Disinhibition of the orbitofrontal cortex biases goal-directed behaviour in obesity

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Abstract (148/150)

The lateral orbitofrontal cortex (lOFC) receives sensory information about food and integrates these signals with expected outcomes to guide future actions, and thus may play a key role in a distributed network of neural circuits that regulate feeding behaviour. Here, we reveal a novel role for the lOFC in the cognitive control of behaviour in obesity. Goal-directed behaviour is biased in obesity such that in obese animals, actions are no longer influenced by the perceived value of the outcome. Obesity is associated with reduced lOFC inhibitory drive, and chemogenetic reduction in GABAergic neurotransmission in the lOFC induces obesity-like impairments in goal-directed behaviour. Conversely, pharmacological or optogenetic restoration of inhibitory neurotransmission in the lOFC of obese mice reinstates flexible, goal-directed behaviour. Our results indicate that obesity hinders an individual's ability to make value representations about rewards, which in turn may influence how individuals make decisions in an obesogenic environment.

Key words: Obesity, orbitofrontal cortex, electrophysiology, reward devaluation, goal-directed behaviour, cognitive inflexibility, disinhibition, GABAergic

Introduction

Diet-induced obesity is a major health concern many individuals face around the world. Obesity is defined as having a body mass index of greater than 30 kg/m^2 and is associated with multiple comorbid diseases including type 2 diabetes, stroke, cancer and depression[1]. Numerous forces drive the obesity pandemic, including complex environmental and societal changes[2]. Moreover, the transition from consuming traditional nutritional foods to highly marketed, inexpensive, energy dense, palatable foods has exacerbate overeating[3]. These pre-packaged foods are often consumed despite already fulfilled energy requirements[4] as they entice our innate likings of sugars, salts, and fats[5].

Quantitative models have been used to calculate the efficiency of obesity prevention efforts, including the impact of individual behaviours, public health interventions, and government policies. It is incumbent on the individual to "make personal healthy food and activity choices"[6], yet the complexity of the modern food environment and the choices it offers biases decision-making to influence food choices. Prior literature proposes that readily available palatable and energy dense foods usurps an individual's ability to make decisions and control their caloric intake, leading to overconsumption and obesity[7]. How access to obesogenic food alters neural circuits to bias behaviour towards eating beyond satiety remains unclear.

During goal-directed behaviour, decisions and behavioural strategies are flexible as they track the relationship between actions and outcomes. Individuals will adjust their behaviour upon a change in the value of an outcome previously associated with the action. A food reward can be devalued with satiety or by pairing the food with cues predicting sickness, as in conditioned taste avoidance. The development of feeding behaviour that is insensitive to changing reward values has been implicated in obesity, such that humans with obesity[8] and obese rodents[9] demonstrate deficits in reward devaluation.

The ability to attribute value to food choices and guide behaviour is dependent on the orbitofrontal cortex (OFC). Several lines of evidence suggest that an intact OFC is required for goal-directed behaviour, as the disruption of the OFC by lesions or inactivation impairs reward devaluation by satiety[10], sickness[11] and contingency degradation[12]. Furthermore, the OFC is anatomically and functionally situated to influence food intake as it is reciprocally connected with sensory[13], motor [10,14,15], and limbic [16,17] brain regions and is thought to integrate information from these regions to guide decision-making. A current hypothesis is that value representations of food and decision-making mechanisms to control food-intake are disrupted in obesity[18], however, it is unknown if obesity

influences the function of the OFC and how this occurs. Here, we tested the hypothesis that an obesogenic diet impairs goal-directed behaviour by disrupting OFC function.

Results

Obesity impairs reward devaluation.

We adapted three reward devaluation paradigms commonly used to examine changes in goal-directed behaviour[19] to address our research questions in obese mice. Long-term exposure to a high-fat diet led to the development of diet-induced obesity noted by increased body weight, hyperglycemia, as well as decreased glucose clearance reflective of impaired insulin signalling (**Figure 1a-b**).

In the first behavioural paradigm, we first examined the impact of diet-induced obesity on reward devaluation by satiety. Mice were trained to lever press for liquid sucrose rewards on a random ratio (RR) 20 schedule of reinforcement, whereby sucrose delivery follows on average the 20th lever press (**Extended Data Figure 1a**). Once mice displayed stable levels of responding, we devalued the reward outcome (sucrose) by pre-feeding them to satiety using the same sucrose solution prior to a non-reinforced instrumental test session (**Extended Data Figure 1b, Figure 1c**).

Lean mice displayed reward devaluation (**Figure 1d-g**), indexed by reduced responding when pre-fed with sucrose in the devalued condition, relative to non-prefed (valued) conditions. This effect was observed when we normalized each animal's lever presses and when we computed the revaluation index (**Figure 1f**). The revaluation index (lever presses valued state – lever presses devalued state) / (lever presses valued state + lever presses devalued state) indicates the degree of goal-directedness during outcome revaluation, such that a positive revaluation index reveals the strength of devaluation. In contrast, obese mice were impervious to the effects of the change in value of sucrose, as they displayed comparable levels of responding under both valued and devalued conditions (**Figure 1d-f**). This was apparent when we analyzed total and normalized lever presses and the revaluation index.

Importantly, this was not due to differences in overall lever pressing (**Figure 1g**). We further confirmed this by reanalyzing our devaluation data in lean and obese mice that had matched total lever presses (30 or less total, valued + devalued). Even under these stricter inclusion criteria, lean mice display reward devaluation, whereas obese mice do not (**Extended Data Figure 1c-f**). In a separate cohort of mice, we then examined the amount of effort lean or obese mice will expend to obtain sucrose. Lean and obese mice displayed comparable levels of responding for sucrose on a progressive ratio schedule of reinforcement, suggesting that they are in a similar motivational state (**Figure 1h-k**). Finally, when responses during the devaluation session were reinforced, lean mice continued to devalue sucrose, whereas obese mice did not (**Extended Data Figure 1g-h**). Taken together, these data indicate that while lean mice reduce their actions for sucrose when sated, obese mice do not.

Our second paradigm examined the impact of diet-induced obesity on sickness-induced reward devaluation. Prior to dietary manipulation, mice were conditioned over three sessions to associate flavoured gelatine with lithium chloride (LiCl)-induced malaise (**Figure 2a-c**). Both groups consumed significantly less of the LiCl-paired gelatine flavour when tested one day after sickness (**Figure 2d-g**). In contrast, after 3 months exposure to low or high fat diets, lean mice maintained conditioned taste avoidance to the LiCl-paired flavour, whereas obese mice consumed comparable amounts of the valued and devalued gelatine (**Figure 2h-k**). The devaluation strength is reflected by a significant difference in revaluation index between diet groups (**Figure 2j**). When sated with either grape or orange Koolaid™, both obese and lean mice readily consumed a novel flavour (**Extended Data Figure 2a-d**), indicating that the lack of LiCl devaluation was not due to obesity-induced changes in flavour discrimination. Thus, obese mice displayed impaired reward devaluation by conditioned taste avoidance.

The third paradigm examined the impact of diet-induced obesity on contingency degradation, a measure of the relationship between action and outcome (**Figure 3a**). Contingency is the causal association between an action (lever pressing) and its consequences (sucrose delivery). Mice were

trained on a positive contingency whereby increased lever presses yielded increased sucrose delivery. During testing, we reversed the lever contingency so that lever pressing delayed sucrose delivery (negative contingency). While lean mice quickly adapted their behaviour to match the new negative contingency, obese mice took longer to modify their actions (**Figure 3b**).

We next examined if these effects were due either to exposure to the energy-dense diet or to obesity. To test this, both lean and obese mice were switched to a low-fat diet for 7 days during RR training and prior to testing for satiety-induced devaluation. Obese mice maintained their significant weight difference from lean mice during the low-fat diet exposure (**Extended data Figure 3a**). After 7 days low-fat diet exposure, lean mice devalued sucrose, whereas obese mice continued to respond regardless of the change in value of sucrose (**Extended data Figure 3b-e**). The impairment in devaluation of obese mice was reflected as a decrease in revaluation index (**Extended data Figure 3f**). In summary, these data demonstrate clear discrepancies in the value attributed to food rewards and related actions by lean and obese mice. While lean mice change their behaviour depending on internal state and prior experiences, obese mice show marked impairments in behavioural adjustment to the current value of food rewards, lasting beyond the duration of obesogenic diet exposure.

Obesity alters the function of lOFC neurons.

The lateral OFC (lOFC) has emerged as a hub for assessing information about the consequences of rewards and orchestrating flexible, goal-directed behaviour[10,20]. We hypothesized that obesity alters the activity of lOFC principal output neurons. To test this, we performed whole-cell electrophysiology recordings in brain slices containing the lOFC from lean and obese mice (**Figure 4a**). There was no difference in the resting membrane potential of lOFC pyramidal neurons of lean or obese mice (**Figure 4b**). We also measured the number of action potentials in response to current steps of increasing amplitude, and calculated an excitability slope as a measure of the relative excitability of lOFC

pyramidal neurons. lOFC pyramidal neurons from obese mice were more excitable than those of lean mice (**Figure 4c-e**). OFC pyramidal neurons are tightly controlled by the coordinated action of local inhibitory interneurons[21]. Therefore, we tested if GABAergic disinhibition underlies the enhanced excitability of pyramidal neurons. Picrotoxin-induced inhibition of GABAergic transmission increased the excitability of pyramidal neurons from lean, but not obese mice (**Figure 4e**), suggesting that increased neuronal excitability of obese mice may be due to decreased inhibition. To test this, we isolated and quantified miniature inhibitory postsynaptic currents (mIPSCs) onto lOFC pyramidal neurons. The frequency, but not the amplitude of mIPSCs were decreased in obese relative to lean mice in lOFC pyramidal neurons (**Figure 4f-h**), suggesting a decrease in presynaptic GABA release and consistent with previous findings from our lab[22]. Thus, diet-induced obesity reduces inhibitory drive onto lOFC pyramidal neurons leading to increased excitability.

Thus far, we have demonstrated that diet-induced obesity induces deficits in reward devaluation and reduces inhibitory control of lOFC principal output neurons. To causally link these synaptic changes with behaviour, we tested two hypotheses. First, we hypothesized that lOFC GABAergic neurotransmission is necessary for reward devaluation. Secondly, we hypothesized that enhancing lOFC GABAergic neurotransmission in obese mice will restore the activity of pyramidal neurons and behavioural performance. We targeted lOFC inhibitory neurons using vesicular GABA transporter-cre ($VGAT^{cre}$) mice, and reduced their activity with local infusion of a cre-dependent inhibitory Designer Receptor Exclusively Activated by Designer Drug (DREADD; $hM_4D(Gi)$), which is activated by the inert ligand clozapine n-oxide (CNO; **Figure 5a,b and Extended Data Figure 4a**). CNO decreased the firing rate of lOFC GABAergic neurons (**Figure 5c,d**). Next, we examined whether disinhibition of the lOFC influenced reward devaluation. While mice expressing a control reporter in lOFC GABAergic neurons exhibited satiety induced devaluation in response to CNO, mice expressing $hM_4D(Gi)$ in lOFC GABAergic neurons showed impaired satiety-induced reward devaluation (**Figure**

5e,f, Extended Data Figure 4c-e). Consistent with these effects, disinhibition of the lOFC also impaired LiCl-induced reward devaluation (**Figure 5g-h, Extended Data Figure 4f-h**). Taken together, these data indicate that lOFC GABAergic transmission is necessary for goal-directed behaviour.

We then employed 2 strategies to test if enhancing lOFC GABAergic neurotransmission in obese mice would restore the activity of pyramidal neurons and behavioural performance. The first strategy involved optogenetic activation of lOFC local inhibitory neurons. To do this, we expressed channelrhodopsin2 (ChR2) in GABAergic interneurons in the lOFC of lean and obese VGAT^{cre} mice (**Figure 6a-b, Extended Data Figure 5a-e**), and confirmed that diet-induced obesity increases the excitability of lOFC neurons in these mice (**Figure 6b-e**). Photostimulation of GABAergic terminals (5 x 1s 5Hz pulse trains at 4 mW) reduced the hyperexcitability of lOFC pyramidal neurons of obese mice (**Figure 6c-e, Extended data figure 5e**). To assess if enhancing lOFC GABAergic neurotransmission reinstates reward devaluation in obese mice, a fibre-optic cannula was implanted in layer 2/3 of the lOFC (**Figure 6f,g, Extended Data Figure 5d-e**), and lean and obese mice were trained to lever press for sucrose on a RR20 reinforcement schedule (**Extended Data Figure 5h-j**). Photostimulation did not alter lever pressing or locomotor activity in lean or obese mice (**Extended data Figure 5g,i**). Lean mice displayed reward devaluation in the presence of the non-ChR2 activating light (589nM) or the ChR2 activating wavelength (473 nM; **Figure 6g, h**). In response to the non-activating wavelength, obese mice did not display reward devaluation (**Figure 6j-k**). However, activation of lOFC inhibitory neurons (5x 1s 5Hz pulses of 473nm light) 5 min prior to the 10 min behavioural test, rescued reward devaluation in obese mice (**Figure 6j-l**). The restoration of devaluation in obese mice was evident by an increase in the revaluation index of obese mice when lOFC inhibitory neurons were stimulated (**Figure 6l**).

In a second strategy, we used a pharmacological approach to enhance lOFC GABAergic neurotransmission by employing a selective GAT-1 GABAergic transporter inhibitor, NNC-711 (**Figure 7**). Consistent with data reported in Figures 4d and 6d, lOFC pyramidal neurons from obese mice had

increased excitability compared to those of lean mice (**Figure 7b-c**). Application of NNC-711 (10 µM) to lOFC slices restored excitability of pyramidal neurons in obese mice without significantly altering those of lean mice (**Figure 7b-c, Extended Data Figure 6a-c**). We tested if intra-lOFC NNC-711 could restore satiety-induced devaluation in obese mice (**Figure 7d, Extended data Figure 6d-i**). Intra-lOFC NNC-711 did not alter the ability to devalue sucrose in lean mice (**Figure 7e-f**) nor did it alter locomotor activity (**Extended data 6f**). In contrast, obese mice receiving lOFC vehicle infusions again failed to display reward devaluation (**Figure 7g-i, Extended Data Figure 6h-i**). However, lOFC infusions of NNC-711 prior to testing restored reward devaluation in obese mice (**Figure 7g-i**), again without having an effect on locomotor activity (**Extended data 6f**). Taken together, restoring lOFC pyramidal neuron firing activity by either boosting GABAergic firing with optogenetics or GABAergic tone via a GAT-1 blocker can restore reward devaluation in obese mice without altering that in lean mice.

Discussion

The data presented here demonstrate a causal role of lOFC GABAergic transmission in obesity-induced impairment in reward devaluation. Long-term exposure to a high-fat diet led to the development of diet-induced obesity and subsequent disruption of goal-directed behaviour in three different reward devaluation paradigms. In obese mice, GABAergic tone onto pyramidal neurons was decreased, resulting in associated hyperexcitability of these principal output neurons. Furthermore, reduced GABAergic neurotransmission disrupted goal-directed behaviour in lean mice, suggesting that lOFC GABAergic neurotransmission is necessary for devaluation induced by selective satiety and conditioned taste avoidance. Finally, increasing GABAergic neurotransmission in obese mice, by pharmacological or optogenetic methods, restored lOFC pyramidal neuron excitability and reward devaluation behaviour. Thus, impairments in the valuation of rewards associated with obesity may underlie continued overeating and may impede weight loss efforts.

Diet-induced obesity disrupts goal-directed behaviour

We demonstrate that diet-induced obesity disrupts goal-directed behaviour in three different reward devaluation tasks. Two of these tasks, satiety and conditioned taste avoidance, involve devaluing the outcome whereas the third task, contingency degradation, involves devaluing the action to obtain the outcome. While impairment on satiety-induced devaluation tasks has been previously reported in obese rodents[9], and humans[8], it was unclear if this was due to altered satiety processing, a failure in associative learning, or inflexible behaviour. The impairments in reward devaluation observed here are unlikely to result from a failure of associative learning. Obesity-induced deficits in devaluation were observed in the conditioned taste avoidance experiment, where conditioning occurred prior to exposure to an obesogenic diet. Additionally, devaluation was restored in obese mice with enhanced lOFC GABAergic tone, suggesting that these associations had been initially made.

We also examined whether differences in motivational state contributed to performance on devaluation tasks in lean and obese mice. Although there was no significant difference in total lever presses between lean and obese mice during the test, obese mice consistently made fewer responses throughout training, which is in keeping with reduced instrumental actions of obese rodents observed in previous reports[23,24]. The reduction in instrumental responding may be attributed to a downshift in the expected value of the reward compared to their home cage diet[23]. We tried to mitigate this effect by using a higher sucrose concentration during instrumental training, 30% compared to the 9% sucrose present in the high fat diet. An alternative explanation for decreased instrumental responding of obese mice may be due to general attenuation of locomotor and exploratory behaviour, as previously observed in obese mice[25]. Consistent with this, we observed an overall decrease in locomotion in obese compared to lean mice, regardless of intra-OFC manipulation. To directly test for different motivational

states between lean and obese mice, we tested instrumental responding on a progressive ratio in mice that had been previously trained to lever press multiple times to receive sucrose. In this experiment, we observed no significant differences in the breakpoint, sucrose received or maximal number of lever presses between lean and obese mice, indicating that these mice will expend similar effort to obtain sucrose. Finally, when lever presses were matched for lean and obese mice, we observed a significant reward devaluation in lean, but not obese mice, suggesting that impairment in devaluation in obese mice is not due to a difference in motivational state, but rather a change in the action/outcome relationship.

Alternative explanations for impaired reward devaluation in obese mice are that obese mice may be insensitive to sensory feedback or have disrupted sensory specific satiety. Indeed, obesity-prone rats have decreased taste sensitivity compared to obesity-resistant rats[26]. We initially tested if a reminder exposure of sucrose during the test was sufficient to induce devaluation. As expected, lean mice devalued sucrose in a reinforced paradigm, however obese mice continued to press for sucrose in the devalued state, regardless of sucrose reinforcement. We also performed a taste discrimination test to determine if mice could discriminate between different flavours of sucrose as well as exhibit sensory specific satiety. In this task, mice were given prolonged access to flavoured sucrose in a water bottle in their home cage, subsequently mice were offered a choice between sucrose of a different flavour or that of the same flavour. Both lean and obese mice consumed more sucrose of a different flavour, suggesting that both lean and obese mice exhibited sensory specific satiety and could distinguish between flavours. Taken together, the inability of obese mice to devalue rewards is not due to altered motivational state, disrupted sensory specific satiety, or poor associative learning, but rather is most likely due to impairments in goal-directed behaviour.

Obesity reduces inhibitory tone in the lOFC and disinhibits principal output neurons.

Not only was goal-directed behaviour impaired, we also observed neurophysiological changes in the lOFC of obese mice. GABAergic release probability onto lOFC pyramidal neurons was reduced in obese mice. This is consistent with previous work showing that obese rats with 24h access to a cafeteria diet had reduced GABAergic release probability onto layer II/III pyramidal neurons in the lOFC[22]. Obese mice, from 3 different cohorts, also demonstrated enhanced excitability of pyramidal neurons. We propose the enhanced excitability of lOFC pyramidal neurons is due to disinhibition rather than a change in intrinsic excitability. First, previous work demonstrated that the excitability of lOFC pyramidal neurons from obese rats is not changed in the presence of synaptic blockers[22]. Secondly, the $GABA_A$ receptor antagonist, picrotoxin, restored excitability of lOFC neurons from obese mice to that of lean mice, without significantly altering the excitability of pyramidal neurons of lean mice. Thirdly, increasing GABAergic tone by either optogenetically enhancing the firing rate of lOFC GABAergic neurons, or using a GAT-1 blocker restores the excitability of lOFC pyramidal neurons from obese mice to that of lean mice. GABAergic interneurons form axo-somatic synapses, and are well positioned to coordinate principal output neuronal firing[21,27]. Thus, disruption of GABAergic release onto pyramidal neurons in obese mice, likely dysregulates the coordinated firing of principal neurons, ultimately leading to altered behavioural performance. Taken together, diet-induced obesity disinhibits lOFC neurons and this effect can occur across species and diet type.

Reward devaluation requires appropriate GABAergic synaptic drive onto lOFC pyramidal neurons.

Our results support the hypothesis that reward devaluation requires sufficient inhibitory tone in the lOFC. Using chemogenetics, inhibition of lOFC GABAergic neurons of lean mice disrupts both satiety-induced reward devaluation as well as devaluation by conditioned taste avoidance. Importantly, inactivation of the OFC does not alter the palatability of food rewards[11], suggesting that the impairment in devaluation is likely related to altered goal-directed

behaviour. Indeed, parvalbumin-containing (PV+) interneurons in the OFC facilitate cognitive flexibility as mice with reduced PV+ expression have impaired reversal learning[28]. Diet can influence perineuronal net expression around PV+ interneurons of the OFC[29], and this could potentially influence their synaptic transmission[30]. Therefore, PV+ interneurons are a likely target for obesity-induced changes in OFC function and future work should investigate the interneuron subtype and mechanisms of altered synaptic transmission influenced by obesity.

Chemogenetic inactivation of the OFC or its striatal outputs impairs satiety-induced reward devaluation in rats[14]. While this may seem to contrast our results showing disinhibition of the OFC impairs devaluation, we propose that any change in the network-like firing activity of OFC output neurons, whether through disinhibition or complete inhibition, will impair the ability of the mouse to update actions based on the current reward value. This suggests that this functional circuit is sensitive to changes in firing patterns and that any perturbations in activity in these cortical-striatal pathways would alter reward devaluation behaviour and cognitive flexibility.

Augmenting GABAergic tone restores devaluation in obese mice

Given that intact OFC GABAergic function is required for reward devaluation and boosting GABAergic function can restore the appropriate firing rate of pyramidal neurons of obese mice, we hypothesized that we could restore goal-directed behaviour in obese mice by increasing GABAergic function. Indeed, we found that enhancement of GABAergic tone with a GAT-1 reuptake inhibitor restores reward devaluation in obese mice without significantly affecting that of lean mice. Similarly, optogenetic activation of GABAergic neurons restores reward devaluation in obese mice. These results are not due to altered locomotor activity as neither intra-OFC NNC-711 nor optogenetic stimulation of

GABAergic neurons influenced distance travelled in an open field. Interestingly, optogenetic stimulation of lOFC GABAergic neurons was done prior to behavioural testing. Because the effects of optogenetic stimulation lasted throughout the 10 min test session, this photostimulation could be inducing a long-term potentiation of GABAergic synaptic transmission to mediate the improvement in behavioural performance. Taken together, we causally demonstrate that GABAergic synaptic transmission underlies reward devaluation, and that increasing GABAergic tone in the lOFC of obese mice restores devaluation of rewards.

These data propose that obesity-induced changes in lOFC function impedes one's ability to update actions based on current information and suggests that obesity-induced perturbations in lOFC functioning may be an underlying mechanism that contributes to a vicious cycle, wherein individuals continue to eat beyond satiety. Currently, there are five approved drug therapies for long-term weight management and only two have demonstrated minimal weight loss efficacy. Thus, the development of new therapies is of critical importance and our findings that inhibitory drive in the orbital regions of the frontal lobes impacts reward processes provide a novel putative target for potential therapeutics.

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Data Accessibility

Data will be made available upon request.

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Figure legends

Figure 1: Diet-induced obesity induces deficits in satiety-induced reward devaluation.

a) In the reward devaluation by selective satiety task, mice with long term exposure to a 60% high-fat (obese n=31) diet gained more weight than mice with long term exposure to a 10% low-fat (lean n=35) diet. Unpaired T-test: $t_{(64)}$=10.88, p<0.0001****.

b) Mice fed a high-fat diet (obese n=5) had reduced insulin sensitivity than mice fed a low-fat diet (lean n=5) as indicated by blood glucose (mM/L) concentrations prior to (time 0) and following (15-210 minutes) an intraperitoneal injection of 20% D-glucose solution. Two-way RM ANOVA: diet effect: F (1,

8) = 69.09, p<0.0001****, time effect: F (11, 88) = 82.50, p<0.0001****, time x diet interaction: F (11, 88) = 7.493, p<0.0001****.

c) Selective satiety-induced reward devaluation procedure.

d) Lean (n=35) mice displayed reward devaluation as indicated by decreased lever presses in the devalued compared to the valued condition. Obese mice (n=31) did not display reward devaluation as indicated by comparable lever presses in the valued and devalued conditions. RM two-way ANOVA: devaluation effect, F(1,64)=7.8, p=0.0067**, diet group x devaluation interaction, F(1,64)=5.8, p=0.0187*, Sidak's multiple comparisons test, lean: p=0.0006***, obese: p=0.9561.

e) Normalized lever presses (valued: valued / (valued + devalued), devalued: devalued / (valued + devalued) of lean (n=35) and obese mice (n=31) in the valued and devalued conditions. Wilcoxon t-test, lean mice: p<0.0001****, obese mice: p=0.7452.

f) Obesity decreased the revaluation index ((lever presses valued – lever presses devalued)/(lever presses valued + lever presses devalued)). Unpaired t-test: lean (n=35), obese (n=31), $t_{(64)}$=4.109, p=0.0001***.

g) Total number of lever presses (valued + devalued) of obese mice (n=31) compared to lean mice (n=35) during the reward devaluation task. Unpaired t-test: $t_{(64)}$=1.886, p=0.0638.

h) Weights of lean (n=15) and obese (n=11) mice in the progressive ratio test. Unpaired t-test: $t_{(24)}$=13.25, p<0.0001****.

i) Number of lever presses of lean (n=15) and obese (n=11) mice during progressive ratio. Unpaired t-test: $t_{(24)}$=5.521, p=0.1412.

j) Number of sucrose reinforcers received by lean (n=15) and obese (n=11) mice during progressive ratio. Unpaired t-test: $t_{(24)}$=1.296, p=0.2072

k) Breakpoint obtained by lean (n=15) and obese (n=11) mice during progressive ratio. Unpaired t-test: $t_{(24)}$=1.234, p=0.2293.

Figure 2: Diet-induced obesity induces deficits in conditioned taste avoidance.

a) Weights of mice in the CTA experiment during conditioning (pre-diet) and following exposure to either the low-fat (n=10) or high-fat diet (n=12). RM Two-way ANOVA: Diet effect $F(1,20)=75.01$, $p<0.0001$, Time effect $F(1,20)=179.3$, $p<0.0001$****, Diet x time interaction $F(1,20)=49.20$, $p<0.0001$****. Sidak's multiple comparisons test: pre-diet lean vs. post-diet lean p= 0.0007*** pre-diet obese vs post-diet obese p<0.0001****.

b) Conditioned taste avoidance reward devaluation procedure.

c) Consumption (g) of the valued and devalued gelatine during the three days of taste avoidance conditioning (pre-diet) of lean (n=10) and obese mice (n=12). Three-Way ANOVA: Day x devaluation interaction: $F(1.391, 27.82) = 12.33$, $p=0.0006$, Day effect: $F(1.832,36.63) = 10.84$, $p=0.0003$, Valued vs. devalued effect: $F (1, 20) = 24.42$, $p<0.0001$, diet effect: $F (1, 20) = 0.02218$, $p=0.8831$. Tukey's multiple comparisons test: Pairing Day 3 valued vs. devalued: p = 0.0379*, Pairing Day 3 obese valued vs. devalued: p = 0.0015**.

d) Consumption (g) of the valued and devalued gelatine during the CTA test prior to exposure to the diets (lean n=10, obese n=12). RM Two-way ANOVA: Diet x devaluation interaction: $F(1,20) = 0.9552$, p = 0.3401. Devaluation effect $F(1, 20) = 60.98$, $p<0.0001$, diet effect: $F (1, 20) = 0.1227$, $p=0.7297$.

e) Normalized consumption (valued: valued / (valued + devalued), devalued: devalued / (valued + devalued) of the valued and devalued gelatine during the CTA test. Paired t-test: Lean $t_{(9)}=6.783$, $p<0.0001$ ****, obese $t_{(11)}=11.52$, $p<0.0001$****.

f) Revaluation index of pre-diet lean (n=10) and pre-diet obese (n=12) mice. Unpaired t-test: $t_{(20)}=0.6773$, $p=0.5060$.

g) Total intake (valued + devalued) of gelatine in pre-diet lean (n=10) and pre-diet obese (n=12). Unpaired t-test: $t_{(20)}=1.011$, $p=0.3240$.

h) Lean (n=10) mice displayed reward devaluation as indicated by a decreased consumption of devalued compared to valued gelatine after exposure to the diets. Obese (n=12) mice did not display reward devaluation as indicated by comparable valued and devalued gelatine consumption. RM two-way ANOVA, devaluation effect: F(1, 20)=8.210, P=0.0096**, group x devaluation interaction effect: F(1, 20)=17.92 P=0.0004***. Sidak's multiple comparison test, lean: p=0.0002***, obese: p=0.5410.

i) Post-diet normalized consumption of the valued or devalued gelatine by lean (n=10) or obese (n=12) mice. Paired t-test, lean: $t_{(9)}$=5.482 p=0.0004***, obese: $t_{(11)}$=0.9329, p=0.3709.

j) Obesity decreased the revaluation index. Unpaired t-test: lean (n=10), obese (n=12) mice, $t_{(20)}$=4.681, p=0.0001***.

k) Total consumption (valued + devalued) of gelatine in post-diet lean (n=10) and post-diet obese (n=12) mice. Unpaired t-test: $t_{(20)}$=0.2268, p=0.8229.

Figure 3. Obese mice show impaired performance on the contingency reversal

a) Contingency degradation devaluation procedure.

b) While lean mice quickly adapted their behaviour on day 1 of negative contingency, obese mice were considerably slower to do so. Lever presses of lean (n=21) and obese (n=16) mice during positive contingency (PC) and after the switch to a negative contingency (NC). Two-way ANOVA mixed effects model, day of testing effect, F(1.604, 56.12)=13.30 p <0.0001****, group x day interaction F(4,140)=2.441, p=0.0497*. Lean mice showed reduced lever pressing on Days 1-4 of NC (Dunnett's multiple comparisons test: lean, PC vs. NC1 p=0.0165*, vs. NC2 p=0.0158*, vs. NC3 p=0.0111*, vs. NC4 p=0.0098**). Obese mice only showed reduced lever presses on day 4 of NC (Dunnett's multiple comparisons test: Obese PC vs. NC1 p=0.7933, vs. NC2 p= 0.1318, vs. NC3 p= 0.1066, vs. NC4 p= 0.0276*).

Figure 4. Obesity reduces inhibitory tone in the lOFC and disinhibits principal output neurons

a) Schematic of the electrophysiology recordings.

b) Obesity did not alter the resting membrane potential of lOFC pyramidal neurons. Mean membrane potential (mV) of lean (n=10 cells/3 animals) and obese (n=8 cells/3 animals) mice. Unpaired test: $t_{(16)}$=1.194, p=0.25.

c) Representative recordings of action potentials observed at 100pA, 300pA and 500pA current steps from lOFC pyramidal neurons of lean and obese mice.

d) Diet-induced obesity increased the excitability of lOFC pyramidal neurons as indicated by frequency-current (F-I) plots of action potentials at current injections from 0pA to 500pA of lean (n=8 cells/3 animals) and obese (n=8 cells/3 animals) mice. RM two-way ANOVA: current step effect F(20,672)=298.7 p<0.0001****, diet effect F(3,672)=73.82 p<0.0001****, current step x diet interaction F(60, 672)=1.602 p=0.0035**.

e) Diet-induced obesity increased the excitability of lOFC pyramidal neurons and picrotoxin-induced disinhibition only changed the firing of pyramidal neurons from lean mice. Mean excitability slope (slope of linear regression from individual cells, x=current step y=number of action potentials) of lOFC pyramidal neurons of lean in aCSF (n=8 cells/3 mice), lean in picrotoxin (n=11 cells/3 mice), obese in aCSF (n=8 cells/3 mice), obese in picrotoxin (n=11/3 mice). Two-way ANOVA: picrotoxin effect F(1,32)=5.010 p=0.0323*, picrotoxin x diet interaction F(1,32)=11.86 p=0.0016**. Dunnett's multiple comparisons, lean: aCSF vs picrotoxin p=0.0007*** and lean aCSF vs obese aCSF p=0.0339*.

f) Representative mIPSC recordings of lOFC pyramidal neurons of lean and obese mice.

g) Diet-induced obesity (obese n=9 cells/4 mice, vs. lean n=10 cells/4 mice) increased the frequency of mIPSCs onto pyramidal neurons. Unpaired t-test: $t_{(17)}$ = 2.94, p= 0.0091**.

h) Diet-induced obesity did not alter the amplitude of mIPSCs recorded from pyramidal neurons of lean (n=10 cells/4 mice) or obese (n=9 cells/4 mice) mice. Unpaired t-test: $t_{(17)}$ = 1.754, p= 0.0975.

Bars represent means. Error bars (b,e,g,h) and shading (d) represent s.e.m.

Figure 5: Disinhibition of the lOFC impairs reward devaluation

a) Strategy for chemogenetic targeting of lOFC inhibitory neurons.

b) Schematic representations of hM4D(Gi) expression in the lOFC. Numbers correspond to anterior distance from Bregma (mm).

c) Schematic of patch-clamp electrophysiology experiments on $VGAT^{cre}$ neurons expressing hM4D(Gi) in the lOFC.

d) CNO application (10 µM) reduced the firing of LOFC inhibitory neurons Insert: Averaged response before and after CNO. N = 6 cells/ 3 mice. Wilcoxon t-test: p=0.0312*.

e) VGAT^{cre} mice expressing mCherry (n=7) display reward devaluation following VEH and CNO (IP, 2 mg/kg) indicated by reduced lever presses in the devalued condition. RM two-way ANOVA, mCherry: CNO x devaluation interaction: F(1,6)=0.1556 p=0.7069. Consistent with our a priori hypothesis that both groups would devalue, there was a devaluation main effect F(1,6)=26.18 p=0.0022**, Sidak's multiple comparisons test mCherry VEH p=0.0209*, mCherry CNO p=0.0111*. VGAT^{cre} mice expressing hM4D(Gi) (n=9) display reward devaluation following injection of VEH, but not CNO. RM two-way ANOVA: CNO x devaluation interaction: F(1,16)=1.077, p=0.3147, devaluation effect: F(1, 16)=2.524, p=0.1317; drug effect: F(1, 16)=8.794 p=0.0091**. Our a priori hypothesis was that the VEH group, but not CNO group, would devalue. Sidak's multiple comparisons test hM4D(Gi) VEH p=0.024*, hM4D(Gi) CNO p=0.3467.

f) Normalized lever presses of VGAT^{cre} mice expressing mCherry (n=7) or hM4D(Gi) (n=9) in the lOFC following IP vehicle or CNO in the valued or devalued conditions. Paired t-tests: Control + vehicle: $t_{(6)}$ = 6.305, p=0.0007***, Control + CNO: $t_{(6)}$ = 5.324, p=0.0018**, hM4D(Gi) + vehicle: $t_{(8)}$ = 6.816, p=0.0001***, hM4D(Gi) + CNO: $t_{(8)}$ = 0.1889, p=0.8549.

g) VGAT^{cre} mice expressing mCherry (n=12) display reward devaluation following VEH and CNO (IP, 2mg/kg) indicated by decreased gelatine consumption in the devalued condition. RM two-way ANOVA, mCherry: CNO x devaluation interaction: F(1,11)=0.0008, p=0.97. Consistent with our a priori hypothesis that both groups would devalue, there was a devaluation effect: F(1,11) = 19.72 p=0.001 ***, Sidak's multiple comparisons test mCherry VEH p=0.0004***, mCherry CNO p=0.0004***. VGAT^{cre} mice expressing hM4D(Gi) (n=13) display reward devaluation following injection of VEH but not CNO. RM two-way ANOVA: hM4D(Gi): VEH vs CNO, F(1,12)=5.664 p=0.0348*, drug x devaluation interaction F(1,12)=9.492 p=0.0095**, Sidak's multiple comparisons test: hM4D(Gi) VEH: p=0.008**, hM4D(Gi) CNO: p=0.6784.

h) Normalized consumption in the valued or devalued conditions of VGAT^{cre} mice expressing mCherry (n=12) or hM4D(Gi) (n=13) in the lOFC after vehicle or CNO. Paired t-tests: Control + vehicle: $t_{(11)}$ = 7.720, p<0.0001****, Control + CNO: $t_{(11)}$ = 7.510, p<0.0001****, hM4D(Gi) + vehicle: $t_{(11)}$ = 5.686, p=0.0001***, Control + CNO: $t_{(11)}$ = 1.150, p=0.2744.

Figure 6. Optogenetically restoring inhibitory drive in the lOFC of obese mice rescues goal-directed behaviour

a) Schematic representations of ChR2 expression in the lOFC for electrophysiology experiments. Numbers correspond to anterior distance from Bregma (mm).

b) Schematic of patch-clamp electrophysiology of lOFC pyramidal neurons.

c) Representative recordings of action potentials at 100pA, 300pA and 500pA current injections in lOFC pyramidal neurons from obese mice before and after photostimulation (473nm) of inhibitory interneurons.

d) Obesity increases the excitability of lOFC pyramidal neurons and activation of GABAergic interneurons in obesity restores the excitability. F-I plot of lean (n = 9 cells/4 mice), obese (n = 7 cells/4 mice) and obese + 473 nM photostimulation of lOFC GABAergic neurons (n = 7 cells/4 mice). RM two-way ANOVA: current step effect F(20,400)=140.7 p <0.0001****, current step x group interaction F(40,400)=1.820 p= 0.0023**. Tukey's multiple comparisons test: lean vs. obese p= 0.0004***, obese vs. obese + photostimulation p= 0.0002***, lean vs. obese + photostimulation p= 0.9774.

e) Mean excitability slope (linear regression slope of individual cells, x=current step y=number of action potentials) of lOFC pyramidal neurons of lean (n=9 cells/4 mice) or obese (n = 7 cells/4 mice) with no photostimulation or lean (n=9 cells/4 mice) or obese (n = 7 cells/4 mice) with 473 nm photostimulation. Two-way ANOVA: diet effect: F(1,14)=1.396 p=0257, photostimulation effect: F(1,14) = 33.58, p<0001***, Diet x photostimulation interaction F(1,14)=2.141 p=0.1655.

f) Strategy for optogenetic targeting of lOFC inhibitory neurons.

g) Photostimulation in lean mice (589nM (n = 7) vs. 473nM (n = 7)) did not alter reward devaluation by selective satiety. Lever presses in the valued and devalued conditions following 589nM and 473nM photostimulation. Two-way RM ANOVA: interaction: F (1, 12) = 0.0324, p=0.8599, devaluation effect: F (1, 12) = 8.178, p=0.0144*, Photostimulation effect: F (1, 12) = 0.1306, p=0.7241.

h) Normalized lever presses in the valued and devalued condition of lean mice following photostimulation (589nM (n = 7) vs. 473nM (n = 7)). Light activation did not alter devaluation. Paired t-test: 589nM: $t_{(6)}$ = 2.813, p=0.0306*, 473nM: $t_{(6)}$ = 4.220 p=0.0056**.

i) Schematic representations of ChR2 expression in the lOFC for devaluation experiments. Numbers correspond to anterior distance from Bregma (mm).

j) Lever presses in the valued or devalued state of obese mice following 589nm (inactive, n = 6) and 473nm (active, n = 6) photostimulation. RM two-way ANOVA revealed a significant devaluation effect (F(1,10)=5.232, p=0.0452*), no photostimulation effect (589nm vs 473nm, F(1,10)=0.00459, p=0.9473) and a devaluation x photostimulation interaction (F(1,10)=17.83, p=0.0018**). A Sidak's multiple comparison test showed that while obese animals with 589nm light did not devalue (valued vs devalued, p=0.3617), obese+473nm devalued (valued vs devalued, p=0.0019**).

k) Normalized lever presses of obese mice (n=6) in the valued or devalued condition following 589nm or 473nm photostimulation. Paired t-test, inactive 589nm: $t_{(5)}$ = 1.590, p=0.1726, active 473nm: $t_{(5)}$ = 3.983, p=0.0105.

l) During inactive (589nM) light, significant group differences in revaluation index were observed with lean (n = 7) animals displaying a positive revaluation index and mice with obesity (n = 6) displaying a negative one. During active (473nM) light, the revaluation of both diet groups was positive and no group difference was observed. Two-way RM ANOVA: diet x light interaction: F (1, 11) = 7.849, p=0.0172*, diet effect: F(1,11) = 3.443, p = 0.0905, photostimulation effect: F (1,11) = 7.004, p = 0.0227*. Sidak's multiple comparison test: 589 nm (inactive) light lean vs. obese p=0.0057**; 473 nm (active) light lean vs. obese p=0.3143.

Figure 7. Pharmacologically restoring inhibitory drive in the lOFC of obese mice rescues goal-directed behaviour

a) Representative recordings of action potentials observed at 100pA, 300pA and 500pA injections in lOFC from obese mice in the presence of aCSF or NNC-711 (10 µM).

b) Obesity increases the excitability of lOFC pyramidal neurons and enhancement of inhibitory neurotransmission via application of NNC-711 restores excitability. F-I plot of pyramidal neuronal activity from lean (n = 8 cells/4 mice), obese (n = 10 cells/4 mice), and obese + NNC-711 (n = 10 cells/6 mice) mice. RM two-way ANOVA: current step effect F(2.068,49.63)=170.5, p<0.0001****, diet effect F(2,24)=6.029, p=0.0076**, current step x diet interaction F(40,480)=5.317, p<0.0001****. Tukey's multiple comparisons test: lean vs. obese p<0.0001****, lean vs. obese + NNC-711 p=0.1713, obese vs. obese + NNC-711 p<0.0001****.

c) Excitability slope of pyramidal neurons from the F-I plot of pyramidal neuronal activity from lean (n = 8 cells/4 mice), obese (n = 10 cells/4 mice), and obese + NNC-711 (n = 10 cells/6 mice) mice. NNC-711 (10 µM) significantly reduced the firing of lOFC pyramidal neurons from obese mice compared to vehicle + obese. Two way RM ANOVA: NNC-711 effect: F (1, 30) = 9.641, p=0.0041. Diet effect: F (1, 30) = 2.375, p = 0.1338, Diet x VEH vs. NNC interaction: F(1,30)=2.336, P = 0.1369. Tukey's multiple comparisons test: obese vehicle vs. obese NNC-711 p=0.0057**.

d) Strategy for pharmacological enhancement of lOFC inhibitory neurotransmission.

e) Lever presses of lean mice (n=14) in the valued (closed bars) and devalued (open bars) conditions following bilateral lOFC infusions of either vehicle or NNC-711. Two-way RM ANOVA: Interaction: F (1, 26) = 1.573, p = 0.2209, vehicle vs. NNC-711 effect: F (1, 26) = 0.0005995, p=0.9807, devaluation effect: F (1, 26) = 15.14, p=0.0006***. Our a priori hypothesis was that both groups would devalue. Sidak's multiple comparison's: lean vehicle: p = 0.14, lean NNC: p = 0.0024.

f) Normalized lever presses (valued: valued / (valued + devalued), devalued: devalued / (valued + devalued) of lean mice (n=14) in the valued and devalued conditions following bilateral lOFC infusions of either vehicle (Paired t-test: $t_{(13)}$=2.784, p=0.0155*) or NNC-711 (Paired t-test: $t_{(13)}$=3.175, p=0.0073**).

g) Revaluation index ((lever presses valued – lever presses devalued)/(lever presses valued + lever presses devalued)) of lean (n=11) or obese (n=12) mice following lOFC infusion of either vehicle or NNC-711. Two-way RM ANOVA: diet effect: F(1, 28) = 6.755, p=0.0148*, NNC-711 effect: F (1, 28) = 5.446,

p=0.027*, Interaction: F (1,28) = 1.926, p = 0.176. Sidak's multiple comparisons test: lean vehicle vs. NNC-711 p=0.7721, obese vehicle vs. NNC-711 p=0.0114*

h) Lever presses in the valued or devalued state of obese mice following lOFC infusions of vehicle (n=16) or NNC-711 (n=16). RM two-way ANOVA: devaluation x OFC infusion interaction F(1,30)=11.27 p=0.0022**, Devaluation effect: F(1,30) = 1.667, p = 0.2066, drug effect: F(1,30) = 0.6471, p = 0.4275. Obese mice receiving lOFC VEH did not show reward devaluation (Sidak's multiple comparisons test: obese + vehicle: p= 0.2852). Obese mice receiving lOFC NNC-711 displayed reward devaluation (Sidak's multiple comparison test: obese + NCC-711: p= 0.0052**).

i) Normalized lever presses of obese mice (n=16) following lOFC infusions of vehicle or NCC-711. Obese mice receiving lOFC vehicle did not display reward devaluation (Paired t-tests, valued vs. devalued: $t_{(15)}$=1.919, p= 0.0796). Obese mice receiving lOFC NNC-711 display reward devaluation (Paired t-tests, valued vs. devalued: $t_{(15)}$=3.426, p=0.0041**).

REWARD DEVALUATION BY SELECTIVE SATIETY

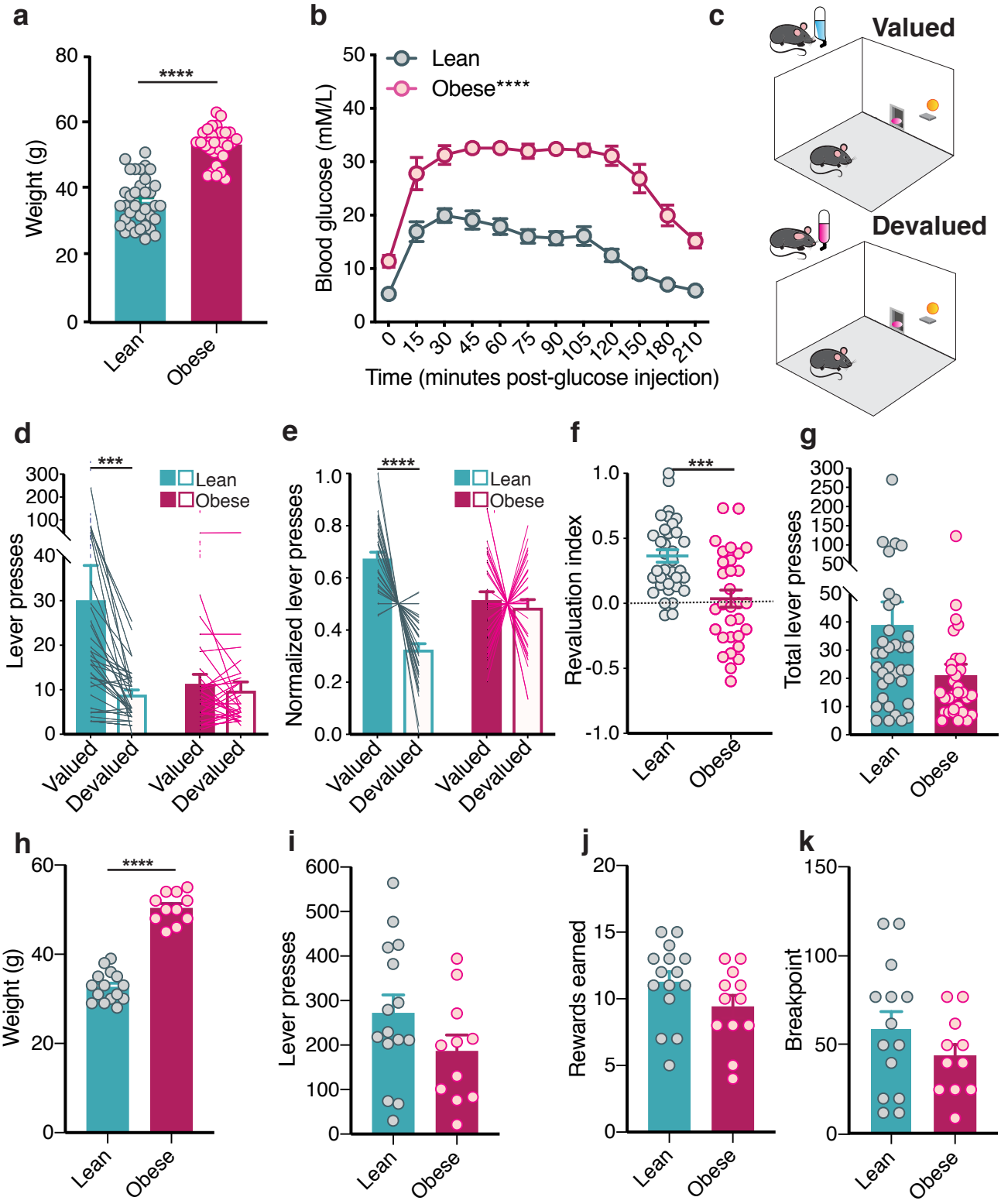


Figure 1

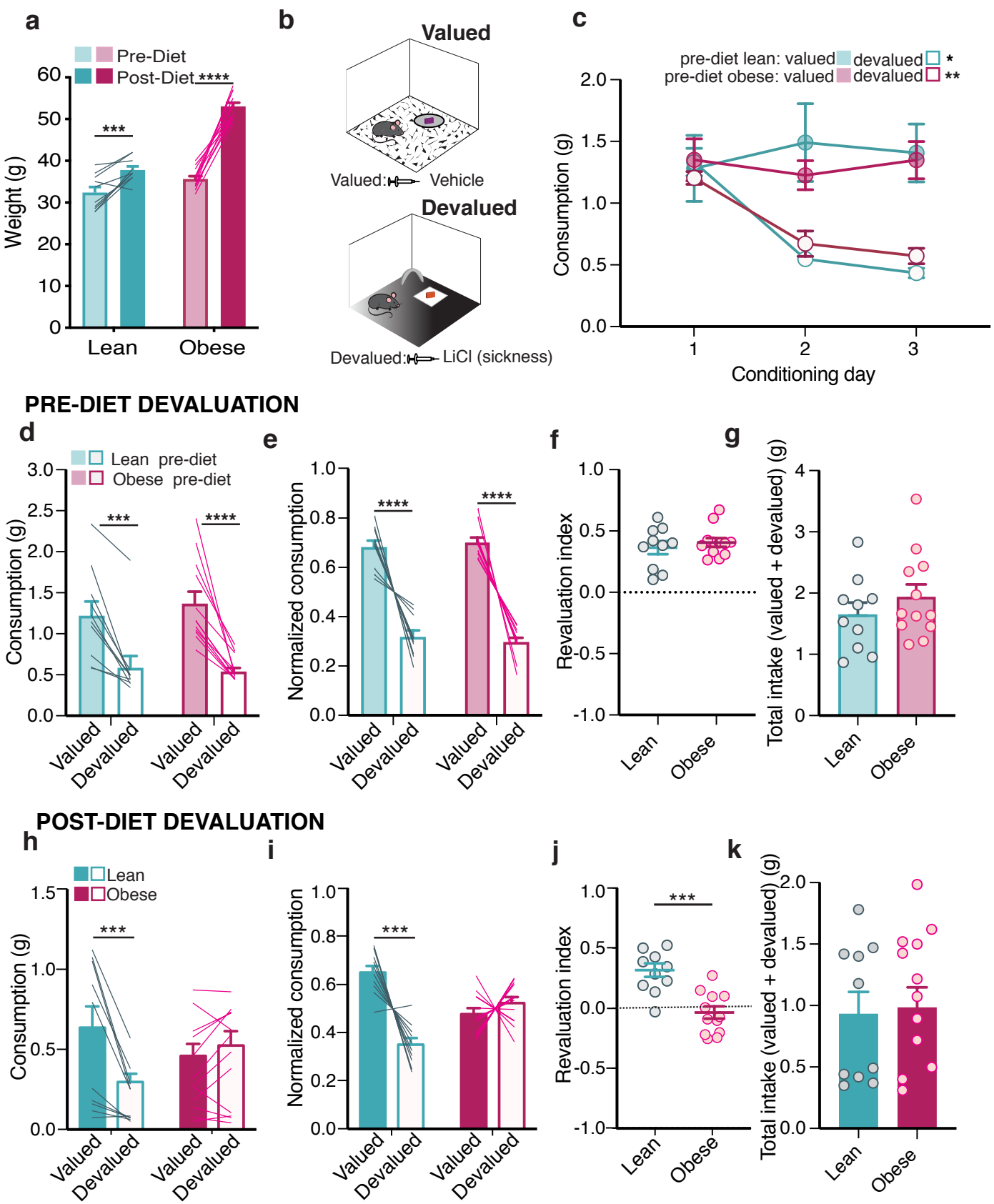


Figure 2

CONTINGENCY REVERSAL

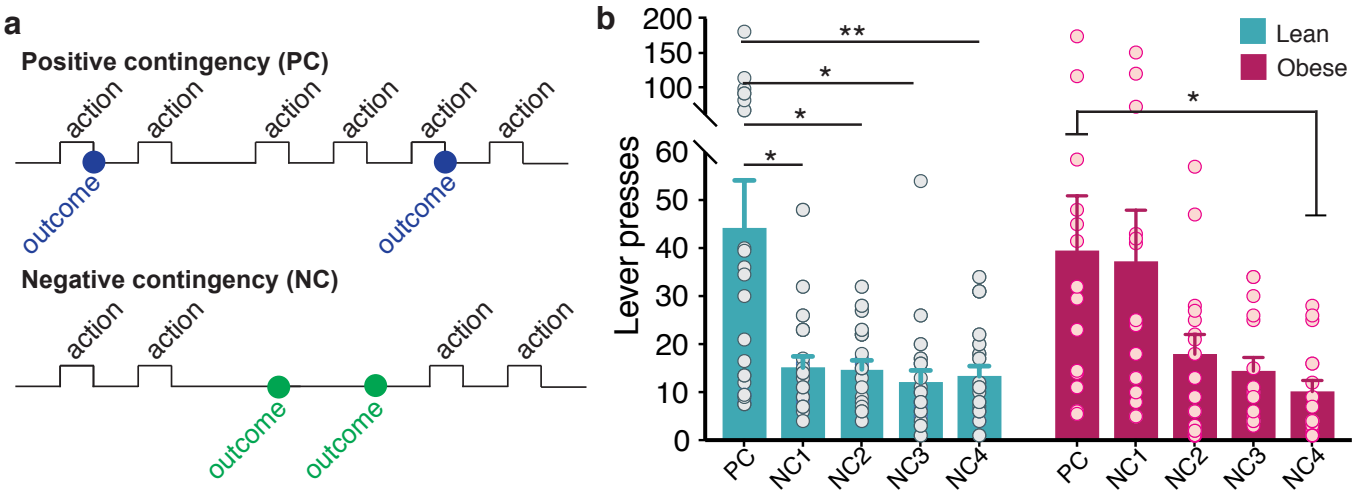


Figure 3

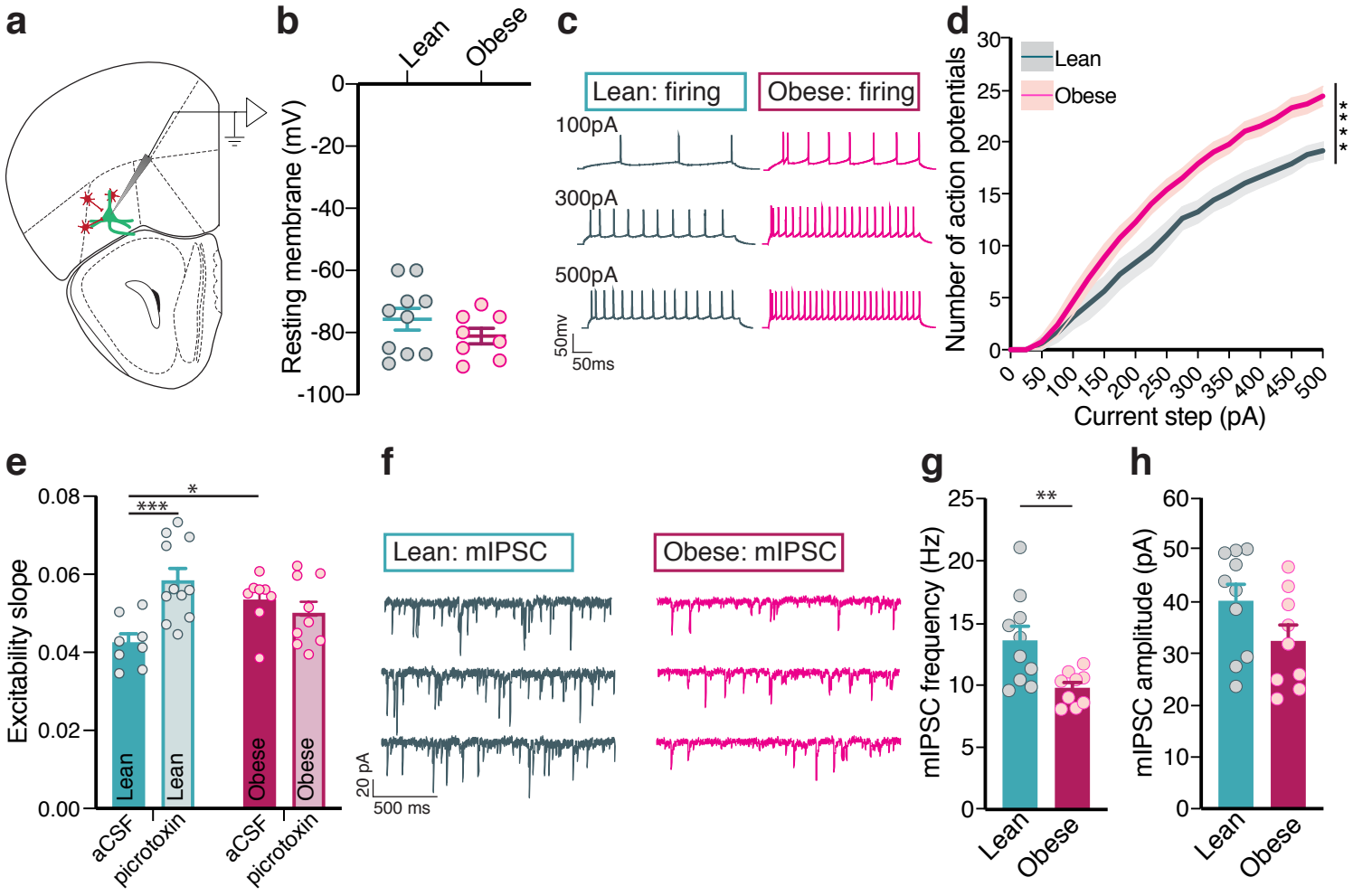
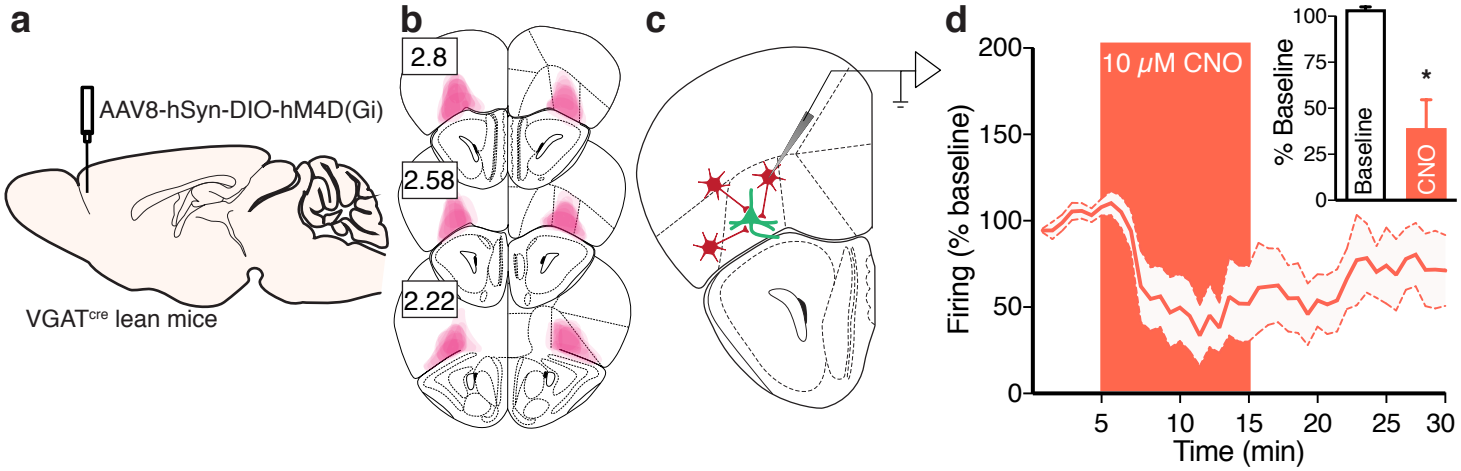
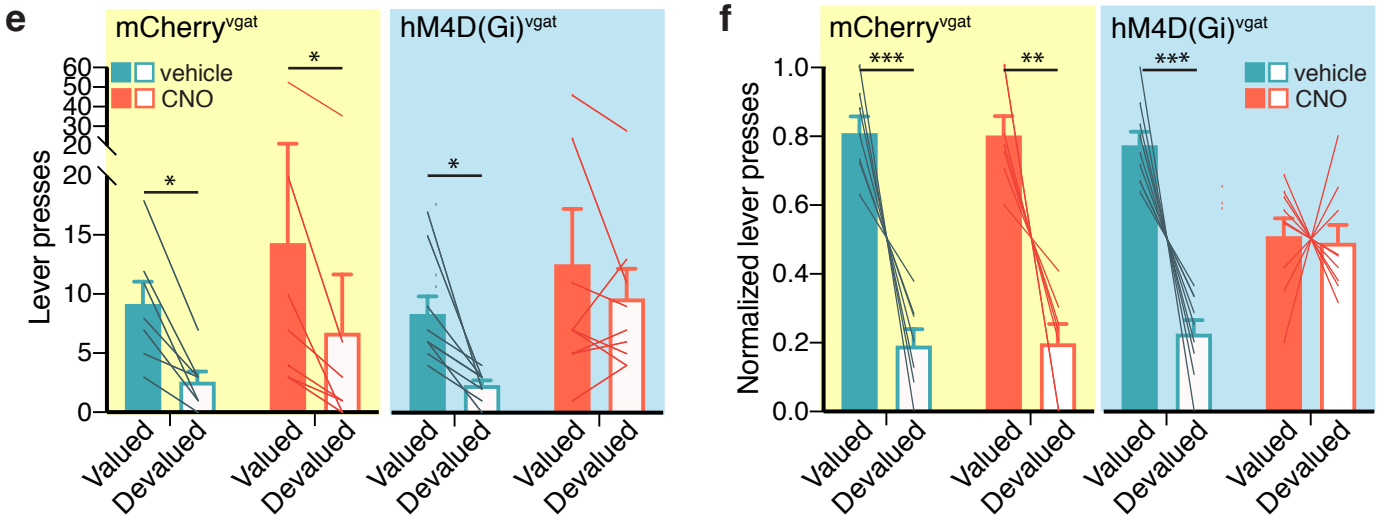


Figure 4



REWARD DEVALUATION BY SELECTIVE SATIETY



REWARD DEVALUATION BY CONDITIONED TASTE AVOIDANCE

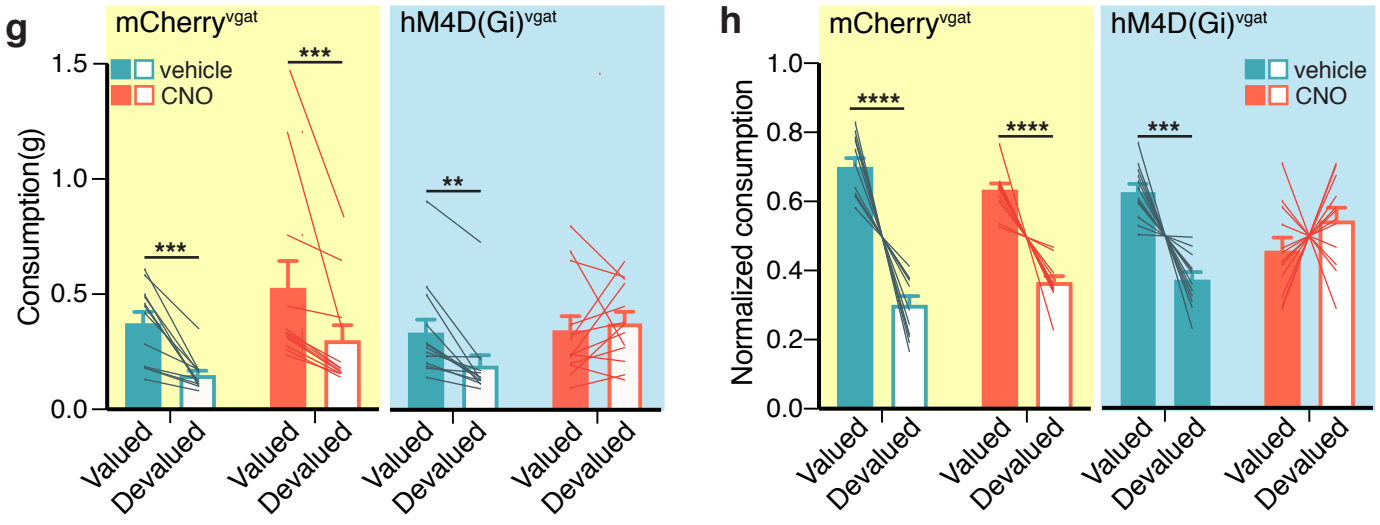


Figure 5

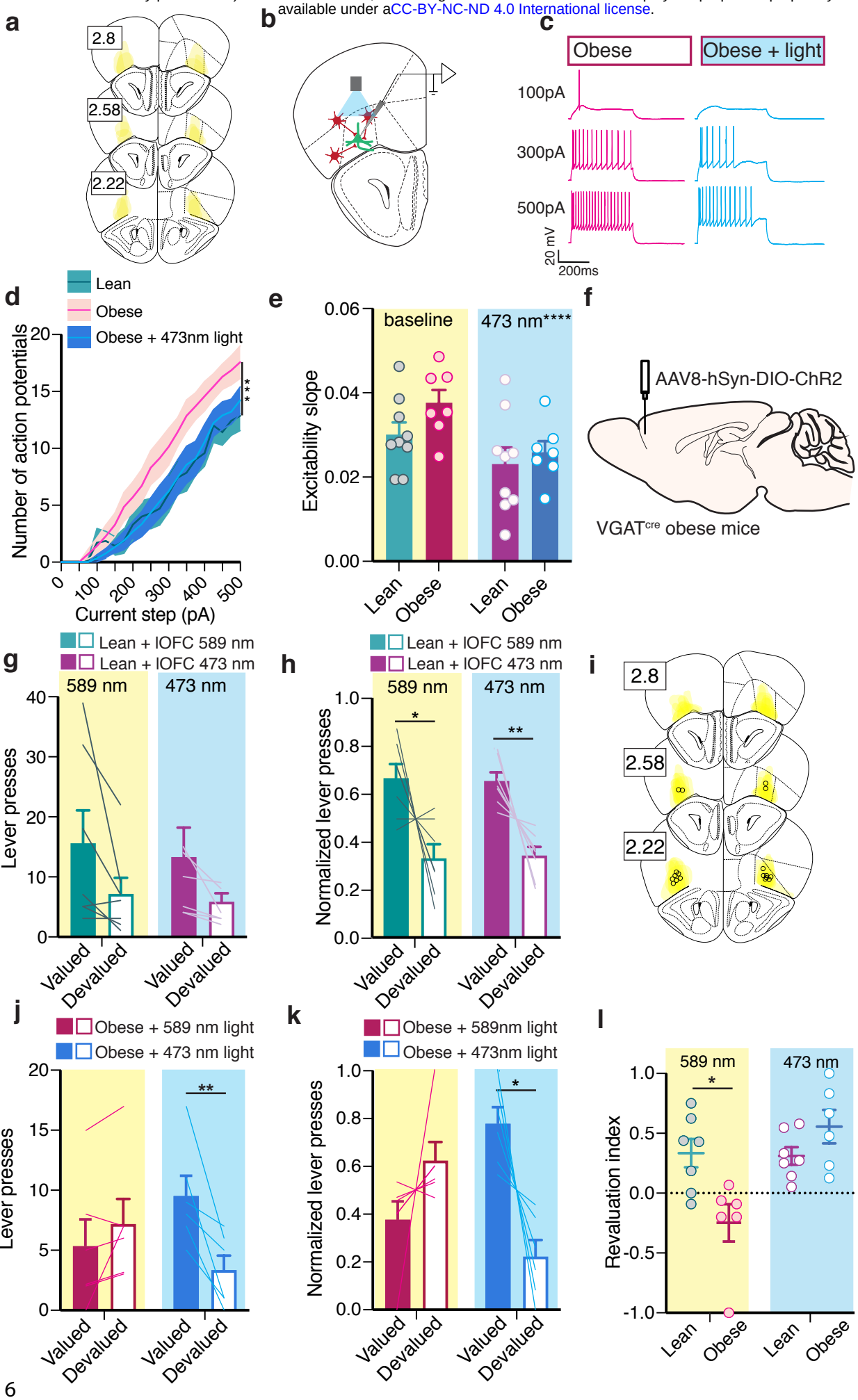


Figure 6

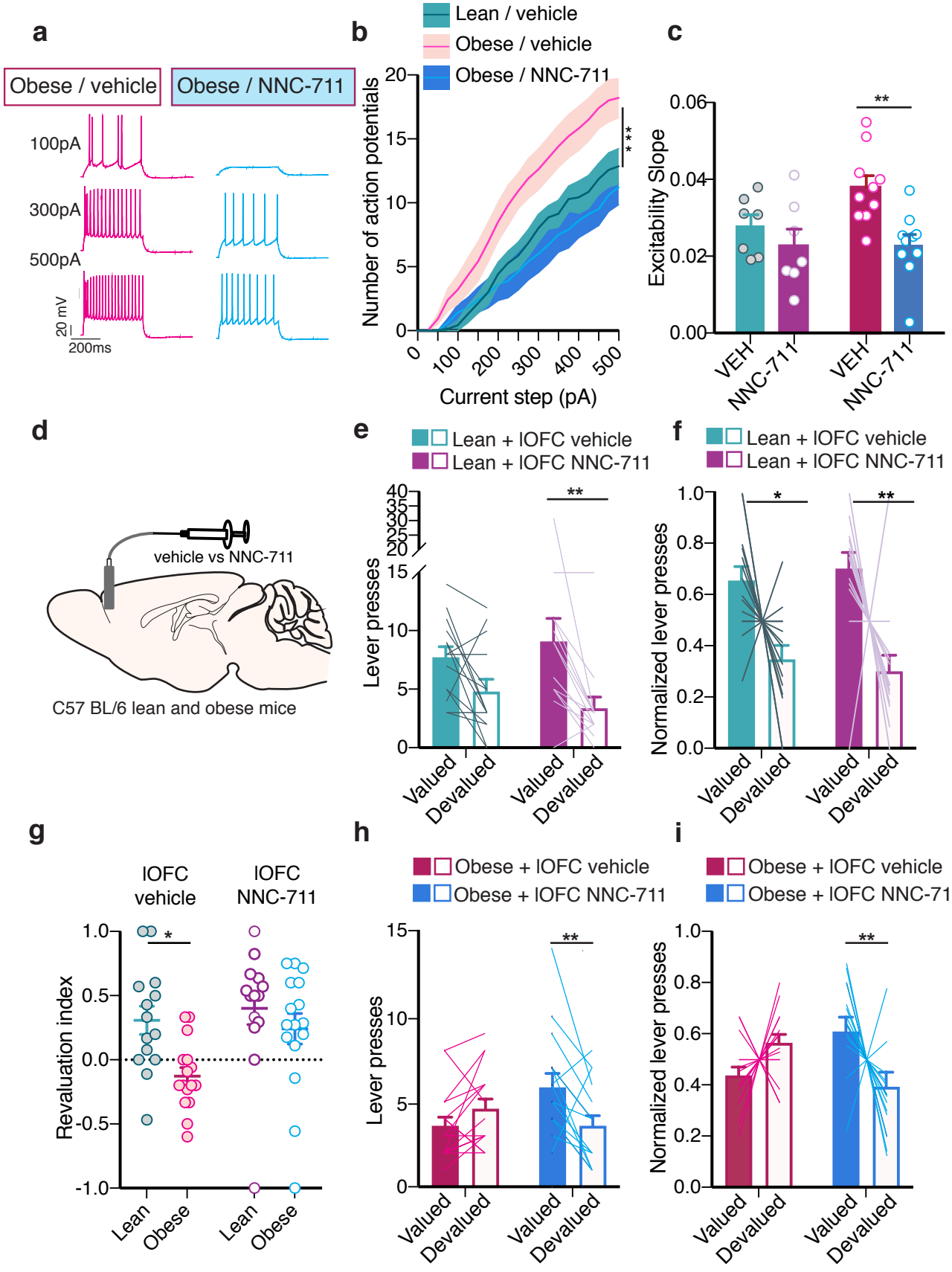
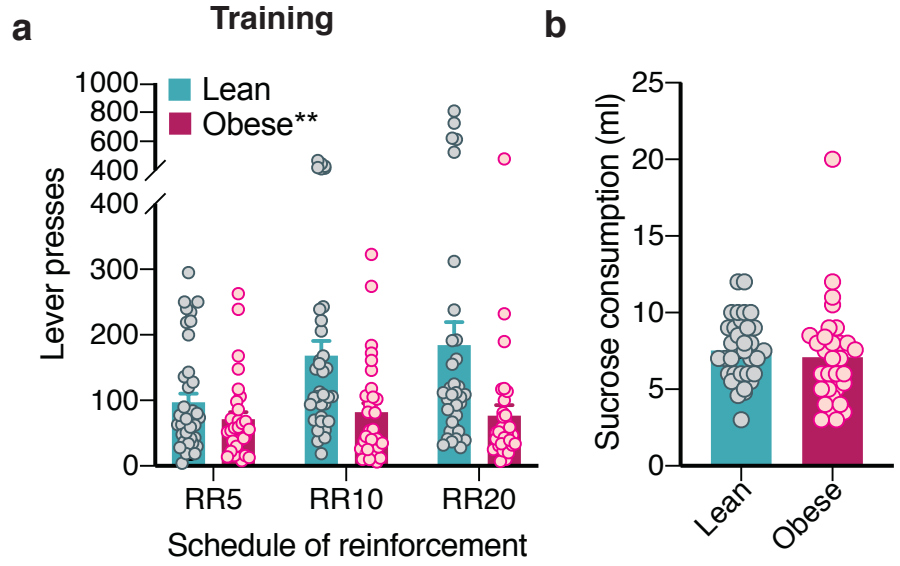
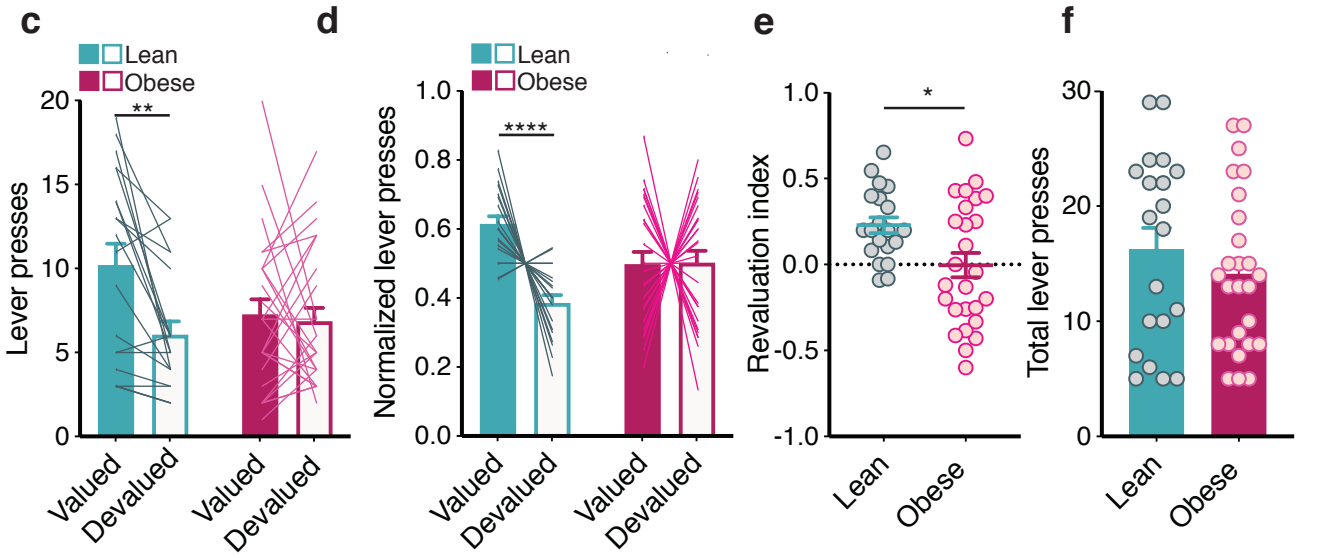


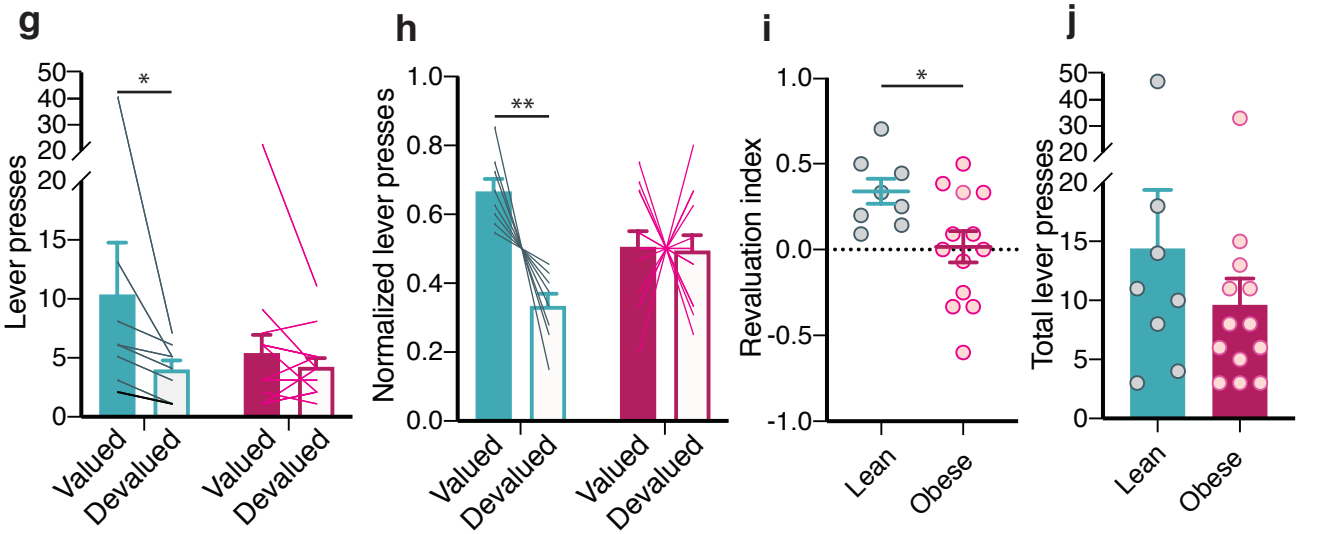
Figure 7



Selective Satiety: matched for lever pressing

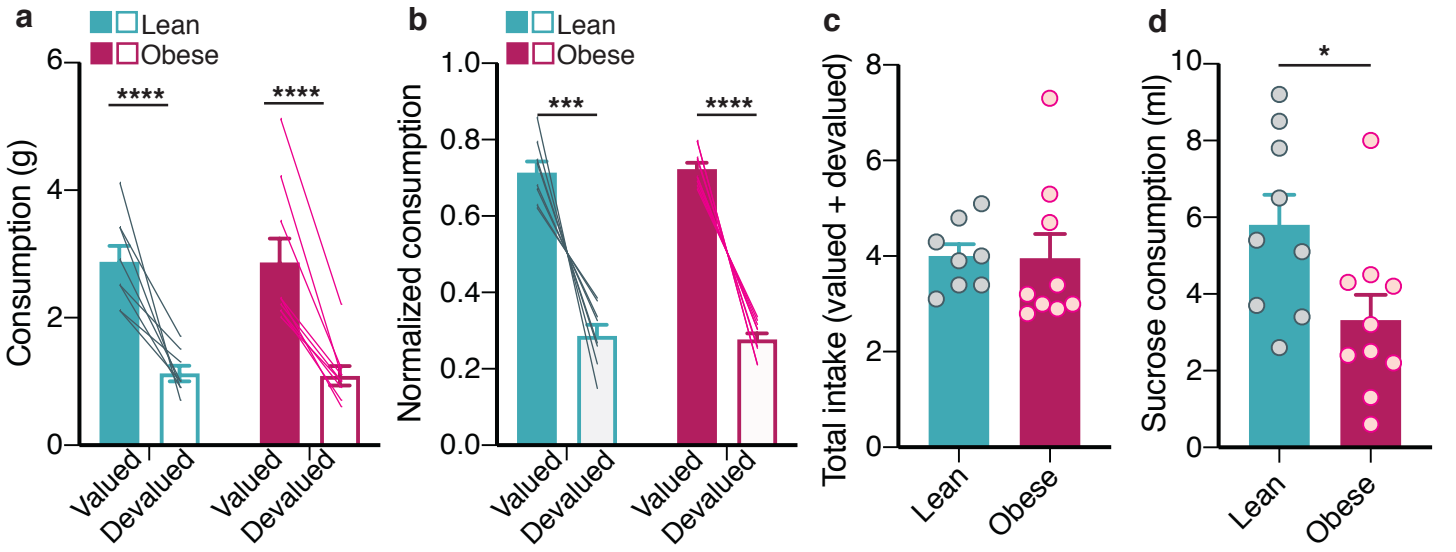


Selective Satiety: sucrose delivery during testing

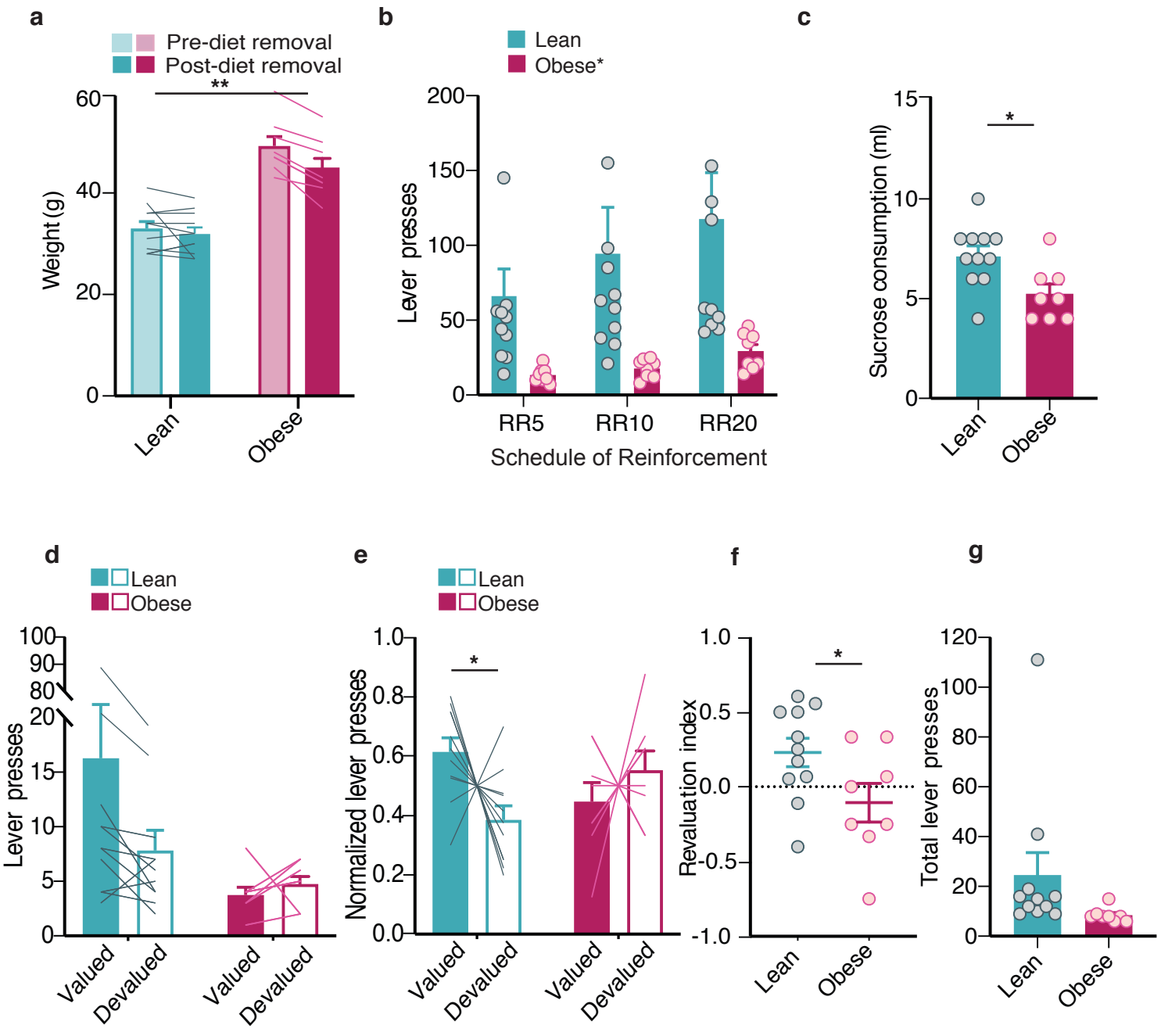


Extended data figure 1

Taste discrimination

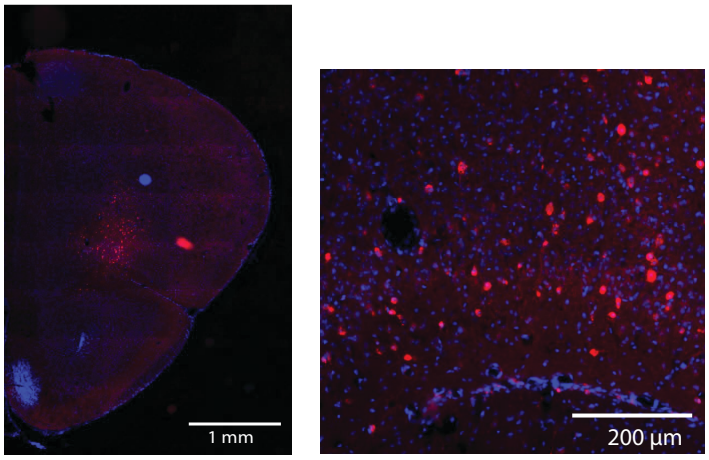


Extended data figure 2

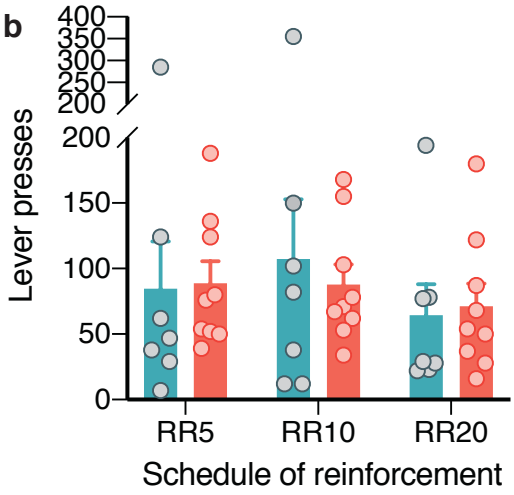


Extended data figure 3

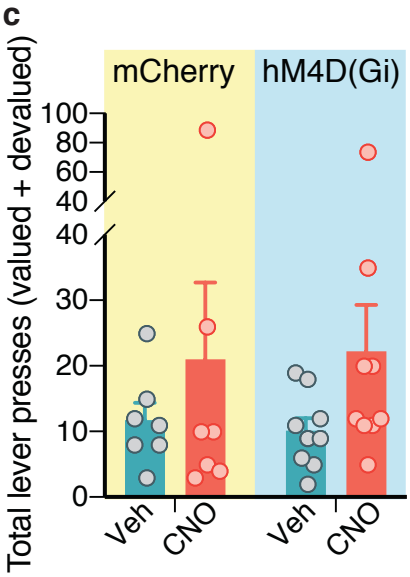
Selective satiety

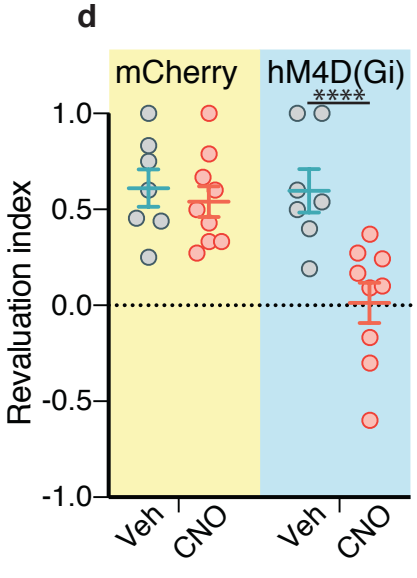


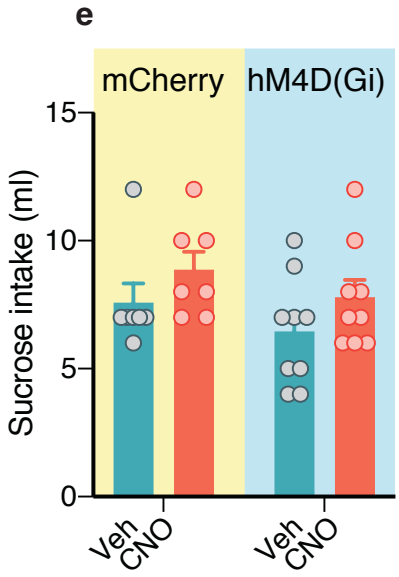
Training



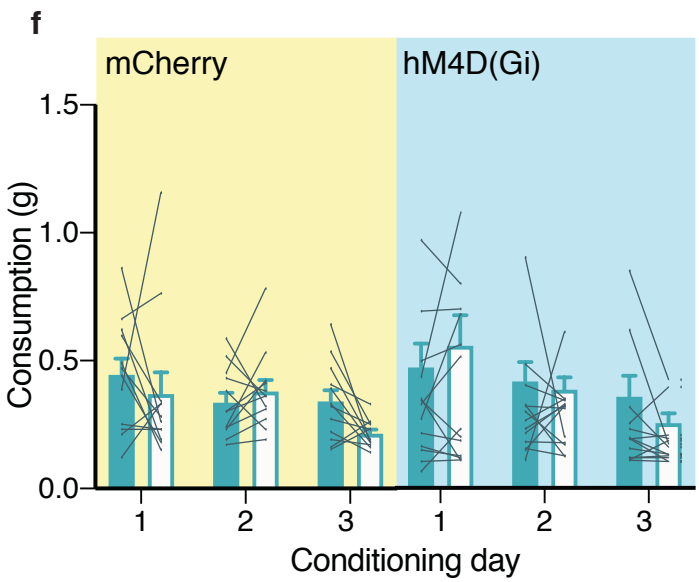
Selective satiety



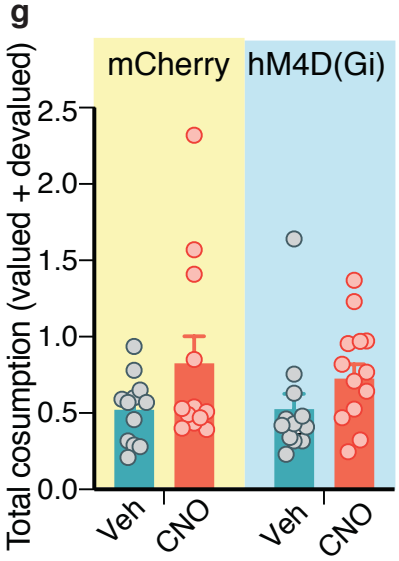


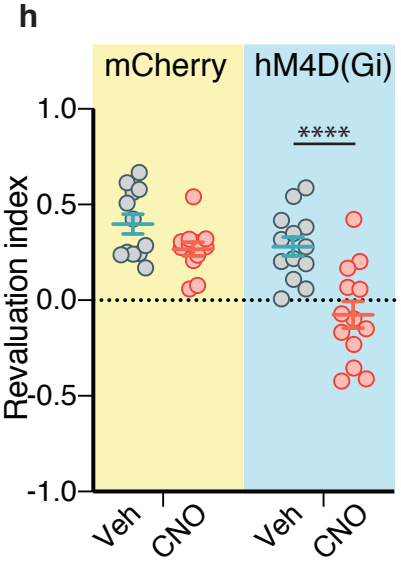


Conditioned taste avoidance training

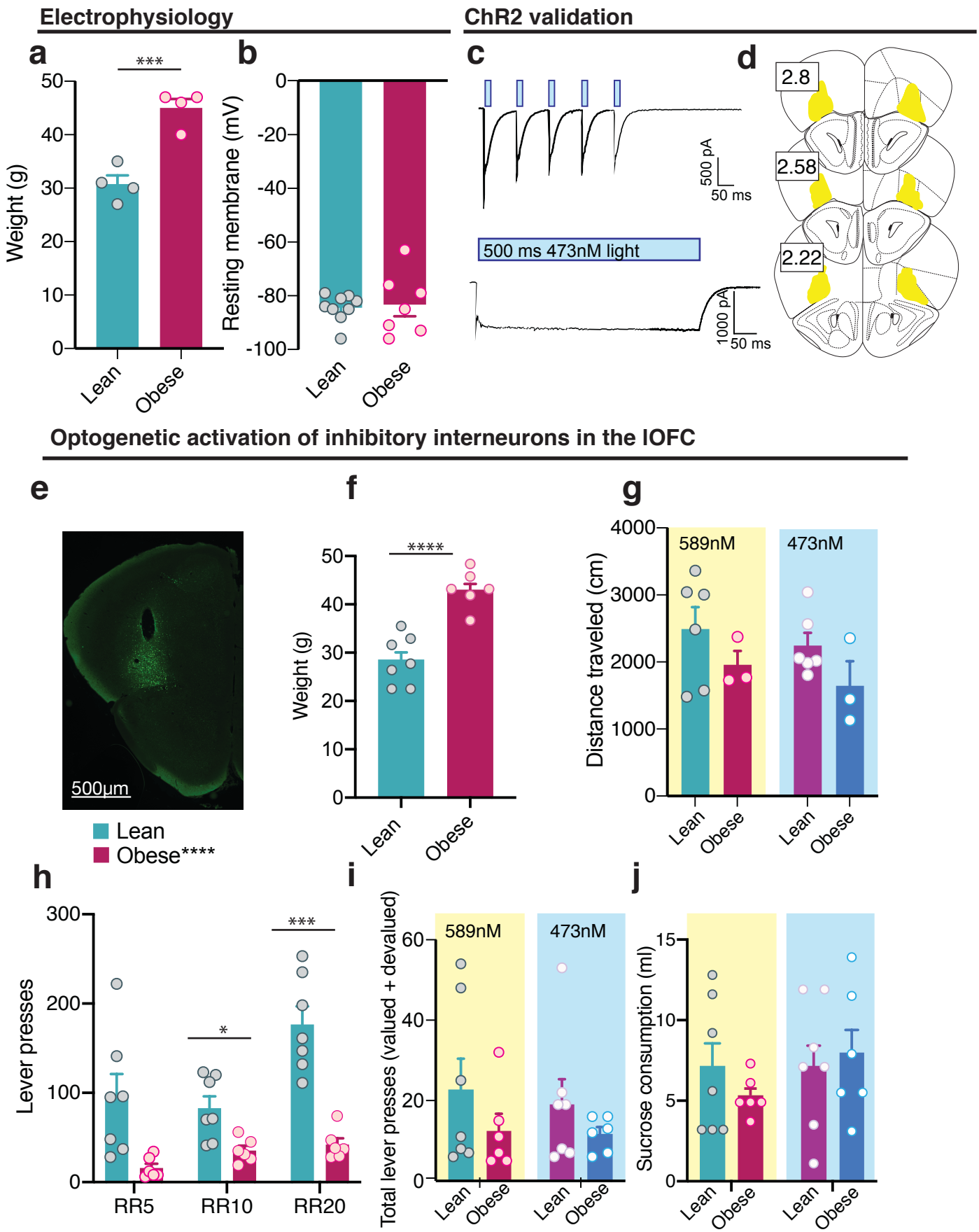


Conditioned taste avoidance



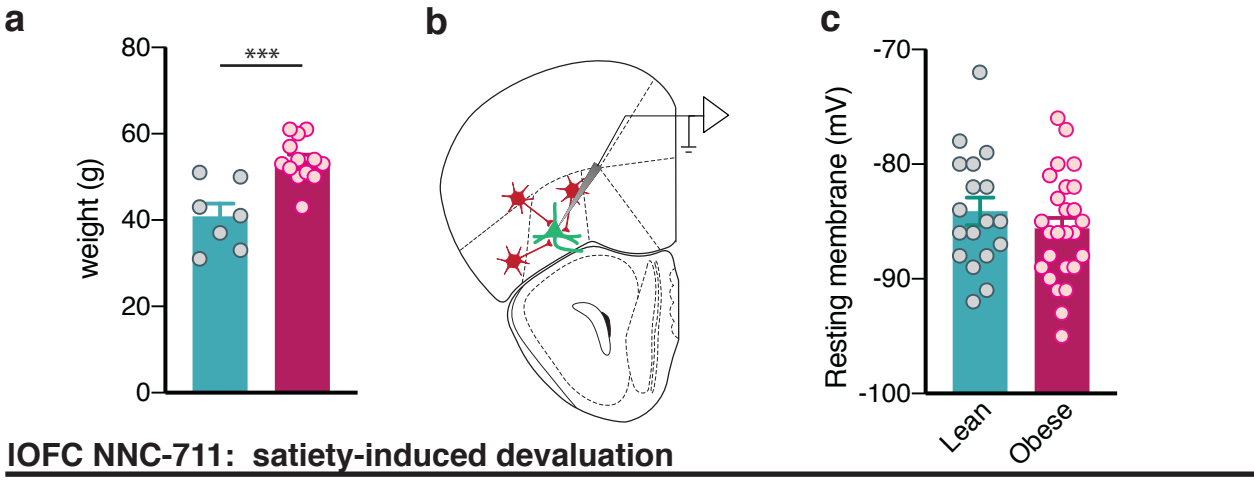


Extended data figure 4

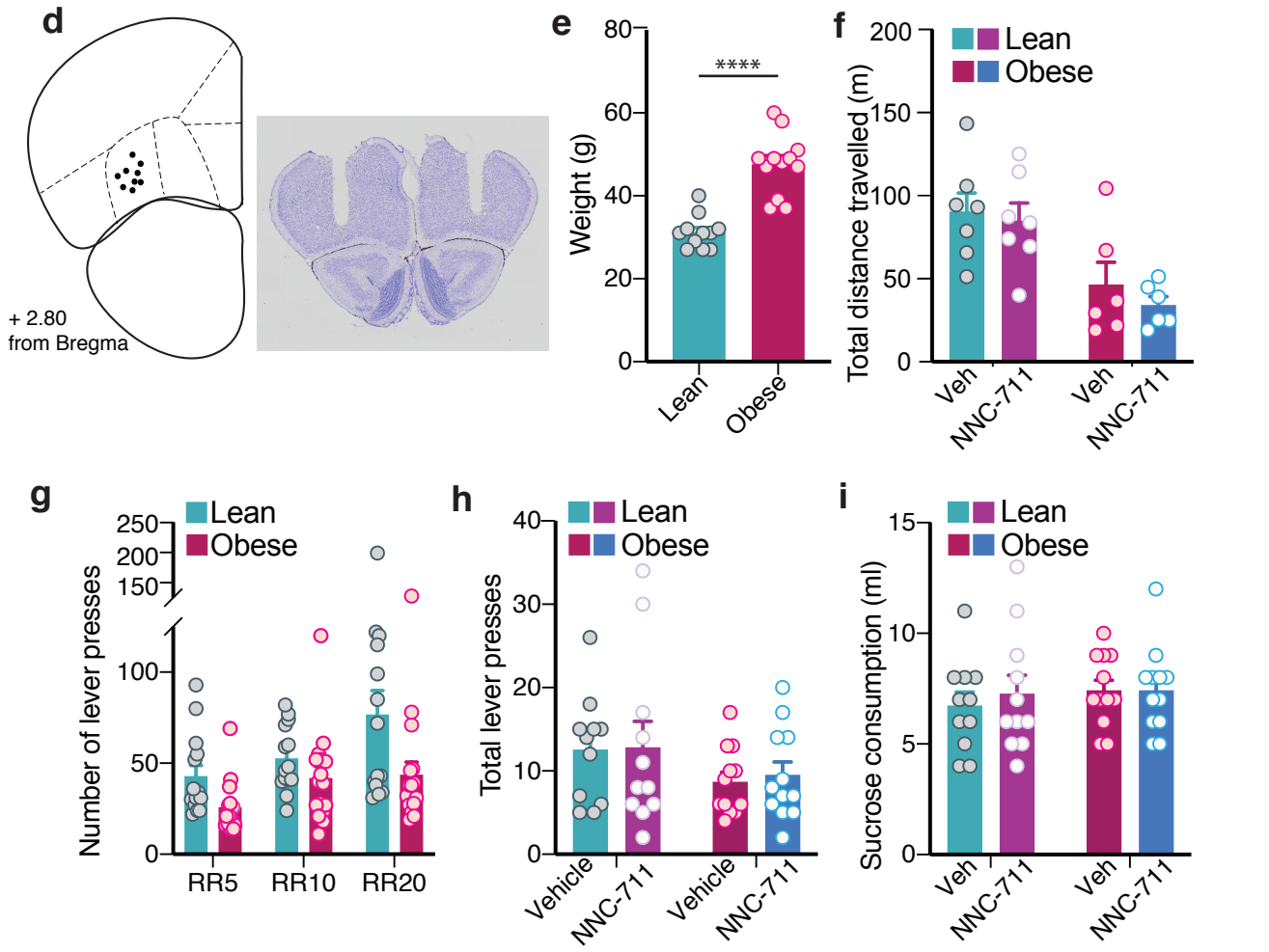


Extended data figure 5

Electrophysiology



IOFC NNC-711: satiety-induced devaluation



Extended data figure 6