

# Visualizing and manipulating brain circuits involved in self-control and alcohol intake

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Disrupted self-control is a recognized cause and consequence of substance use disorders and hence critical for the development and maintenance of the addiction cycle (Jentsch and Taylor, 1999). Here we use a adjusting amounts delay-discounting (DD)(Mitchell, 2004) assay and overnight alcohol drinking procedure (Rhodes al. 2007) to investigate overlapping roles of fronto-striatal cellular ensembles in regulating both self-control and alcohol consumption. For this we use mice with targeted lesions (NMDA-infusions) of the OFC and NAc (Dalley et al. 2008) and transgenic animals that enable activity-dependent cellular visualization and inactivation (cFos-LacZ-GFP/Daun02)(Koya et al. 2009)

## Adjusting amounts delay discounting

At the start of the DD task, animals presented with a choice between two levers delivering two different rewards: a **Small Immediate (SI) reward** – 10 $\mu$ l of sweetened condensed milk delivered *without* delay, and a **Large delayed (LD) reward** – 20 $\mu$ l delivered *with* delay. The delays associated with the LD reward varied across sessions. 5 consecutive responses on same lever caused **reward adjustment**. The reward size associated with the preferred lever **decreased** 5 $\mu$ l, and the reward size associated with the preferred lever **increased** 5 $\mu$ l. Reward adjustments stops at the **indifference point** (i.e., when animal respond on both levers). The delay discounting and bias was calculated as (Mazur, 1987):

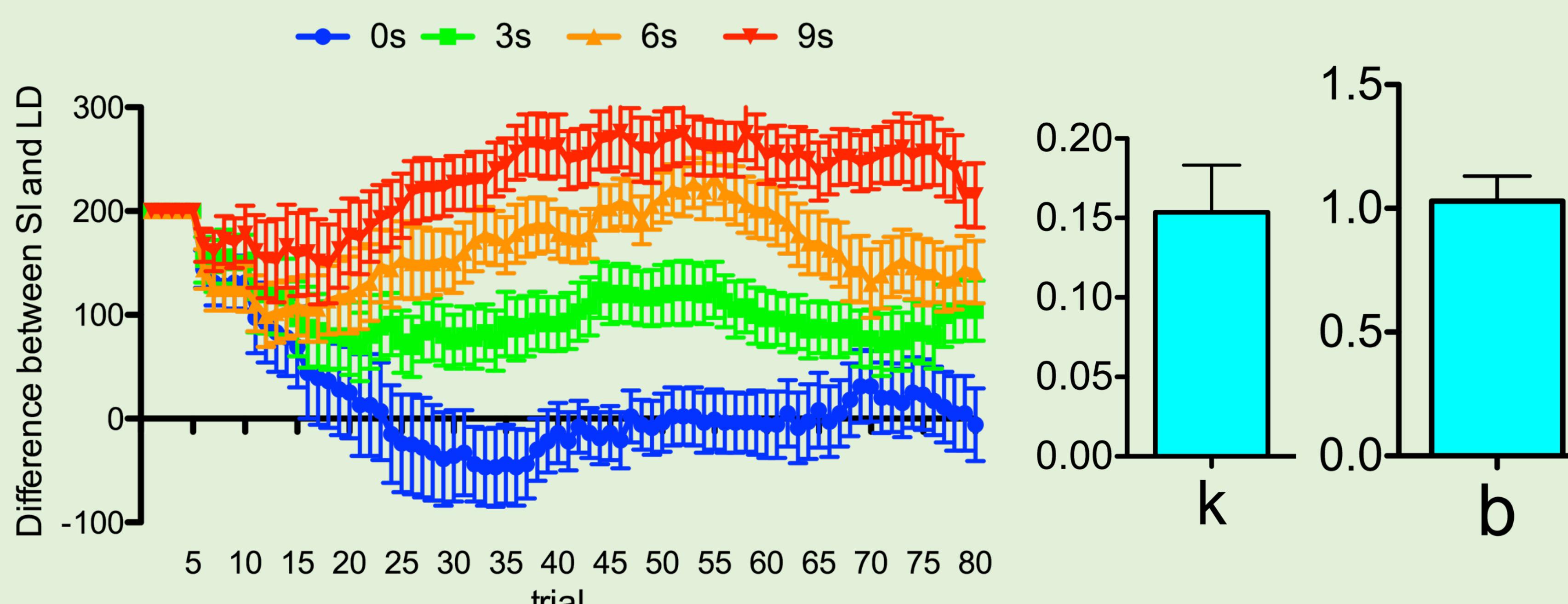
$$V = \frac{bA}{1 + kD}$$

V = amount of SI reward at indifference point  
 D = delay associated with LD reward  
 A = amount of LD reward at indifference point  
 b = preference for LD at 0s-delay sessions (=1 no preference)  
 k = rate of reward devaluation produced by delay (higher values, more discounting)

## Alcohol intake

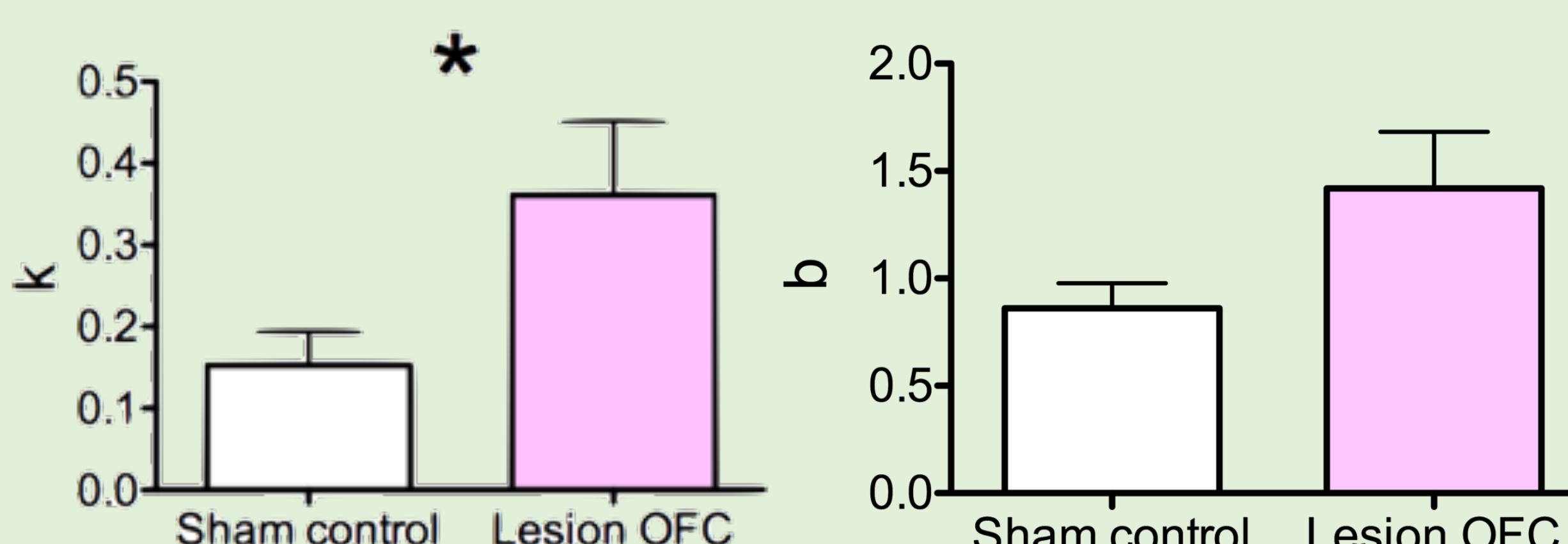
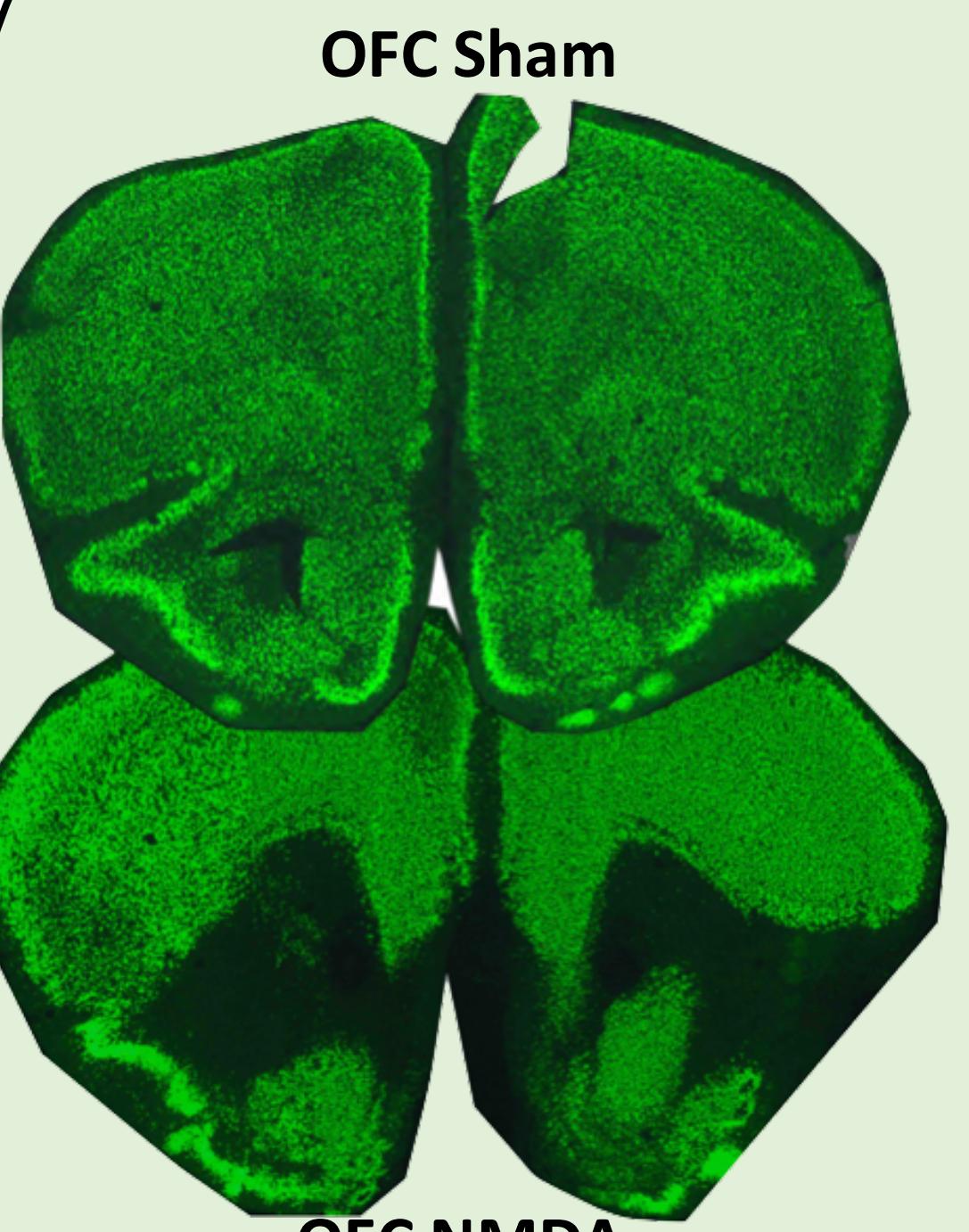
Alcohol intake was assessed through a double-spout lickometer system (water vs. 20% ethanol). Here, animals were single housed for 12 while licks to each spout was monitored. The number of licks to each spout was also confirmed to correlate with liquid intake in the home-cage.

## WT C57BL6/J mice show reliable delay discounting in an operant adjusting amounts procedure

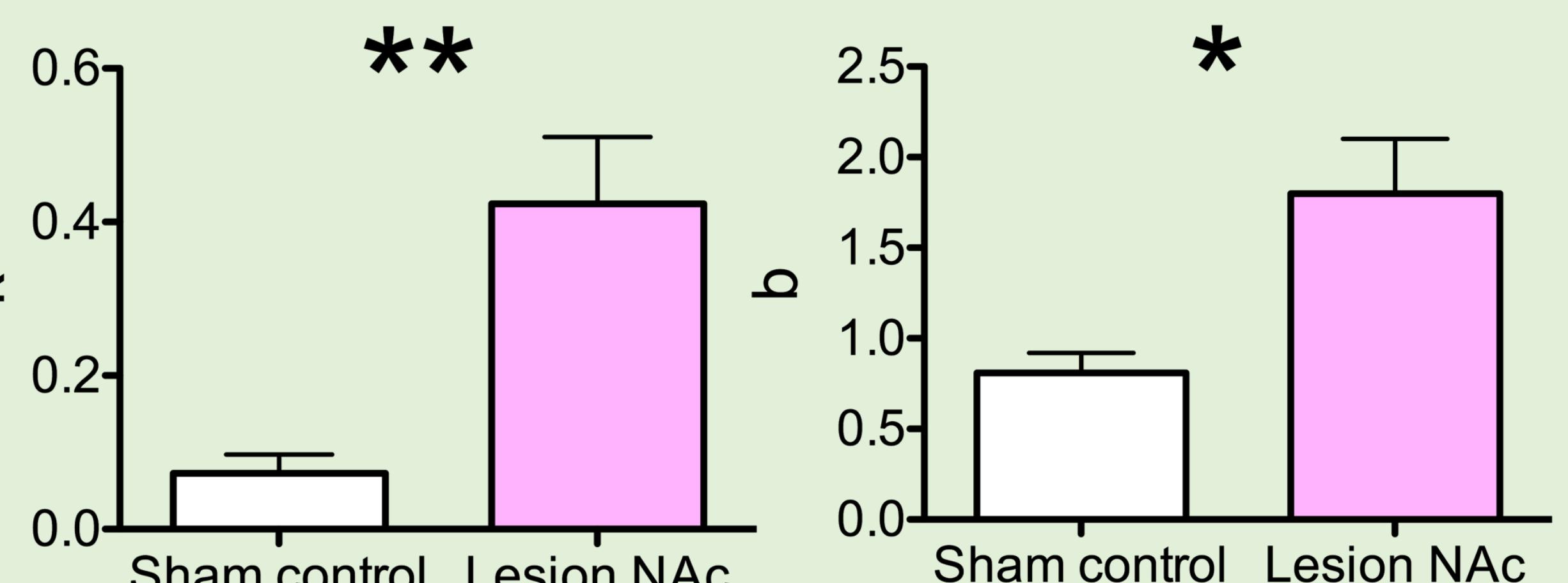
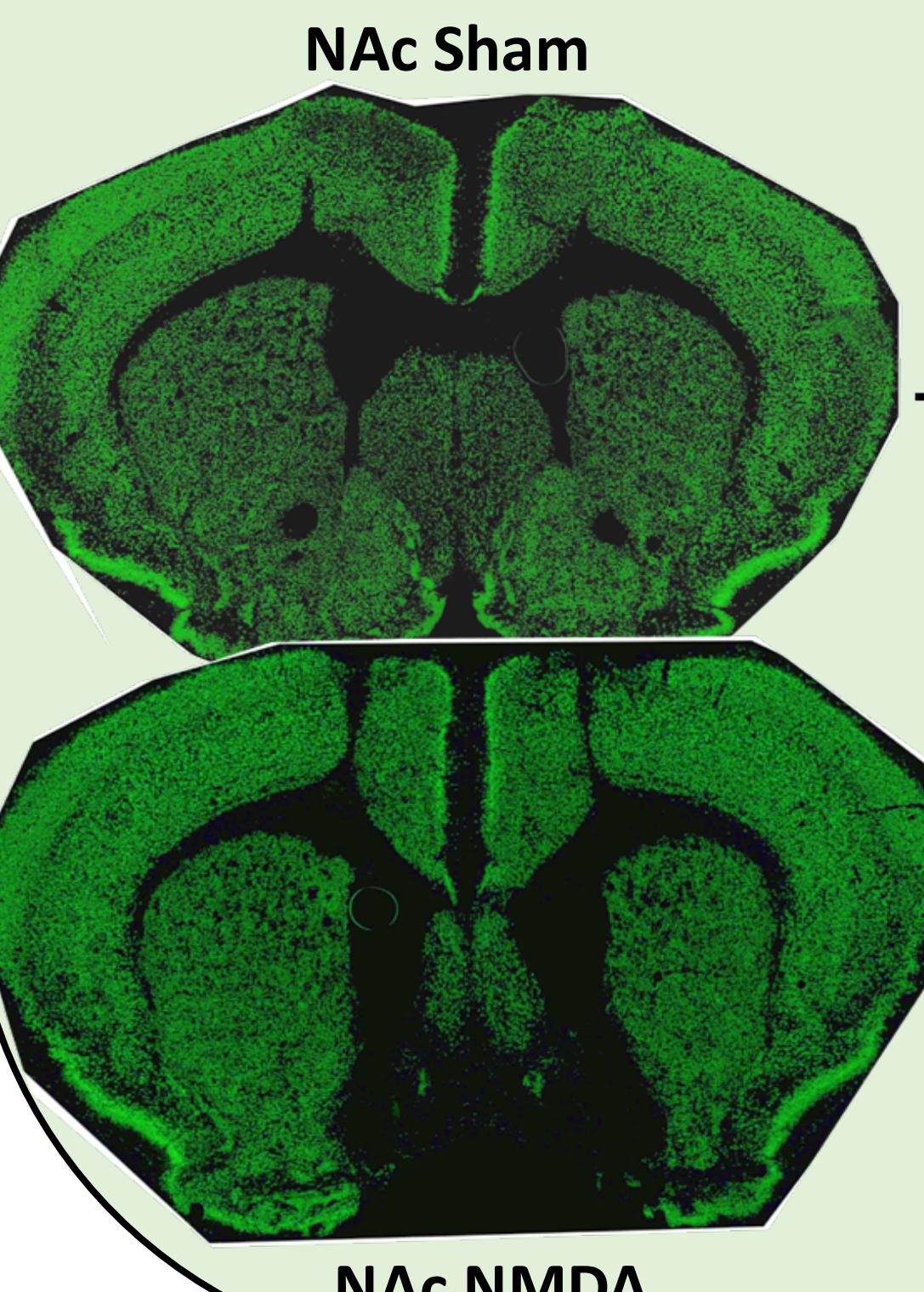


Larger reward sizes are required for animals to respond for delayed rewards, with a linear association between delay and reward size (main effect of delay: p < 0.0001, linear effect: p < 0.0001)

## OFC and NAc lesions increase the preference for immediate small reward over large delayed rewards



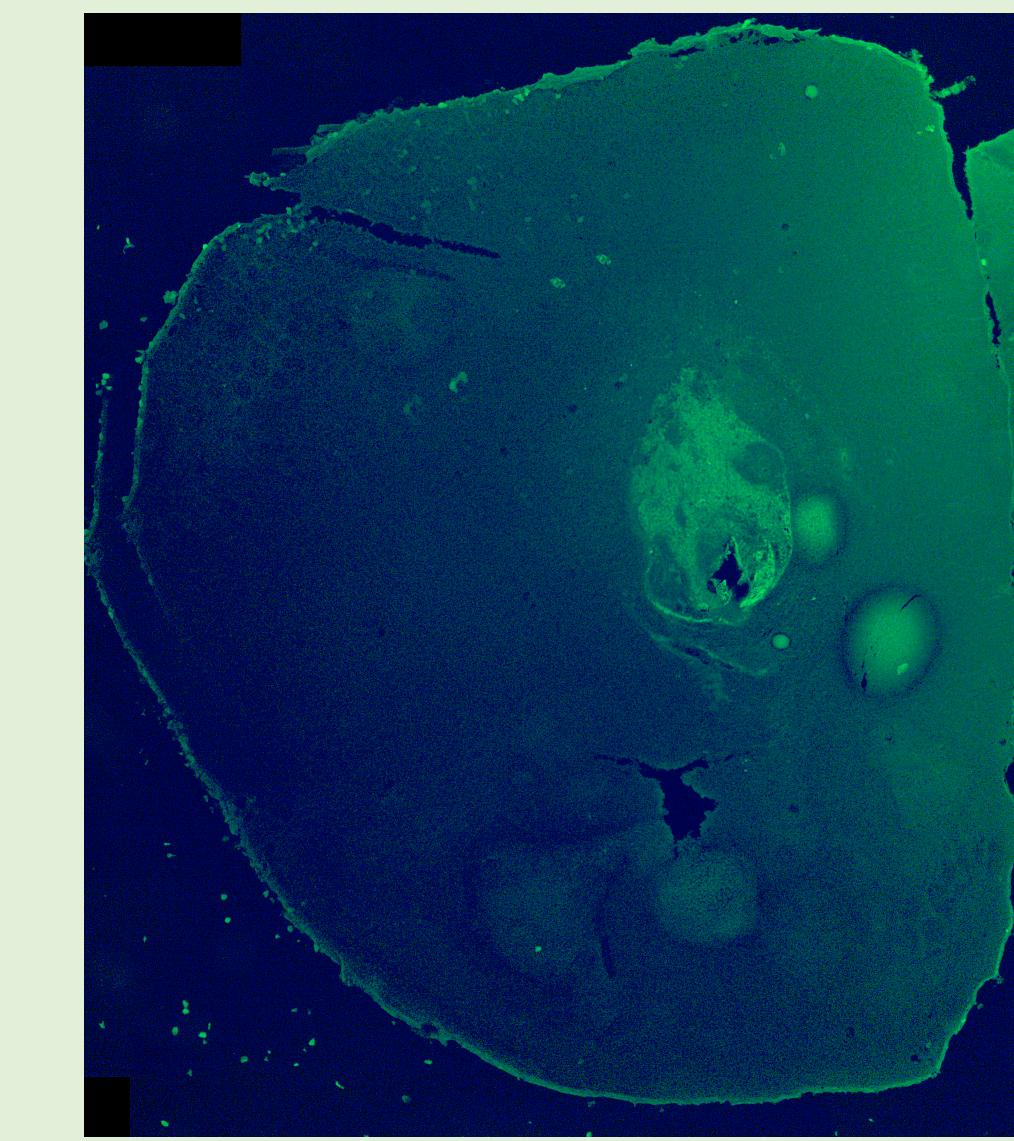
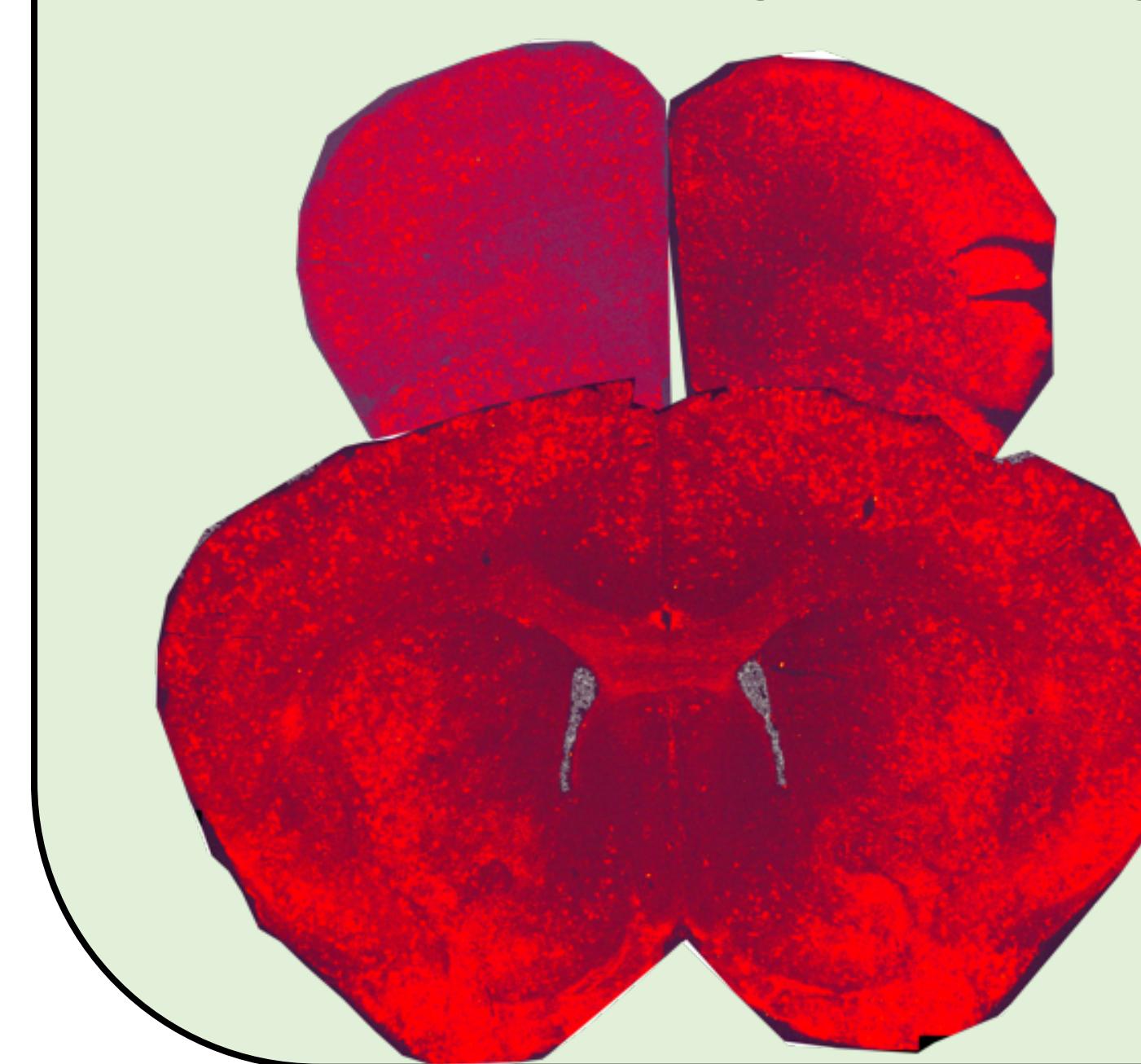
NMDA-induced lesions of the OFC (left) increased k (p = 0.044) and tended to increase b (p = 0.063).



Lesions to the Nac (left) also increased k (p = 0.006) and increased b (p = 0.0024).

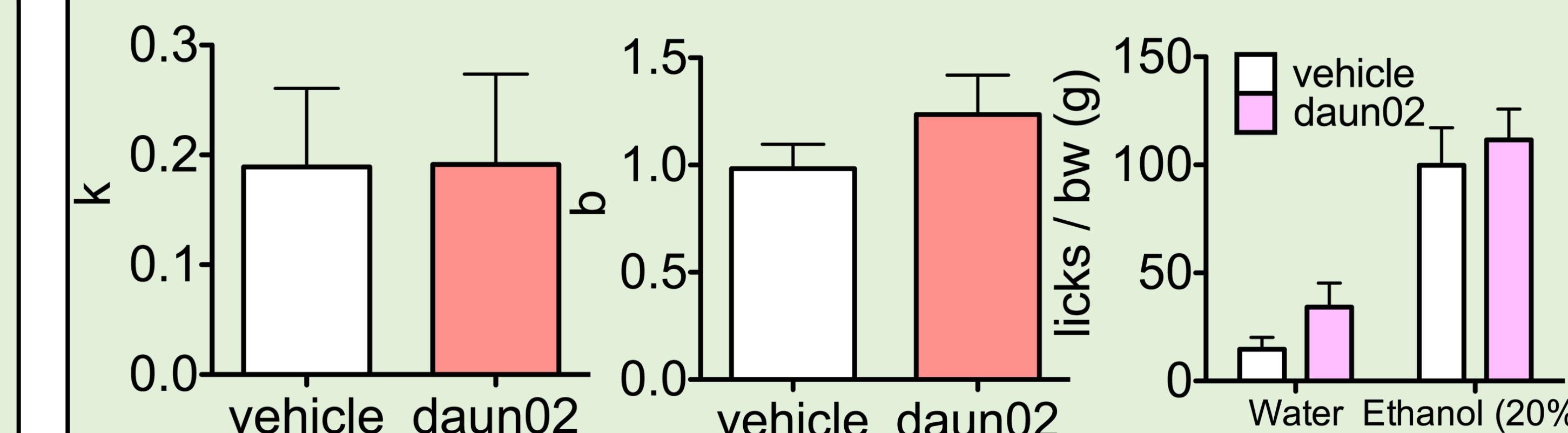
## bGal IHC / daun02 FJB in eGFP/LacZ mice

eGFP+/LacZ+ and eGFP+/LacZ- animals were first trained on DD. Next, the Dox-diet was removed at either 1,2, and 4 weeks prior to being re-tested on DD. This showed a time-dependent expression levels on bGal (example bGal IHC stain at 4 weeks, left). Moreover, eGFP+/LacZ+ animals infused with OFC daun02 (0.5 $\mu$ l / 2  $\mu$ g/0.5 $\mu$ l) were stained with flurojade-B that indicated neuronal degeneration (right)



## NAc daun02 in eGFP+/LacZ+ mice - cohort 1

90 min after DD testing, animals received a single daun02 infusion (0.5 $\mu$ l of 2  $\mu$ g/0.5 $\mu$ l daun02 in each hemisphere) and were tested on DD 1 week later. Animals were also tested on 12h drinking for 3 sessions. Next, animals were re-tested in DD for three days, with daun02 infusions performed after each session, and were tested on DD a second time

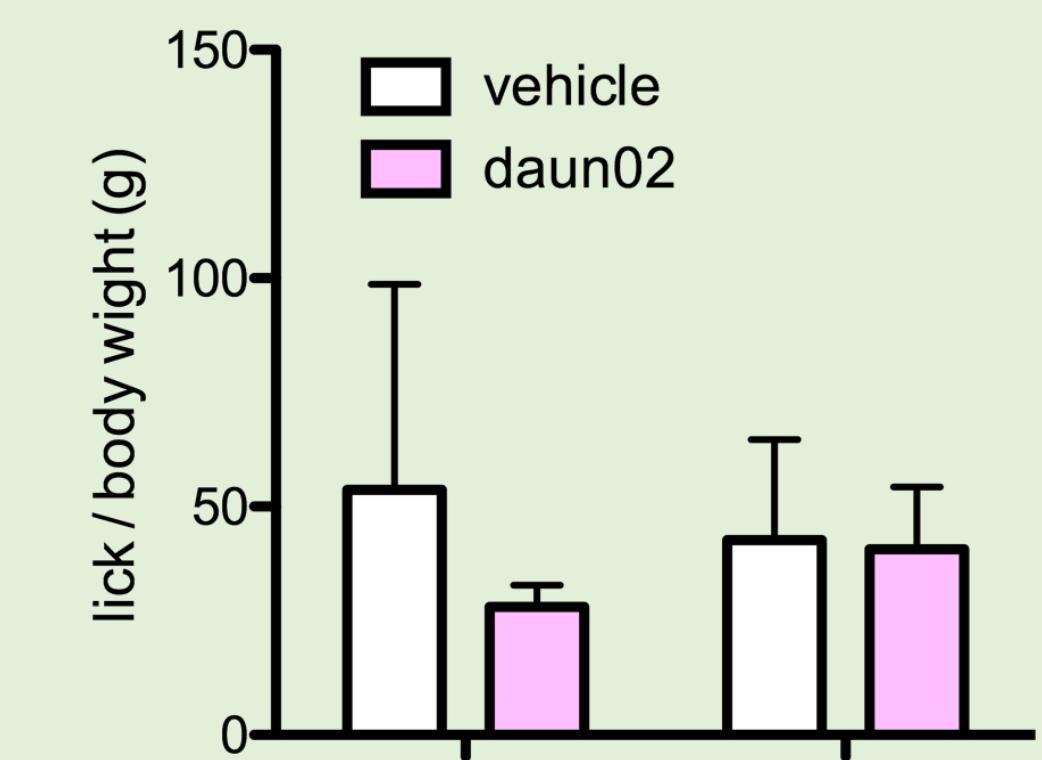


daun02 had no effects on drinking or performance in any of the DD tests

## NAc daun02 in eGFP+/LacZ+ mice – cohort 2

Animals were tested in DD for three days and received daun02 infusions after each session (1 $\mu$ l of 2  $\mu$ g/0.5 $\mu$ l in each hemisphere). Animals were then tested on 12h drinking for 3 sessions

Daun02 had no effects on drinking



## references

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