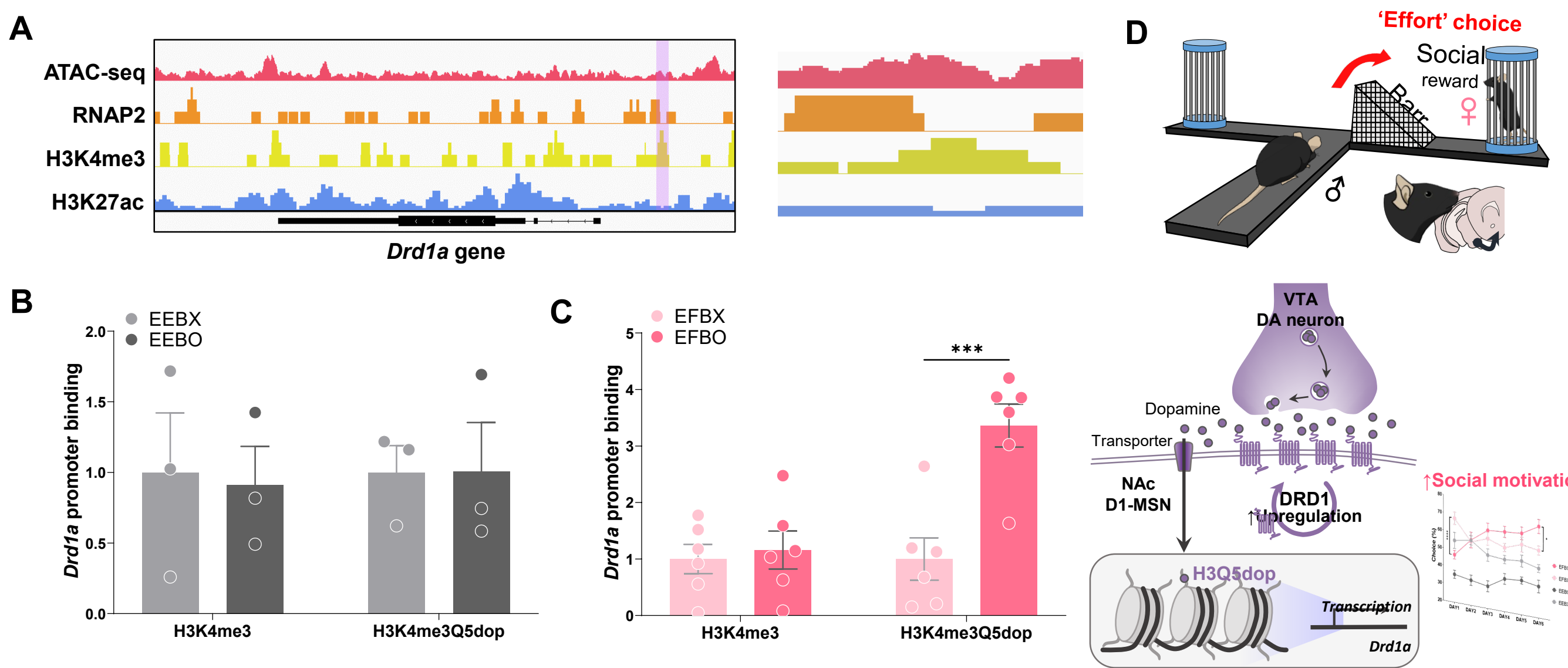


Fig 5. (A) Previously published ATAC-seq and ChIP-seq datasets from the GEO database (ATAC-seq: GSM 5100364, RNAP2: GSM 530181, H3K4me3: GSM 530196, H3K27ac: GSM5904438) were analyzed to find *Drd1a* gene promoter region by integrative genomics viewer IGV2.13.1. ChIP assay showed dopaminylation level at the *Drd1a* promoter region of the (B) EEBX vs. EEBO or (C) EFBX vs. EFBO without significant changes in the number of promoter itself. (D) Schematic summary of dopaminergic hypotheses underlying social motivation behavior.

Acknowledgements

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