nature COMMUNICATIONS

ARTICLE

DOI: 10.1038/s41467-018-04967-2 OPEN

Prolonged abstinence from cocaine or morphine disrupts separable valuations during decision conflict

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Neuroeconomic theories propose changes in decision making drive relapse in recovering drug addicts, resulting in continued drug use despite stated wishes not to. Such conflict is thought to arise from multiple valuation systems dependent on separable neural components, yet many neurobiology of addiction studies employ only simple tests of value. Here, we tested in mice how prolonged abstinence from different drugs affects behavior in a neuroeconomic foraging task that reveals multiple tests of value. Abstinence from repeated cocaine and morphine disrupts separable decision-making processes. Cocaine alters deliberation-like behavior prior to choosing a preferred though economically unfavorable offer, while morphine disrupts re-evaluations after rapid initial decisions. These findings suggest that different drugs have long-lasting effects precipitating distinct decision-making vulnerabilities. Our approach can guide future refinement of decision-making behavioral paradigms and highlights how grossly similar behavioral maladaptations may mask multiple underlying, parallel, and dissociable processes that treatments for addiction could potentially target.

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Cocaine and morphine can both lead to rewiring of neural circuits involved in motivated behavior[1,2]. Although these drugs have different immediate mechanisms of action, theories have suggested that they ultimately converge on a final common dysfunction in mesolimbic dopamine leading to maladaptive reinforcement learning[3,6–10]. However, it has also been hypothesized that malfunctions in decision-making systems with distinct neural circuits are capable of giving rise to multiple addiction etiologies, and that cocaine and morphine may access different malfunctions in those circuits despite producing grossly similar changes in maladaptive goal-oriented behavior[2]. So far, it has not been possible to dissect apart such changes behaviorally[11].

We developed a neuroeconomic task in mice that reveals multiple parallel valuation algorithms and separates decision-making processes of reward conflict into behaviorally deconstructed stages[12]. Food-restricted mice traversed a square maze with four feeding sites (restaurants), each providing a different flavor, with two distinct zones: an offer zone and a wait zone (Fig. 1b, Methods). Tones sounded upon offer zone entry, whose pitch indicated a delay (pseudo-random, 1–30 s) that mice would have to wait if they chose to enter the wait zone in order to receive food reward. Mice could choose to quit during delay countdowns. Importantly, mice had 1 h to forage for their food for the day. Using different flavors instead of pellet number allowed us to measure subjective preferences (Fig. 1c) without introducing differences in time required for food consumption.

The economic key to foraging is the division of time. Time spent choosing in the offer zone, waiting in the wait zone, and remaining at the reward site after receiving food all detracts from time spent making other decisions elsewhere. Critically, choices in each of these three decision modalities (skip vs. enter, quit vs. continue to wait, leave vs. linger) are computationally distinct valuation processes that reflect economic conflict.

We find that repeated exposure to cocaine or morphine produced lasting disruptions in judgments during these instances of economic conflict. Cocaine-abstinent mice displayed impairments in deliberative valuation processes in the offer zone before ultimately accepting economically disadvantageous reward offers. Morphine-abstinent mice displayed impairments in foraging re-evaluative processes in the wait zone when correcting poor snap judgements. Together, these data demonstrate how drugs of abuse can give rise to lasting dysfunctions in fundamentally distinct decision-making valuation algorithms and suggest that individualized treatments tailored to computation-specific processes might ameliorate heterogeneous addiction subtypes.

Results

Separating stages of economic subjective valuations. Mice spent the majority of time lingering at the reward site after earning and consuming a reward (Supplementary Fig. 1). Interestingly, mice lingered longer in more-preferred restaurants (Fig. 1d). This decision to linger rather than leave, where no overt reward is being sought out, may represent a conditioned-place-preference-like effect[13] associated with each restaurant's context.

We calculated offer zone thresholds of willingness to enter as a function of offered delay (Fig. 1e, Supplementary Fig. 2), and found higher thresholds in more-preferred restaurants compared to less-preferred restaurants (Fig. 1e, f). Interestingly, mice took longer in the offer zone deciding to skip than deciding to enter (Fig. 2a–c). Furthermore, decision time took longer when skipping more-preferred restaurants (Fig. 2c). These data suggest that highly desired rewards were more difficult to turn down.

Degree of adherence to thresholds can be measured via slope of fitted sigmoid functions. Steeper (more negative) slopes indicate low likelihoods of threshold violation (e.g., enter above or skip below offer zone thresholds). Threshold slope was less steep in more-preferred restaurants (Fig. 1g), suggesting highly desired reward offers blurred subjective policies to make economically advantageous judgments to skip vs. enter.

We carried out similar analyses in the wait zone for quit decisions. Wait-zone thresholds also increased for more-preferred flavors (Fig. 1e, f). However, wait-zone threshold slope was steeper than offer-zone threshold slope (Fig. 1g), indicating mice were less likely to violate wait-zone thresholds. This meant that wait-zone metrics captured a fundamentally different valuation process than the offer zone: we found no relationship between the two types of thresholds or with lingering time after accounting for ordinal ranking of flavor, even though all three valuation parameters, importantly, agreed on the ordinal ranking of a given flavor (Figs 1d, f, g, Supplementary Fig. 3).

Approach behaviors and economic efficiency of decisions. Disparity between offer- and wait-zone thresholds was greatest (offer zone > wait zone) in more-preferred restaurants (Fig. 1f). In these restaurants, then, mice were more likely to accept offers with a higher cost than subjective value indicated that they should (Fig. 2f). This scenario—entering offers that are greater than wait-zone thresholds—is an explicit economic failure to choose a better alternative over a tantalizing reward offer. In such instances, it would have been economically advantageous to choose to skip in the offer zone.

Because path trajectories can reveal decision-making processes[14], we examined moment-by moment body positions during offer-zone decisions. We found that mice often oriented first toward entering the wait zone before pausing, re-orienting, and then ultimately deciding to skip (Fig. 2a, b). This behavior is a well-studied decision-making phenomenon termed vicarious trial and error (VTE) that reveals on-going deliberation and planning during moments of indecision (Supplementary Discussion)[14–16]. We measured VTE as the absolute integrated angular velocity over the course of a given path trajectory (IdPhi, Supplementary Methods). There was more VTE (IdPhi was larger) during skip decisions in general and particularly so when skipping in more-preferred restaurants (Fig. 2a, d, Supplementary Fig. 4). The presence of VTE suggests that in the offer zone, decisions to skip included a delayed valuation that overrode initial rapid decisions. This provides a potential point of decision-making vulnerability or impairment in self-control—one rooted in failure of a deliberative or planning process when engaged in conflict between a highly desirable reward vs. choosing smarter alternatives—that could be exploited by drugs of abuse.

Interestingly, skipping offers above wait-zone thresholds was more likely to occur the more an animal displayed VTE behavior (Fig. 2e). This suggests that the more a planning process was engaged, the less likely desired rewards could out-compete making smarter choices, independent of offer value (Supplementary Fig. 5). By classifying the amount of VTE required to skip these economic scenarios at least 50% of the time, we found that skipping high delays in more-preferred restaurants required greater amounts of VTE (Fig. 2g). Furthermore, we found enters for offers above versus below wait thresholds were both rapid and indistinguishable in reaction time and VTE (Fig. 2h–k), suggesting reward-taking behaviors were generally snap judgments while reward-opposing behaviors were not.

As noted, mice were more likely to err by entering offers above wait-zone threshold in more- vs. less-preferred restaurants (Fig. 2f). In the wait zone, mice were more likely to quit after enters above than after enters below wait-zone threshold. Moreover, they were more likely to quit while the amount of

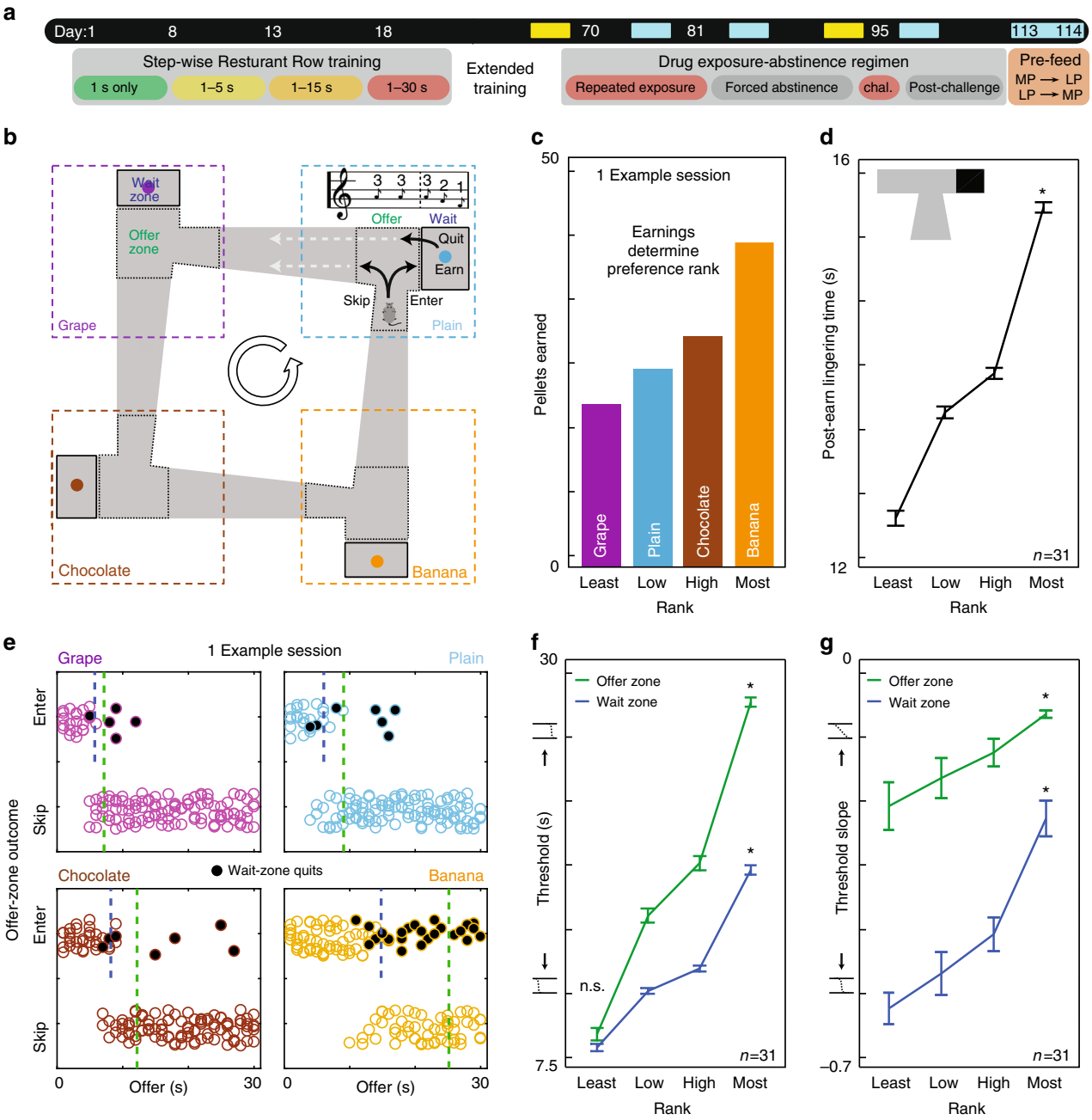


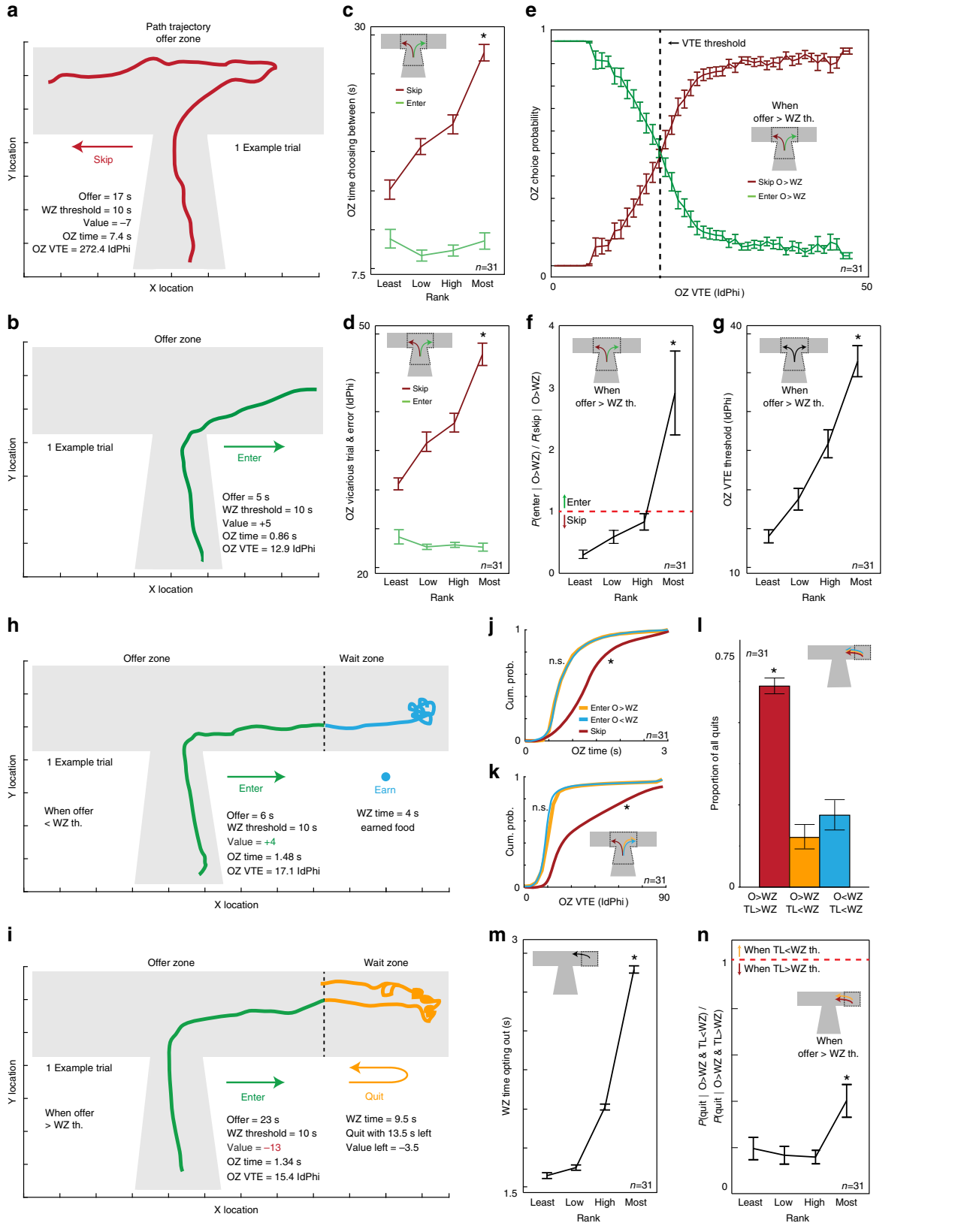
Fig. 1 Multiple valuations in Restaurant Row. **a** Experimental timeline. Timepoints of interest marked in yellow: well-trained at baseline (days 66–70, Figs. 1 and 2); after prolonged abstinence from repeated drug exposure (days 90–94, Fig. 3). Supplementary timepoints are marked in cyan. **b** Mice were trained to run counter-clockwise around a square maze encountering serial offers for flavored rewards in four restaurants. Tone pitch indicated delay length that sounded in the offer zone, but did not countdown until after entering the wait zone. **c** Flavors were ranked from least- to most-preferred by end-of-session earnings each day. Panel shows one example session. Mice showed individual preferences that were stable across days (Supplementary Fig. 2). **d** Kruskal–Wallis (KW) tests revealed mice spent more time lingering at the reward site after earning rewards in more-preferred restaurants before moving on to the next trial (*$P < 0.0001$). **e** Mice entered low delays and skipped high delays in the offer zone, while infrequently quitting once in the wait zone (black dots). Dashed vertical lines represent calculated offer-zone and wait-zone thresholds of willingness to budget time. Green line indicates offer-zone threshold (all offers). Blue line indicates wait-zone threshold (entered offers). **f** KW tests revealed thresholds to enter (offer zone) and earn (wait zone) rewards were higher in more-preferred restaurants (*$P < 0.0001$). Post-hoc Dunn's tests controlled for multiple comparisons revealed disparity between offer- and wait-zone thresholds was greater in more-preferred restaurants (*$P < 0.0001$), generating more enter-then-quit events (least-preferred, not significant, n.s., $P > 0.05$). **g** Slope of threshold fits were higher in the offer zone than wait zone and in more-preferred restaurants (KW test, *$P < 0.0001$). Error bars. ± 1 s.e.m. $N = 31$

countdown time left remaining was still above the wait-zone threshold (Fig. 2l, Supplementary Fig. 6). Thus, wait-zone decisions to quit were advantageous change-of-mind re-evaluations correcting economically unfavorable rapid valuations made in the offer zone. This reveals that mice, despite making economically unfavorable decisions in the offer zone, could remediate those initial snap judgments.

We found that mice took longer to quit in more-preferred restaurants (Fig. 2m), indicating changing one's mind was a tougher decision for highly desired rewards. In fact, mice were

less capable of choosing to quit before crossing wait-zone thresholds in more-preferred restaurants (Fig. 2n). This provides a second potential point of decision-making vulnerability in value conflict between desire and choosing smarter alternatives when re-evaluating and changing one's mind that could also be exploited by drugs of abuse.

Lasting effects of cocaine or morphine on distinct valuations. Rather than model addiction as maladaptive behaviors in direct pursuit of drug, we used the complex economic behaviors in this task to model the sophisticated level of decision conflict that human addicts often struggle with—the conflict between wanting on the one hand vs. knowing better on the other hand. To test



how drugs of abuse can exploit these types of potential decision-making vulnerabilities, well-trained mice after 70 consecutive days of Restaurant Row received either repeated cocaine, morphine, or saline experimenter-administered injections 4 h after each Restaurant Row session that produced psychomotor sensitization (Fig. 1a, Supplementary Fig. 7, Supplementary Methods, Supplementary Discussion)—an escalated locomotor response to repeated drug exposure that has been shown to serve as a behavioral correlate of neural plasticity in cortical and mesolimbic pathways, bio-markers of which in humans are predictive of relapse susceptibility[9,17,18]. Thus, we focused on a timepoint of 2–3 weeks of prolonged abstinence to model the enduring effects of drug use on decision-making processes. Importantly, we did not observe any gross locomotor effects or overall changes in food intake (Supplementary Fig. 8).

Interestingly, we found that offer-zone time and VTE were disrupted following prolonged abstinence from repeated cocaine but not morphine or saline exposure (Fig. 3a–d). Cocaine-abstinent mice showed increased deliberation behavior before entering offers greater than wait-zone thresholds, inverting the normal behavior (Fig. 3a–e, compare Fig. 2i, Supplementary Fig. 11). Cocaine-abstinent mice initially oriented toward skipping these offers, and then re-oriented to accept them anyway (Fig. 3a). This suggests that cocaine-abstinent mice accepted costly offers despite engaging in VTE and deliberating about turning them down.

In contrast, morphine-abstinent mice had a significant increase in wait-zone thresholds compared to baseline, while cocaine-abstinent and saline-treated mice did not (Fig. 3f). Morphine-abstinent mice also showed increased wait zone thresholds compared to saline-treated mice as well as compared to their own offer zone thresholds (Fig. 3f) This is noteworthy because, while morphine-abstinent mice did not differ in making snap judgments to rapidly accept expensive offers (Fig. 3c–e), they were less likely to correct those economic violations in the wait zone in contrast to the saline and cocaine groups (Fig. 3a, b, f). Thus, probability of quitting significantly decreased (Supplementary Fig. 8A). If morphine-abstinent mice did quit, they took significantly longer to do so (Supplementary Fig. 8B). Neither cocaine- nor morphine-related effects appeared after a single drug exposure and was only apparent following abstinence from repeated drug exposure (Supplementary Fig. 9, Supplementary Discussion). Furthermore, devaluation probe sessions using a flavor-specific pre-feeding procedure revealed flexible decision processes were separately employed in the offer zone and wait zone by all animals but differentially influenced depending on history of cocaine or morphine exposure (Supplementary Fig. 10, Supplementary Discussion).

Discussion

Recent findings have suggested that choosing between distant options accesses different valuation processes than choosing to opt out from remaining committed to already accepted offers[19]. We can model such decision framings as fundamentally distinct types of intertemporal choice modalities.

Because VTE behavior occurs in the offer zone, particularly when skipping expensive offers, animals are likely to be engaged in episodic future thinking and deliberation to search and plan for better offers that may lie ahead and resist accepting immediately available highly desired rewards[14]. During VTE, hippocampal representations sweep forward along the path of the animal, alternating between potential goals[20]. Such goal representations are synchronized to reward value representations in the prefrontal cortex and ventral striatum, suggesting outcome predictions are being evaluated serially during VTE[21,22]. This is dissociable from dorsal striatum valuations that occur during rapid decisions when VTE is not engaged[23]. To this end, we modeled two hyperbolic functions discounting the value of the known current and expected next alternative where the discounting rate for an individual is represented by k. The decision change occurs at the intersection of these two hyperbolic functions (Fig. 4a). This well-established neuroeconomic model of choosing between alternatives[24–26] underlies the offer-zone threshold valuation measured on our task (Fig. 4b).

In contrast, quitting the wait zone is an opt-out decision. Such judgments appear in well-studied decision processes common in foraging paradigms[19,27–29]. This can be modeled as a comparison of the hyperbolic temporally discounted value of work remaining compared against the average opportunity cost of reward availability in the rest of the environment (R, Fig. 4c). The intersection of this comparison underlies the wait-zone threshold valuation measured on our task (Fig. 4d).

In deliberative models, studies have modeled changes in the hyperbolic discounting rate k in drug users as steeper, thus overvaluing immediate rewards[30]. These tasks, however, measure k as a product of the outcomes chosen and do not typically characterize the deliberation behaviors that led up to the outcomes selected. Other theories in foraging models have proposed that drug users experience a re-normalization of the average available reward in the world where R decreases and thus decreases the value of alternative options in the rest of the environment[8]. Importantly, economic theory suggests that both of these valuation changes (an increase in k or a decrease in R) could drive recovering addicts to make bad decisions and relapse[2].

Our data revealed no changes in either the offer-zone or wait-zone threshold in cocaine-abstinent animals. From this, we must conclude that whatever decision-making changes occurred in the

Fig. 2 Characterizing deliberation and foraging behaviors. **a**, **b** Example of X–Y locations of a mouse's path trajectory in the offer zone over time during a single trial. **a** Skip decision for a high delay offer. The mouse initially oriented toward entering (right) then ultimately re-oriented to skip (left). Wait-zone threshold minus offer captures the relative subjective value of the offer. Negative value denotes an economically unfavorable offer. **b** Enter decision for positively valued offer; rapid without re-orientations. Reaction time (**c**) and VTE (**d**) behavior was higher for skip compared to enter decisions and only increased in more-preferred restaurants for skip decisions (KW tests, $^*P < 0.0001$). **e** Mice were more likely to skip negatively valued offers the more they displayed VTE behavior. Vertical dashed line indicates the amount of VTE required to skip these offers 50% of the time. **f** Mice were more likely to enter these offers in higher-preferred restaurants, entering more than skipping in only the most-preferred restaurant (KW and Sign tests, $^*P < 0.0001$). **g** Amount of VTE required to reliably skip these offers was higher in more-preferred restaurants (KW tests, $^*P < 0.0001$). **h**, **i** Example of path trajectory in the offer and wait zones. **h** Rapidly entering then earning a positively valued offer. **i** Rapidly entering then quitting a negatively valued offer. **j**, **k** Cumulative probability distribution of offer zone time (**j**) and VTE (**k**) for skips and enters split by offer value. Both types of enter decisions were rapid compared to skips (Kolmogorov–Smirnov (KS) tests, $^*P < 0.05$) and indistinguishable from each other (KS tests, not significant, n.s., $P > 0.05$). **l**, **m** Majority of quits took place for negatively valued offers and while time left was still greater than wait zone thresholds (**l**), despite taking longer to quit in more-preferred restaurants (**m**, KW-D tests, $^*P < 0.0001$). **n** Although mice were more likely to quit negatively valued offers while the amount of time left was still above wait zone thresholds in all restaurants, they were less capable of doing so in more-preferred restaurants (KW and Sign tests, $^*P < 0.0001$). Error bars. ± 1 s.e.m. $N = 31$

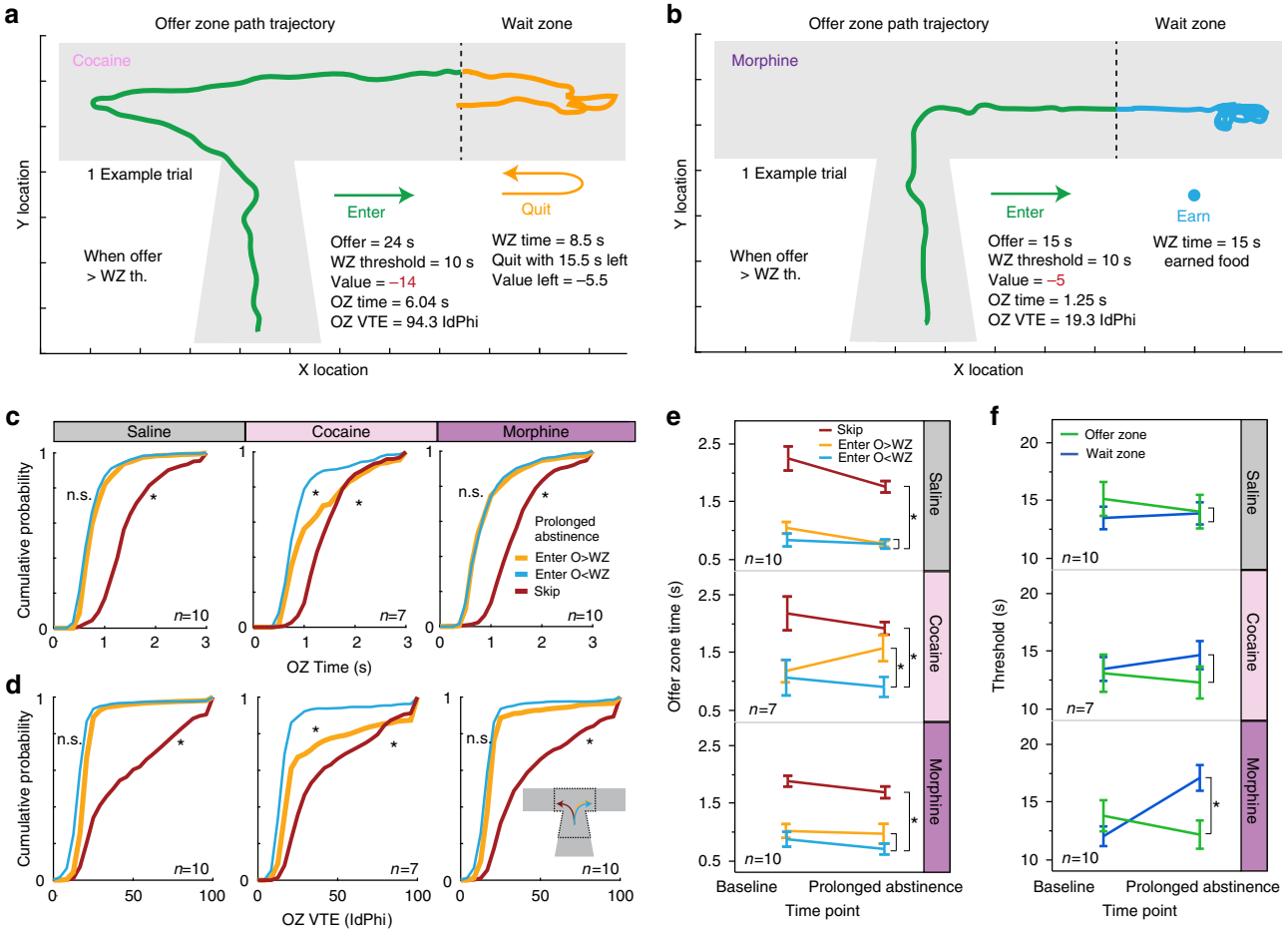


Fig. 3 The effects of prolonged abstinence from repeated drug exposure on choice conflict. **a**, **b** Example of path trajectory in the offer and wait zones for negatively valued economically unfavorable offers. **a** A mouse with a history of repeated cocaine exposure initially oriented toward skipping (left) then ultimately re-oriented to enter (right). Capability of quitting was unaltered. **b** A mouse with history of repeated morphine exposure was less capable of quitting rapidly accepted offers. **c**, **d** Cumulative probability distributions of offer-zone time (**c**) and VTE (**d**) for skips as well as enters split by offer value separated by drug-treatment conditions. Both types of enter decisions were rapid compared to skips and indistinguishable from each other for saline and morphine mice (KS tests, not significant, n.s., $P > 0.05$). Cocaine mice displayed increased time and VTE before accepting negatively valued offers (KS tests, $^*P < 0.05$). **e**, **f** Repeated measures Friedman tests correcting for multiple post-hoc Mann–Whitney tests reveal cocaine-specific changes (**e**) in offer zone deliberation time when entering economically disadvantageous offers and morphine-specific changes (**f**) increasing wait-zone thresholds ($^*P < 0.05$). Error bars. ± 1 s.e.m. *N* per group (saline $N = 10$, cocaine $N = 7$, morphine $N = 10$) listed on respective plots

cocaine-abstinent animals, it did not shift the crossover points in deliberative or foraging valuation algorithms. What we did find is an increase in offer-zone deliberations for costly offers. This effect could occur as a consequence of a change (increase) in offer-zone choose-between hyperbolic discounting rate *k* (Fig. 4e, f, i). An increase in *k* in both hyperbolic curves in a deliberative model can change the shape of the curves without changing the crossover point. Because hyperbolic discounting curves decrease in steepness as one moves out along the curve, this would effectively decrease discriminatory resolution when choosing between costly offers (Fig. 4i). We argue this is why cocaine-abstinent mice struggled before giving in to accepting expensive offers anyway despite deliberating.

Our data revealed no change in the offer-zone threshold, but did find a right shift in the wait-zone threshold of morphine-abstinent animals. This cannot occur due to an increase in the hyperbolic discounting rate *k* because such a change in a foraging model would shift the crossover point to the left and decrease the wait-zone threshold, which is the opposite of our observed behavioral findings (Fig. 4c, d). Instead, in a foraging model, a decrease in *R* or the average expected value in the rest of the environment relative to a given reward opportunity would shift the crossover point to the right only in the wait zone. Thus, we argue that this right shift in the willingness to wait out a delay once started in the wait zone is due to the effect of morphine diminishing the average rate of reward *R* expected in the world (Fig. 4g, h). This concept is consistent with recent theories of opioid abuse that suggest other rewards in the world are re-normalized and pale in comparison after having experienced morphine[2]. Taken together, we highlight two dissociable points of failure in decision making exploited uniquely by two drugs of abuse—before making bad deliberative judgments versus re-evaluations after making bad snap judgments.

These findings are particularly relevant to a timepoint when recovering addicts who are on the verge of relapse struggle with making the right decisions. Our work highlights the notion that complex valuation processes can be carefully modeled in animal behavior. Disruptions in deliberative processes separate from foraging processes can suggest distinct circuit-specific computations that can go awry in different forms of addiction.

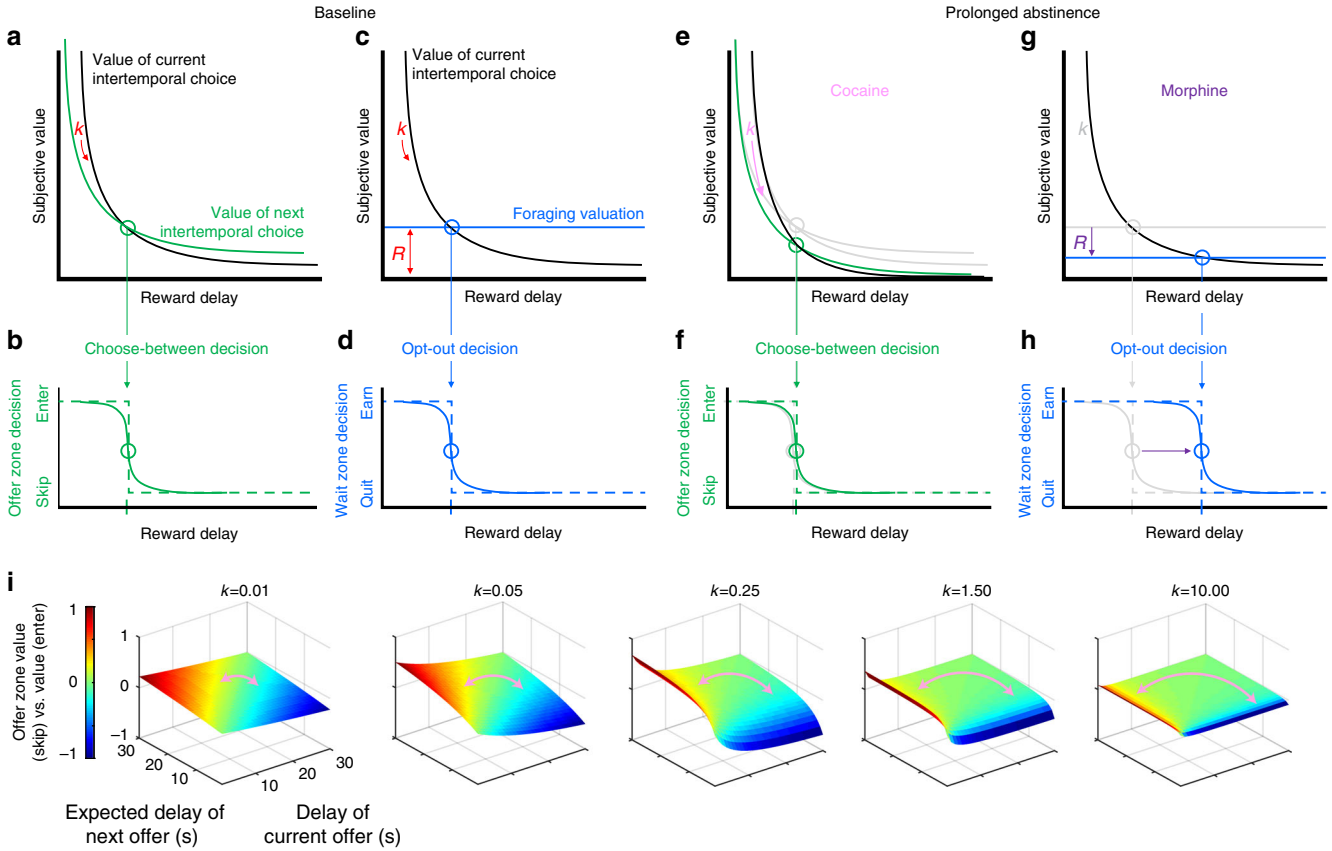


Fig. 4 Neuroeconomic modeling of separable computation-specific changes in decision conflict valuation algorithms. **a**–**d** Baseline. **a** Deliberative model: hyperbolic temporal discounting function of the current choice (black) is compared against a second hyperbolic temporally discounted function of the expected next choice (green), with a discounting rate *k* (red). **b** Offer zone choose-between thresholds are derived from this intersection. **c** Foraging model: hyperbolic temporal discounting function (black) of work remaining with discounting rate *k* (red) is compared against the average opportunity cost of reward availability in the rest of the environment, *y*-intercept *R* (red). **d** Wait-zone opt-out thresholds are derived from this intersection. **e**–**i** Modeling the effect of our drug delivery and forced abstinence manipulation. **e** Our data in mice with a history of repeated cocaine exposure are consistent with an increase in the *k* parameter in offer-zone deliberative valuation model, which yields no change in offer-zone thresholds (**f**), but yields increased indecision particularly for economically unfavorable high cost offers (**i**). **g** Our data in mice with a history of repeated morphine exposure are consistent with a decrease in the *R* parameter in the wait-zone foraging valuation model, which leads to an increase in the wait-zone threshold (**h**)

Many studies examining the lasting neurobiological changes induced by different drugs of abuse, including psychostimulants and opioids, generally propose a unified theory of addiction common to most abused substances that converges on overlapping changes in synaptic plasticity within the mesolimbic reward system[31]. The majority of these studies focus on changes in glutamatergic and dopaminergic signaling in the ventral tegmental area and nucleus accumbens[31]. However, there are reports of contrasting or opposing lasting neurobiological changes induced by cocaine and morphine, including differential effects on accumbens spine density, synaptic remodeling, and gene expression[32–35]. We suggest that taking into account the information processed within these circuits as well as other circuits during discrete aspects of decision-making computations is critical in order to understand multi-faceted, potentially dysfunctional valuation processes that can ultimately drive addiction-related behaviors.

Our data uncover unique computation-specific etiologies separated within the same trial that may be underlying different forms of addiction that more traditional behavioral paradigms may not be sensitive enough to detect. We propose that computation-specific therapeutic interventions are likely necessary to ameliorate addiction subtypes that disrupt, in different ways, the decision to use despite knowing better.

Methods

Mice and training. 32-C57BL/J6 male mice, 13 weeks old, were initially trained in Restaurant Row. Mice were single-housed at 11 weeks of age in a temperature- and humidity-controlled environment with a 12-h-light/12-h-dark cycle with water ad libitum. Mice were food restricted and trained to earn their entire day's food ration during their 1 h Restaurant Row session. Experiments were approved by the University of Minnesota Institutional Animal Care and Use Committee (IACUC; protocol number 1412A-32172) and adhered to the National Institutes of Health (NIH) guidelines. Mice were tested at the same time every day in a dimly lit room, were weighed before and after every testing session, and were fed a small post-session ration in a separate waiting chamber on rare occasions to prevent extremely low weights according to IACUC standards (not <85% free-feeding weights). Reliable behavioral measures were previously achieved on this task with sample sizes as small as five animals. Therefore, we ensured that sample sizes were no smaller than 7 animals, even after attrition. We started with 32 mice. One mouse died before treatment assignment and is not included in any analysis; three mice were lost due to cocaine and are not included in any cocaine-related comparisons. Analyses across time include the same animals. No data points were removed due to outliers.

Drug exposure. Animals were randomly assigned to receive either saline, cocaine, or morphine treatments, counterbalancing groups across as many behavioral parameters as possible. After 70 days of training mice were injected with saline (0.9% NaCl) for 3 days in order to get them acclimated to the stress of injections. Restaurant Row testing took place during the day during their light phase. Only on special days when injections were to be administered, these took place in the dark phase in the evening after Restaurant Row testing for that day completed. Acute injection-induced locomotor activity was monitored in the 90 min immediately

following drug injections in a separate locomotion chamber, not in the Restaurant Row apparatus. All injections were volume corrected after measuring mouse body weights right before injections. Next, mice received 12 evenings of repeated drug or saline control injections. This is a standard and well-established drug-treatment regimen known to produce robust and long-lasting drug-related changes, particularly after prolonged abstinence, to model a behavioral stage just before relapse. Overall, our goal was to measure how decision processes were affected by repeated drug use, rather than acutely when animals were on drug. Thus, it is the prolonged abstinence timepoint ~2 weeks following the 12th drug injection that is of importance. Experimenters that handled animals during Restaurant Row testing were blinded to drug group. Behavior testing in Restaurant Row was fully automated. Behaviorally analyses were also automated across all animals using Matlab.

Statistical analyses. All statistical analyses were carried out using JMP Pro 13 Statistical Discovery software package from SAS. Statistical significance was assessed using non-parametric statistical tests, as the data were not normally distributed (offer-zone time, offer-zone VTE, wait-zone quit time, post-earn linger time, and offer- and wait-zone thresholds all reject normal distributions using the Kolmogorov–Smirnov–Lilliefors test for goodness of fit, $P < 0.01$). Described below are the statistics used for each main figure, where applicable. Statistics for Supplementary Figures are detailed in corresponding figure captions or in the Supplementary Discussion. All error bars are expressed as ±1 s.e.m. Asterisks used in figures are intended to direct attention to comparisons of interest.

Main figure statistics. Figures 1a–c, e, 2a, b, e, 2h, i, 3a, b, and 4a–i are illustrative in nature, single-session examples, or intended to demonstrate derivation of a higher-order metric summarized for comparison in a separate figure, and thus analyses reports are deemed not appropriate or not included.

The Kruskal–Wallis (KW) test was used as a non-parametric equivalent to the parametric one-way analysis of variance (ANOVA) test in Figs. 1d, f, g, 2c, d, f, g, m, n to test dependent measures against flavor rankings (or against the three conditions described in Fig. 2l). Post-hoc analyses controlling for multiple comparisons were performed using Dunn's test to preserve pooled variance from the KW test in order to compare conditions in a pairwise manner. Much of these comparisons included testing flavor rankings pairwise (e.g., most-preferred to least-preferred) as well as to compare values of the same flavor ranking across levels of an separate factor stated on each figure (e.g., skip vs. enter, offer zone vs. wait zone). KW tests were significant across rank on all metrics in the above figures ($P < 0.0001$) except in Fig. 2c, d for the enter condition ($P > 0.05$). Dunn's tests showed that the most-preferred flavor was significantly greater than the least-preferred flavor on all metrics in the above figures ($^*P < 0.0001$). Dunn's test also showed that offer-zone thresholds and slope were greater than wait-zone thresholds and slope (Fig. 1f, g, $^*P < 0.0001$), except between threshold types in least-preferred restaurants (Fig. 1f, $P > 0.05$). Dunn's test also showed that skips were greater than enters in both offer-zone time and VTE in all restaurants (Fig. 2c, d, $^*P < 0.0001$). Lastly, KW and Dunn's tests on quitting behavior in Fig. 2l confirm economically efficient quits made up the majority of quit events in the wait zone ($^*P < 0.0001$).

In addition to the significant interactions across rank in Fig. 2f, n, the Sign test was used to assess if behavior in each restaurant was above or below the 1:1 ratio line on economic inefficiency in the offer zone (Fig. 2f) and the wait zone (Fig. 2n). Data above the 1:1 ratio line, or a positive sign, indicate economically inefficient behavior. Only behavior in the offer zone of the most-preferred flavor was above the 1:1 ratio line (Fig. 2f, $P < 0.0001$), and not for other flavors in the offer zone nor any flavor in the wait zone (Fig. 2n, $P > 0.05$).

The Kolmogorov–Smirnov test was used to assess differences in cumulative probability distributions of offer-zone time and VTE in Figs. 2j, kj–k and 3c, d. Our comparison of interest was between enters for offers above wait-zone threshold and enters for offers below wait-zone threshold, which at baseline were not statistically different from each other in both time and VTE (Fig. 2j, k, $P > 0.05$). This was replicated at the prolonged abstinence timepoint in both the saline and morphine groups ($P > 0.05$), but not cocaine group ($^*P < 0.01$) for both offer-zone time and VTE (Fig. 3c, d).

The Friedman test was used as a non-parametric equivalent to the parametric one-way ANOVA with repeated measures in Fig. 3e, f when comparing behaviors across two timepoints (baseline and prolonged abstinence). Only in the cocaine group did offer-zone deliberations when entering expensive offers increase. Simulations controlling for differences in offer distributions were run in Supplementary Fig. 11. Only in the morphine group did wait-zone thresholds significantly increase across timepoints ($^*P < 0.05$), while offer-zone thresholds did not, nor either threshold in the saline and cocaine groups ($P > 0.05$). Post-hoc analyses using Mann–Whitney tests while correcting for multiple comparisons allowed for non-parametric comparisons at either timepoint between offer-zone and wait-zone behaviors between decision types or between drug conditions. At the prolonged abstinence timepoint, in the morphine group, wait-zone thresholds were significantly higher than offer-zone thresholds ($^*P < 0.05$), which were no different at baseline or at either timepoint in the saline and cocaine groups ($P > 0.05$). Lastly, wait-zone thresholds at the prolonged abstinence timepoint in the morphine group was significantly higher than the saline group ($^*P < 0.05$), while comparisons of wait-zone thresholds between cocaine and saline animals were no different at the prolonged abstinence timepoint ($P > 0.05$).

Modeling. The model in Fig. 4i was generated via Matlab simulations where we calculated the probability of entering vs. skipping offers as a function of increasing delays from 1 to 30 s of two offers (the current offer (d_1), and the expected next offer (d_2)). Each panel shows how the shape of the value function ($V = 1/(1 + k \times d_1) - 1/(1 + k \times d_2)$) changes with increasing k (increasing impulsively hyperbolic functions).

For additional information see Supplementary Methods.

Data availability. Data available on request from the authors.

Received: 19 February 2018 Accepted: 1 June 2018
Published online: 28 June 2018

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Acknowledgements

We thank members of the Thomas and Redish labs for technical assistance. This research was supported by R01 DA019666, R01 DA030672, R01 MH080318, MnDRIVE Neuromodulation Research Fellowships, the Breyer-Longden Family Research Foundation, MSTP NIGMS 5T32GM008244-25, GPN NIGMS 5T32GM008471-22, and F30 DA043326 NRSA.

Author contributions

B.M.S. performed the experiments, analyzed the data, and wrote the manuscript. A.D.R. and M.J.T. supervised the project and co-wrote the manuscript.

Additional information

Supplementary Information accompanies this paper at https://doi.org/10.1038/s41467-018-04967-2.

Competing interests: The authors declare no competing interests.

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Supplementary Information

Prolonged abstinence from cocaine or morphine disrupts separable valuations during decision conflict

Sweis et al.

Included in this document:

Supplementary Methods

Pellet training
Mice underwent 1-week of pellet training before being introduced to the Restaurant Row maze. During this period, mice were taken off of regular chow and introduced to a single daily serving of BioServ full nutrition 20mg pellets in excess (5g). This serving consisted of a mixture of chocolate-, banana-, grape-, and plain-flavored pellets. Next, mice (hungry, before being fed their daily ration) were introduced to the Restaurant Row maze 1 day prior to the start of training and were allowed to roam freely for 15min to explore, get comfortable with the maze, and familiarize themselves with the feeding sites. Restaurants were marked with unique spatial cues. Feeding bowls in each restaurant were filled with excess food on this introduction day.

Restaurant Row training
Task training was broken into 4 stages. Each daily session lasted for 1hr. At test start, one restaurant was randomly selected to be the starting restaurant where an offer was made if mice entered that restaurant's T-shaped offer-zone from the appropriate direction in a counter-clockwise manner. During the first stage (day 1-7), mice were trained for 1 week being given only 1s offers. Brief low pitch tones (4000Hz, 500ms) sounded upon entry into the offer-zone and repeated every second until mice skipped or until mice entered the wait-zone after which a pellet was dispensed. To discourage mice from leaving earned pellets uneaten, motorized feeding bowls cleared any uneaten pellets upon wait-zone exit. Left over pellets were counted after each session and mice quickly learned to not leave the reward site without consuming earned pellets. The next restaurant in the counter-clockwise sequence was always and only the next available restaurant where an offer could be made such that mice learned to run laps encountering offers across all four restaurants in a fixed order serially in a single lap. Mice quickly learned not to run in the incorrect direction. During the second stage (day 8-12), mice were given offers that ranged from 1s to 5s (4000Hz to 5548Hz, in 387Hz steps) for 5 days. Offers were pseudo-randomly selected such that all 5 offer lengths were encountered in 5 consecutive trials before being re-shuffled, selected independently between restaurants. Again, offer tones repeated every second in the offer-zone indefinitely until either a skip or enter decision was made. In this stage and subsequent stages, in the wait-zone, 500ms tones descended in pitch every second by 387Hz steps counting down to pellet delivery. If the wait-zone was exited at any point during the countdown, the tone ceased and the trial ended, forcing mice to proceed to the next restaurant. Stage 3 (day 13-17) consisted of offers from 1s to 15s (4000Hz to 9418Hz) for another 5 days. Stage 4 (day 18-70) offers ranged from 1s to 30s (4000Hz to 15223Hz) and lasted until mice showed stable economic behaviors. We used 4 Audiotek tweeters positioned next to each restaurant powered by Lepy amplifiers to play local tones at 70dB in each restaurant. We recorded speaker quality to verify frequency playback fidelity. We used Med Associates 20mg feeder pellet dispensers and 3D-printed feeding bowl receptacles fashioned with mini-servos to control automated clearance of uneaten pellets. Animal tracking, task programming, and maze operation was powered by AnyMaze (Stoelting).

Restaurant Row Metrics
Vicarious trial and error behavior (VTE) was measured as the absolute integrated angular velocity of a mouse's x and y position over the course of time and distance from tone-onset upon entry into the offer-zone until exiting the offer-zone (either toward the wait-zone or toward the

corridor heading to the next restaurant). From this, we could capture the degree to which animals interrupted smooth offer zone passes with pause-and-look re-orientation behaviors, known as vicarious trial and error (VTE).[1] The physical hemming-and-hawing characteristic of VTE is best measured by calculating changes in velocity vectors of discrete body x and *y* positions over time as *dx* and *dy*. From this, we can calculate the momentary change in angle, *Phi*, as *dPhi*. When this metric is integrated over the duration of the pass through the offer zone, VTE is measured in the offer zone as the absolute integrated angular velocity, or *IdPhi*, until either a skip or enter decision was made. Reaction time in the offer-zone was also measured in this period.

Reaction time to quit was also measured in the wait-zone from tone-count-down-onset until exit from the wait-zone prematurely before a pellet is earned. Post-earn-consumption-and-lingering-time was measured from pellet delivery-onset until the first exit was made out of wait-zone. In an earlier pilot study, cameras were placed in the wait-zone in order to observe lingering behaviors. After immediate pellet consumption, mice exhibited no unusual behaviors other than occasional grooming and checking the empty pellet receptacle for varying lengths of time before exiting and proceeding to the next restaurant.

Offer- and wait-zone thresholds were measured for each session by fitting sigmoid functions to zone choice outcomes as a function of offer delay, restaurant by restaurant. Inflection point and slope of each sigmoid fit was calculated. In order to calculate the value of the offer on any given trial, thresholds were re-calculated in a leave-one-out analysis excluding the current trial. We then used wait-zone threshold minus offer to calculate value.

Economic conflict inefficiency (Fig. 2F,2N) was measured both for the offer-zone (Fig. 2F) and wait-zone (Fig. 2N). This metric characterized how mice responded to an economically unfavorable offer (an offer where the delay was greater than wait-zone threshold). The ratio of the probability of entering the wait-zone for offers above the wait-zone threshold relative to skipping them was calculated in each restaurant as a function of rank. Similarly, in the wait-zone, after mice had already accepted such offers greater than wait-zone threshold, we characterized how long it took an animal to quit such an offer. If mice took so long that the amount of time remaining when quitting was less than wait-zone threshold, that was characterized as an economically inefficient quit. The ratio of the probability of quitting these offers after they counted down passed wait-zone thresholds relative to quitting before the countdown passed wait-zone thresholds was calculated in each restaurant as a function of rank.

In order to control for the possibility that the analysis of changes in VTE in the offer-zone in economically unfavorable acceptances (taking offer-zone deals that are above the wait-zone thresholds) could have been affected by unequal or different distributions of offers based on trial type (e.g., skipping offers, entering offers above threshold, or entering offers below threshold), we generated simulated shuffled data sets of reaction time and VTE when both skipping and entering offers below threshold matching the same trial-by-trial distributions of offer lengths as those subsets of trials where mice entered offers above threshold. In Fig. 2J-K and Fig. 3C-D, this ensures any changes seen in offer-zone behaviors, particularly when entering economically favorable vs. unfavorable offers, are not skewed by differences in distribution of trials of different offer lengths (Supplementary Fig. 11, Supplemental Discussion).

Drug exposure regimen and locomotor sensitization

This drug treatment regimen is a simple, straightforward yet powerful means of producing robust and long-lasting behavioral and neurobiological changes linked to aspects of addiction such as incentive sensitization and neural plasticity in the mesocorticolimbic dopamine system.[2-4] By looking at a time point during prolonged abstinence, we intended to characterize changes that may reflect the life-long decision-making problems seen in recovering addicts. Long-lasting forms of neurobiological plasticity changes are observed at these prolonged abstinence time points coinciding with and causally linked to escalation of craving. Such plasticity measurements predict relapse susceptibility in human addicts.[5]

Injections took place in the evening 4 hours post-Restaurant Row testing. Our goal was to expose animals to drugs of abuse outside of testing hours, to be especially sure drug has cleared the animals' system before the next day's behavior. Furthermore, we wanted to avoid the effects of acute withdrawal on each day of Restaurant Row testing during the drug exposure phase. Repeated Restaurant Row testing during the drug exposure phase was not intended to capture instances when drug is on board, nor was it intended to compare changes between first and subsequent drug exposures, nor was it intended to analyze the effects of immediate cessation of repeated drug administration on decision-making. Instead, the goal was to interrogate decision-making after prolonged abstinence. Repeated Restaurant Row testing during the drug exposure phase and early abstinence was mainly intended to (1) ensure the animals did not unlearn the task day to day, and (2) maintain regular self-earned food-intake amounts contingent upon task performance rather than giving the animals non-contingent food or days off.

In the evening at the time of each drug injection, mice were placed in large locomotion monitoring boxes with tracking cameras fixed above automatically measuring distance traveled using AnyMaze software (Stoelting). Mice were placed in the boxes for 20min before being injected intraperitoneally with saline and then monitored for 90min post-injections. Then mice were divided into three groups: saline (n=10), cocaine (n=10), and morphine (n=10). One mouse out of the original 31 was excluded because it never learned the task. Mice were then injected with their respective treatment for 12 consecutive nights while being tested in Restaurant Row regularly. For the drug groups, mice were given lower doses (15mg/kg cocaine, 10mg/kg morphine) on the first and last nights and received repeated higher doses (30mg/kg cocaine, 20mg/kg morphine) on the intermediate 10 nights. Three mice were lost during the drug phase in the cocaine group and were excluded from analyses. Mice were then put through a forced abstinence period for 2 weeks while regularly being tested in Restaurant Row.

In addition to the prolonged abstinence timepoint that is the main focus of the drug paradigm, we also introduced animals to an acute drug challenge at the end of the ~2 weeks of abstinence timepoint. This was intended to probe responsivity to a drug prime and assess degree of locomotor sensitization that typically incubates over prolonged abstinence and can be expressed upon drug-re-exposure. Locomotor sensitization was measured as the psychomotor response measured immediately following drug injection at this timepoint compared to psychomotor response measured immediately following drug injection on the 12th evening of the repeated drug exposure sequence. We randomly injected mice 3 times with saline across the evenings before

experiencing this acute drug challenge, again, to acclimate the animals to the stress of injections in preparation for the forthcoming drug-re-exposure challenge.

Mice were challenged in the evening with a single low dose of drug same dose as the 1st and 12th night of drug in the repeated drug exposure sequence, being re-exposed to the same drug administered previously. Saline mice were divided into two groups of n=5 to receive a low dose of either cocaine or morphine for the first time, acutely. Despite the small sample size, this split was done to ensure that sensitized locomotion in response to a single dose was present only in animals with a history of repeated drug exposure. This comparison was statistically significant even with samples of n=5. This replicates work from our lab and numerous others.[2-4] Regardless, the primary analyses (comparing baseline to prolonged abstinence) occurred before the saline group was split and statistics were done with the complete saline group as control.

Following the acute drug-re-exposure challenge, Restaurant Row was tested regularly during the day for an additional 2-3 weeks. Because there were no lasting drug effects on any animal behavior in the formerly saline animals after the acute drug-re-exposure challenge session which took place ~20 days before the pre-feeding probe sessions (described below), this group served as control conditions for the pre-feeding probe sessions.

Devaluation/Invigoration Pre-feeding Probe Sessions

The pre-feeding probe sessions were performed at the end of the experiment and were intended to elucidate if rapid decisions or snap-judgments were flexible or inflexible processes. Devaluation probes are often used to differentiate goal-oriented (flexible and thus sensitive to devaluation) and habitual (inflexible and thus insensitive to devaluation) decision processes.[6-10] The devaluation probe in our task allowed us to rule-out habitual processes. There was no further testing after the pre-feeding probes as the experiment ended and all mice were retired.

Mice were pre-fed 30-60min before testing in an amount equivalent to what they typically earned in their most-preferred restaurant. Since each animal showed individual revealed preferences (i.e. different animals like different flavors best), we fed each animal its most-preferred flavor on one day and its least-preferred on the next. Since some animals received their most-preferred flavor on the first-day of pre-feeding while others received their least-preferred flavor on the first-day of pre-feeding (randomly selected and counter-balanced), day two of pre-feeding flipped this assignment. There were no order effects and no lasting body weight changes on day one versus day two of pre-feeding, so we pooled together the first and second day of pre-feeding to look at group differences between being fed one's most-preferred flavor versus least-preferred flavor.

The fact that all groups still showed sensitivity to the pre-feeding probe (although with intricate fine-grained differences between groups described in the Supplementary Discussion), we determined that the decision-processes in Restaurant Row remained flexible and had not transitioned to habit-like processes.

Supplementary Discussion

Vicarious trial and error

A key to interpreting parallel competing valuations in our task during decision-conflict between forward-looking planning and immediate desire-driven responding is the presence or absence of a critical behavioral metric – vicarious trial and error (VTE) – which has extensively been studied in a series of proof of principle publications.[1] We know that VTE is a sign of deliberation but VTE has not yet been measured in an addiction model.

In 2007, Johnson and Redish discovered that during VTE, hippocampal representations swept forward along the path of the animal, alternating between potential goals.[11] This key result has been replicated several times. We know that these sequences align to hippocampal theta cycles.[12] That is, they are theta sequences. However, the sequences during VTE sweep farther than during normal navigation.[13] The sequences proceed all the way to the goal.[12] If an animal is going to run past one goal to another one, the sequences run farther to the second goal.[14] They reflect indecision in the animal. An animal that knows where to go does not show VTE and the sequences only sweep forward to the goal the animal is actually going to go to.[11,15-16]

Furthermore, neurophysiologically, during VTE, reward-related representations appear in the nucleus accumbens (ventral striatum)[17-18] and in the orbitofrontal cortex.[19] Both of these results have been replicated.[20] These data suggest that there is an evaluation going along with the prediction in hippocampus. Neurophysiologically, we know that there is a triple dissociation between hippocampus (sweeps during VTE), ventral striatum (reward representations during VTE), and dorsal striatum (no extra activity during VTE, but slowly learned situation-action pairs).[21] As animals develop regular paths and VTE goes away, the dorsal striatum develops task-bracketing wherein activity appears at the start of the ballistic journey.[22] This result has been replicated.[23] In both of these papers, VTE is negatively correlated to the striatal task-bracketing.

Behaviorally, VTE occurs during times when the animal knows the structure of the world, but does not know what to do on it. VTE occurs when the animal is indecisive about goals and when contingencies change.[19,23-25] Manipulations that force flexibility in tasks lead to an increase in VTE, while manipulations that force regularity in paths lead to a decrease in VTE.[26] Finally, on tasks able to differentiate decisions that require planning (sometimes called model-based) from decisions that reflect cached values (sometimes called model-free), VTE occurs when the decisions show planning (model-based) and disappear when the decisions reflect cached values (model-free).[24,26-27]

In this task, we can take VTE as a sign of indecision and deliberation, and a lack of VTE as a sign of quick, decisive decisions (snap-judgments). In this task, we can reliably detect the difference between VTE and rapid (snap) judgments. Furthermore, we found that when VTE events took place, they did so with delayed onset overriding initial snap judgments in the offer-zone that would have otherwise violated normative economic behavior. This form of delayed deliberative VTE-containing override decisions rescued and prevented economic violations from occurring, importantly only when skipping, and could serve as a behavioral operationalization of knowing better or should not judgments. Sometimes when such slower deliberative VTE process

failed to come online, mice accepted expensive offers only to later reverse that initial rapid commitment by quitting in the wait-zone. This indicated that a re-evaluation process can also occur in the wait-zone. Both override-processes in the offer-zone or wait-zone took longer to override in higher preferred restaurants, capturing an increasingly stronger desire-component of these parallel computational processes.

Sub-optimality

Theories of foraging behavior are rooted in hypotheses of optimizing time allocation in order to maximize reward rate.[28] In Restaurant Row, all flavored pellets are of equal caloric value, and thus any differences in reinforcement rate as a function of cost between flavors must be taken as reflecting an underlying subjective valuation. Mice demonstrated a large variability in subjective flavor preferences from which we found interesting asymmetries and interactions with multiple valuation processes measurable on this task.

If we take into account individual differences in subjective preferences of willingness to wait for rewards (wait-zone thresholds), we can still determine a measure of sub-optimality, normalized to each animal's idiosyncratic preference for each flavor. In order to calculate maximum number of rewards a mouse could earn in each restaurant taking into account subjective flavor preferences, we simulated Restaurant Row sessions yet eliminated wasteful behaviors. To this end, in this model, we forced offer-zone thresholds to match wait-zone thresholds, thus eliminating all quit events. Furthermore, we eliminated differences in offer-zone deliberation time and post-earn lingering time between flavors (by using minimum deliberation time and minimum consumption time collapsed across all restaurants based on each animal's performance). We also used minimum transit time between restaurants based on each animal. These are the times the animal could have used if the only difference between decisions was the underlying willingness-to-wait thresholds between the flavors.

We found that mice overall were sub-optimal on this metric, even after taking into account individual differences in subjective flavor preferences and that prolonged abstinence from repeated drug exposure did not influence this metric (Supplementary Fig. 8D).

We also found that degree of sub-optimality interacted with flavor ranking. That is, mice were more sub-optimal in less-preferred restaurants. This is likely due to the disproportionate excess amount of time spent in the offer-zone, wait-zone, and lingering in more-preferred restaurants. Such disproportionate excess amount time that was removed from our optimal-performance model, when re-allocated optimally, would lead the model to predict disproportionately higher earnings than actual in less-preferred restaurants. This is due to the combination of excess time available, lower thresholds in those restaurants, and greater likelihood of our model encountering low cost offers in those restaurants that can be earned and that would have not been actually encountered otherwise. Thus, this yielded higher predicted than actual reinforcement rates in less-preferred restaurants.

Drug-related effects

Importantly, our decision-making tests are made during times when cocaine and morphine are not on board, and we show that drug exposure after the drug has cleared the animal's system does

not have any persistent effects on locomotor activity or appetite that could confound our interpretations of our decision-making tests (Supplementary Fig. 7).

Acute locomotor and appetite changes are typical effects when drug is on board and could confound behavioral performance on many tasks. The half-life of cocaine is ~1hr and morphine is ~2hr.[29] We tested mice on our task 10 hours after each drug injection (which took place 4 hours post-testing on our task) and well into prolonged abstinence for 2 weeks where we observed our decision-making conflict changes.

We used the following metrics to test for off-target effects of chronic drug: speed of locomotion on the task, number of completed laps, total amount of food earned and total weight gained. We found no differences in any of these metrics between controls and drug-treated mice (or within individuals) across the entire experiment. This lack of change rules out off-target effects on locomotion or appetite as possible confounding factors for our observed changes in decision-making metrics, including VTE (Supplementary Fig. 7).

Furthermore, our effects of drug on decision-making persist 2 weeks after chronic drug exposure at a time point when long-lasting circuit changes in decision-making-related brain areas including the prefrontal cortex, nucleus accumbens, and hippocampus are known to develop and when psychomotor sensitization is expressed - a hallmark and behavioral correlate of repeated drug-induced incubation of plasticity changes replicated numerous times.[2-4,30-35]

Our repeated drug exposure regimen did induce psychomotor sensitization measured in the 90-minute window following drug administration expressed after prolonged abstinence during a drug challenge (Supplementary Fig. 7).

Long-lasting changes in decision-making conflict were observed only after repeated drug exposure, not after acute one-time drug exposure (Supplementary Fig. 9). We examined behavior during the drug-exposure phase (Fig 1A, **cyan timepoint 1**), during early abstinence (Fig 1A, **cyan timepoint 2**), and following the acute drug-re-exposure change after prolonged abstinence (Fig 1A, **cyan timepoint 3**). The main timepoint of interest was after prolonged abstinence from repeated drug use, a timepoint at which psychomotor sensitization is typically expressed, at which neural plasticity in defined circuits develop, and at which recovering addicts struggle to make good decisions before relapsing.[2-4,30-35] Psychomotor sensitization seen after repeated drug exposure has been shown to be a behavioral correlate of drug-induced neural plasticity in specific mesolimbic and striatal circuits. That is, animals that show heightened locomotor responses to drug injections following repeated administration and incubated over prolonged abstinence show drug-induced circuit plasticity while animals that do not show heightened locomotor responses do not exhibit neural plasticity.[36]

Nonetheless, we present additional data during the drug exposure phase, early abstinence, and following the drug-re-exposure challenge primarily intended to express degree of psychomotor sensitization incubated throughout prolonged abstinence (Supplementary Fig. 9). We found no decision-making changes during Restaurant Row during the drug-exposure phase in offer-zone deliberation behaviors (Supplementary Fig. 9A-B, enters comparison, non-significant, Kolmogorov-Smirnov tests, $P>0.05$), nor between the first and last (12^{th}) injection during the

drug exposure phase in thresholds (Supplementary Fig. 9C, wait-zone across time, non-significant, Friedman, $P>0.05$), nor in post-earn lingering time (Supplementary Fig. 9D, lingering time across time, non-significant, Friedman, $P>0.05$).

Looking at the early abstinence time point, we found no changes in offer-zone deliberation behaviors (Supplementary Fig. 9E-F, enters comparison, non-significant, Kolmogorov-Smirnov tests, $P>0.05$), nor between baseline and early abstinence in thresholds (Supplementary Fig. 9G, wait-zone across time, non-significant, Friedman, $P>0.05$), nor in post-earn lingering time (Supplementary Fig. 9H, lingering time across time, non-significant, Friedman, $P>0.05$).

Looking immediately following the drug-re-exposure challenge after prolonged abstinence, we only saw the persisting difference in the cocaine group (Supplementary Fig. 9I-J, enters comparison, cocaine group only, significant, Kolmogorov-Smirnov tests, $*P<0.05$, see Fig. 3C-D for comparison). Interestingly, only in mice with a history of repeated drug exposure, and not in formerly saline-treated mice experiencing drug for the first time at the time of the drug challenge, we saw an increase in wait-zone thresholds immediately before and after the drug-re-exposure challenge (Supplementary Fig. 9K, wait-zone across time, cocaine and morphine, Friedman, $*P<0.05$). Interestingly, in all mice following the drug challenge, we found an increase in post-earn lingering time (Supplementary Fig. 9L, lingering time across time, all mice, Friedman, $*P<0.05$).

Taken together, this suggests that the decision-making changes reported in the main text seen in mice with a history of repeated cocaine and morphine exposure were apparent only after prolonged abstinence and not after a single drug-exposure. Interestingly, all mice appeared to increase lingering time regardless of history of drug use following an acute exposure to drug (Supplementary Fig. 9L). This suggests that hedonic valuations of non-drug rewards can be enhanced during acute withdrawal from drug. An acute drug-re-exposure challenge has been shown in the literature to precipitate reinstatement of drug-seeking behavior as a model of provoking relapse as well as induce neural plasticity changes unique from prolonged-abstinence-induced plasticity.[2-4,30-35] While the main focus of this manuscript was not to actually induce relapse, but rather model decision-making changes just before relapse after prolonged abstinence, it is interesting that drug-re-exposure after prolonged abstinence caused changes in wait-zone thresholds only in mice with a history of repeated drug exposure and not in first-time users (saline-pre-treated mice). This sets the stage for further investigation in future studies to more closely examine decision-making changes at secondary timepoint after relapse.

Devaluation

Referring to **cyan timepoint 4** in Fig. 1A and Supplementary Fig. 10, pre-feeding has been shown to change reward seeking behaviors depending on factors including amount pre-fed, instrumental action being assessed, and reward-selective versus reward-nonselective modulation.[6-10] Pre-feeding-induced devaluation of reward-seeking behaviors has been widely used as a way to probe if behaviors are inflexible, stimulus-response-driven, and thus habit-like versus flexible, response-outcome-driven, and thus goal-directed.[6-10] These two potential responses to a devaluation manipulation such as pre-feeding have been shown to separate behaviors that are differentially driven by separable neural circuits.

We pre-fed mice either their least- or most-preferred flavors in an amount that did not disrupt typical number of laps run or pellets earned (Supplementary Fig. 10A-C, C: Friedman, non-significant, $P>0.05$). Bodyweight did significantly increase following pre-feeding but before testing, yet was normalized by the next day (Supplementary Fig. 10D, before and after feedings, Friedman, significant, $*P<0.05$, before feeding across days, Friedman, non-significant, $P>0.05$).

Wait-zone thresholds were devalued (decreased) in saline and cocaine mice while the thresholds of morphine mice did not change (Supplementary Fig. 10F, Sign test, $*P<0.05$). Only when pre-fed their most-preferred flavor were saline mice devalued in the offer-zone as well (Supplementary Fig. 10E, Sign test, $*P<0.05$). Offer-zone thresholds of cocaine mice interestingly increased, suggesting pre-feeding for these animals carried an invigorating-like food-prime component on this aspect of behavior (Supplementary Fig. 10E, Sign test, $*P<0.05$).

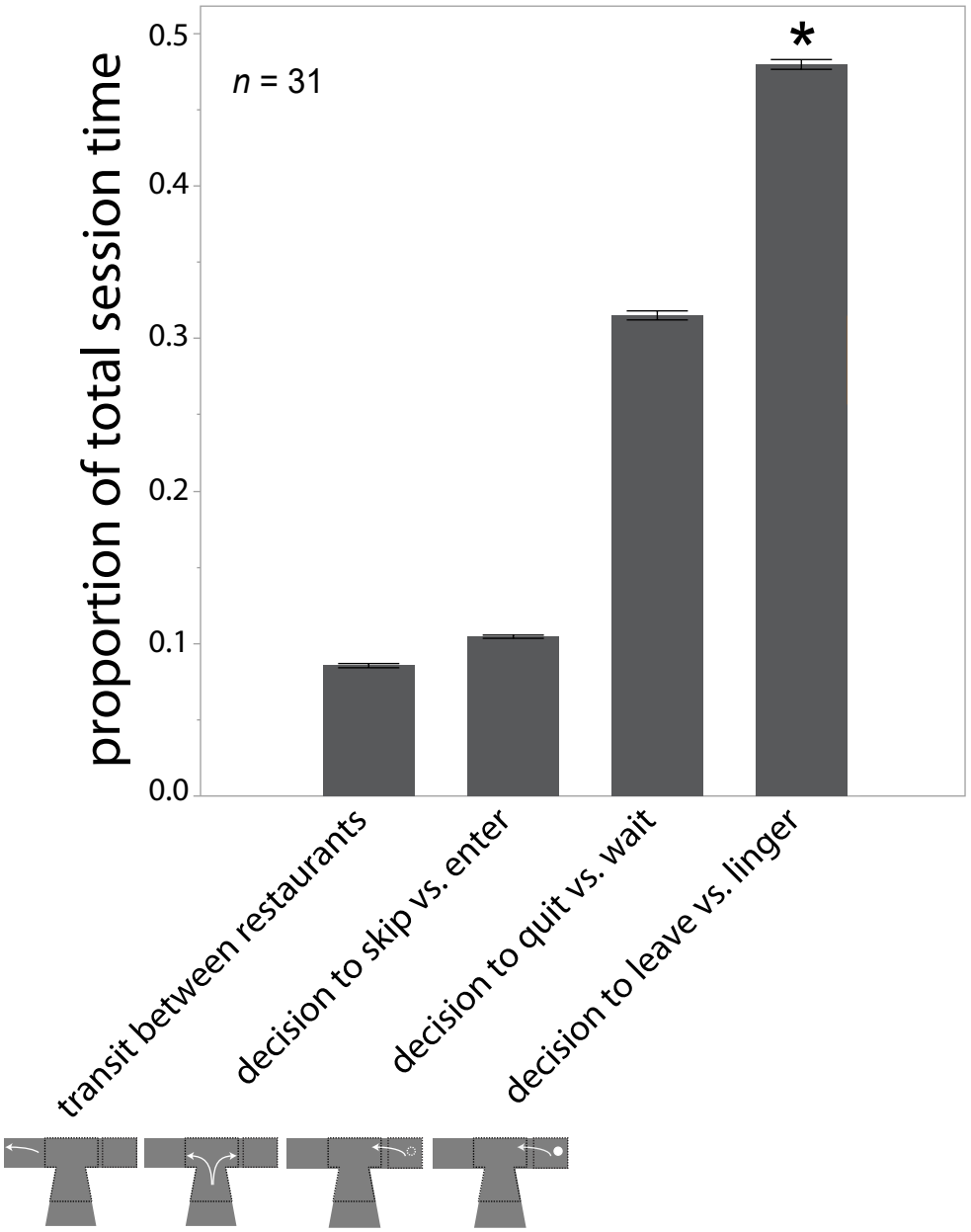
In the offer-zone, deliberation time and VTE when skipping or accepting offers below threshold (economically favorable) was unaltered; however, saline mice accepted offers above threshold (economically unfavorable) more slowly when pre-fed their most-preferred flavor (Supplementary Fig. 10G-H, Sign test, $*P<0.05$), suggesting a shift in the balance of valuation functions. Entering offers above threshold however, just as before, took place after little VTE with no further pre-feeding-induced changes, indicating these events were still snap-judgments (did not involve deliberating about correct alternatives, Supplementary Fig. 10H, Sign test, $P>0.05$). Morphine mice responded just as saline mice did while cocaine mice displayed no changes on this metric (Supplementary Fig. 10G-H, Sign test, $*P<0.05$).

Finally, although lingering remained unchanged in saline-treated mice, morphine-abstinent mice showed invigorated (increased) lingering while cocaine-abstinent mice showed the opposite (Supplementary Fig. 10J, Sign test, $*P<0.05$). Additionally, cocaine-abstinent mice displayed less time spent waiting before quitting (Supplementary Fig. 10I, Sign test, $*P<0.05$). Taken together, pre-feeding revealed changes in dissociable valuation algorithms that were blunted or enhanced based on drug history.

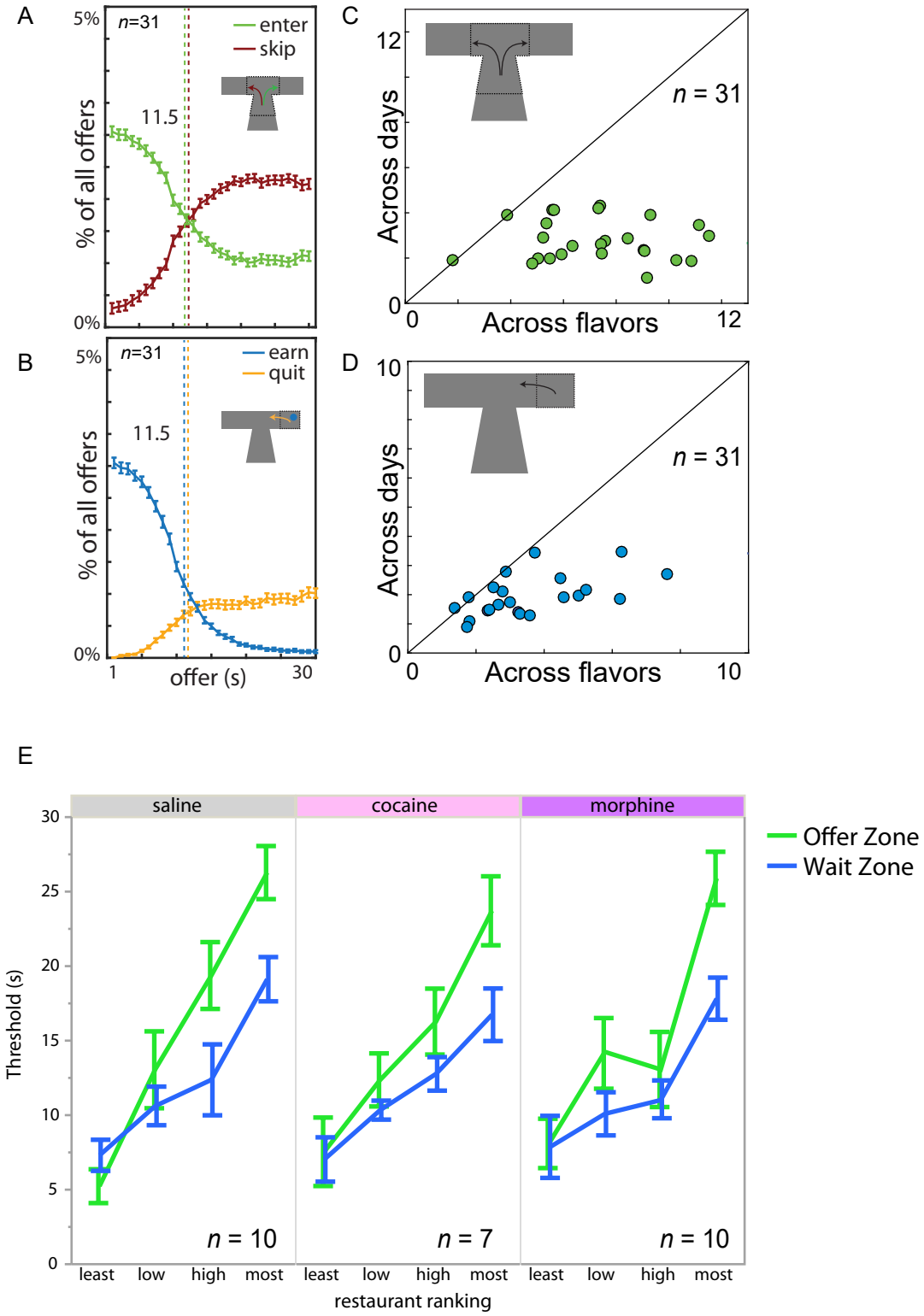
Devaluation experiments can modify the incentive value of instrumental actions and reveal specific encoding of emotional states or craving underlying goal-oriented behavior.[28-31] In appetitive tasks, pre-feeding is one way to accomplish this. Taking advantage of the subjective value properties of rewards and different zones, we found that pre-feeding decreased wait-zone thresholds (indicating devaluation) consistent with satiety effects on incentive processes.[29] These effects were not-flavor specific and seemed to affect appetitive reward taking valuation processes in general. However, only when pre-feeding most-preferred flavors did offer-zone thresholds also decrease. This highlights not only a flavor-specific satiety effect consistent with past reports[6-10] but also a subjective value-specific capacity to modify motivational states unique to choose-between decisions involving highly wanted rewards. Pre-feeding seemed to induce invigoration-like effects in drug-treated mice absent in saline-treated mice. In morphine-abstinent mice, we found increased conditioned-place-preference (CPP)-like lingering, which may reflect enhanced craving and explain why their wait-zone thresholds, which were generally insensitive to change, paradoxically opposed satiety-induced devaluation. In contrast, cocaine-abstinent mice, while sensitive to wait-zone threshold devaluation, paradoxically displayed increased offer-zone thresholds. That is, cocaine-abstinent mice were food-primed to over-value

offers in the offer-zone that were exaggeratedly under-valued in the wait-zone. Thus, the hypothesis that cocaine-abstinent mice may be transitioning into a lower value state once in the wait-zone may explain why they were more likely to quit, quit faster, and spend less time lingering, suggesting the predicted value of accepted rewards were less than expected.

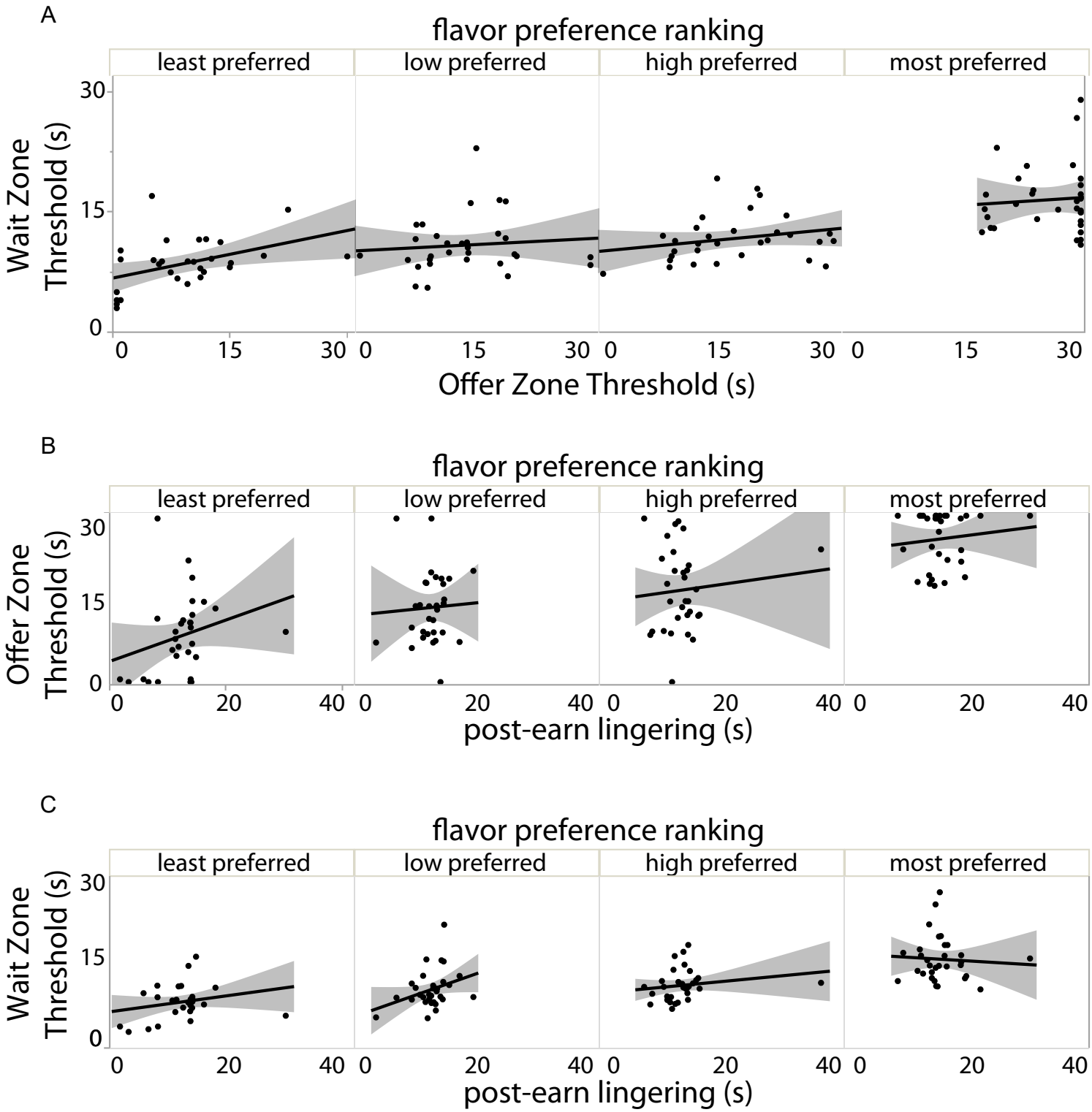
Pre-feeding was not intended to assess drug effects but rather to assess decision flexibility and rule out habitual processes. Because there were no lasting drug effects on any behavior in the formerly saline animals after the acute drug-re-exposure challenge session which took place 20 days before the pre-feeding probe sessions, this group served as control conditions for the pre-feeding probe. Again, the fact that all groups still showed sensitivity to the pre-feeding probe (although with intricate fine-grained differences between groups), we determined that the decision-processes in Restaurant Row remained flexible and had not transitioned to habit-like processes.



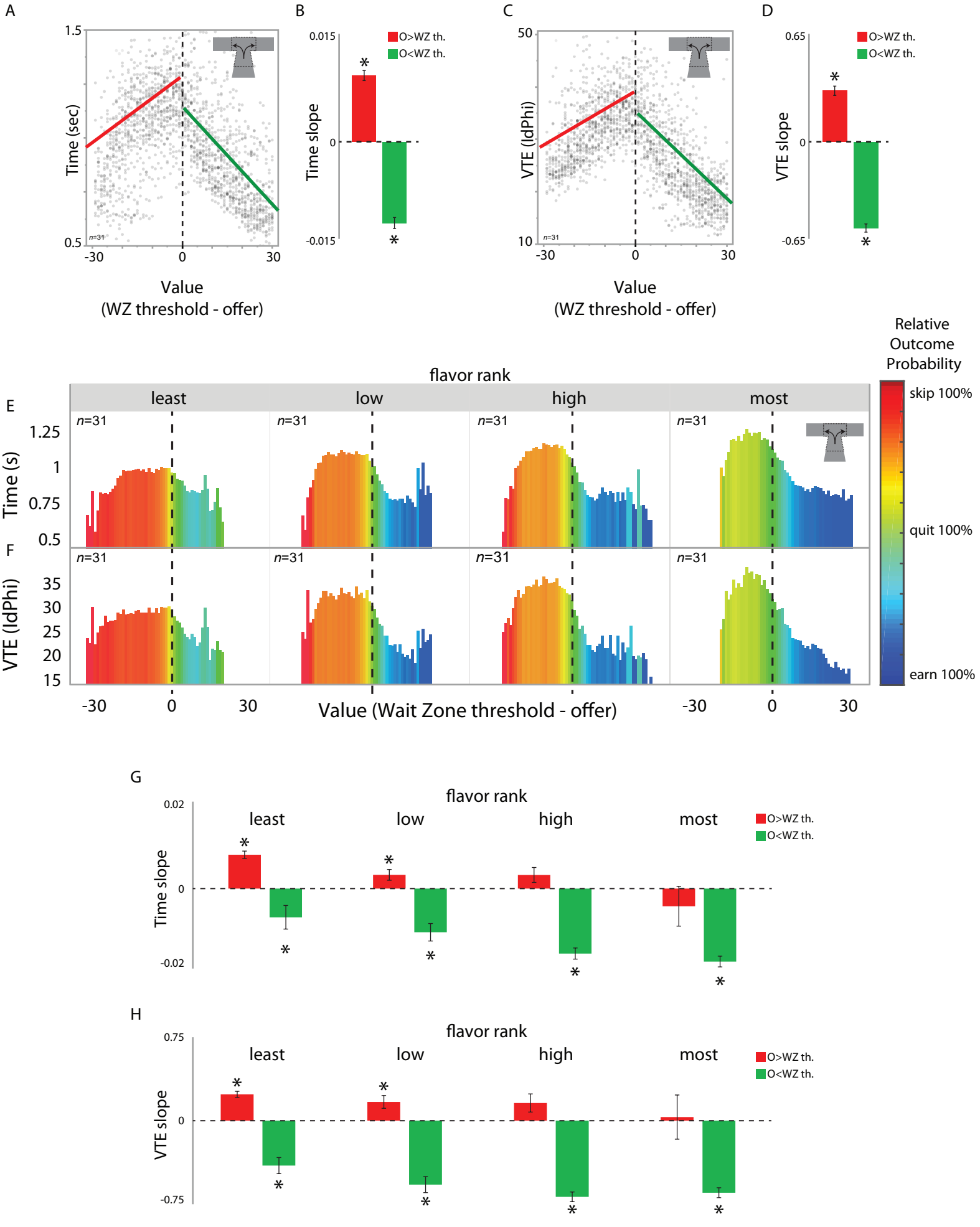
Supplementary Figure 1. Allocation of total session time budget across multiple separate valuation behaviors. (Left to right) Average percent of total session time spent traveling between restaurants, deliberating in the offer-zone (skipping vs. entering, measured between initial tone onset and offer-zone exit), foraging in the wait-zone (investing time before quitting vs. earning pellets, measured between tone countdown onset and premature wait-zone exit or pellet delivery), and consuming food and lingering at the reward-site after earning pellets (measured from time of pellet delivery to wait-zone exit). Majority of total session time was spent lingering at the reward site compared to other task behaviors (Friedman, $P<0.0001$, post-hoc Mann-Whitney comparisons against lingering time, *$P<0.0001$). Error bars. ± 1 SEM. N=31.



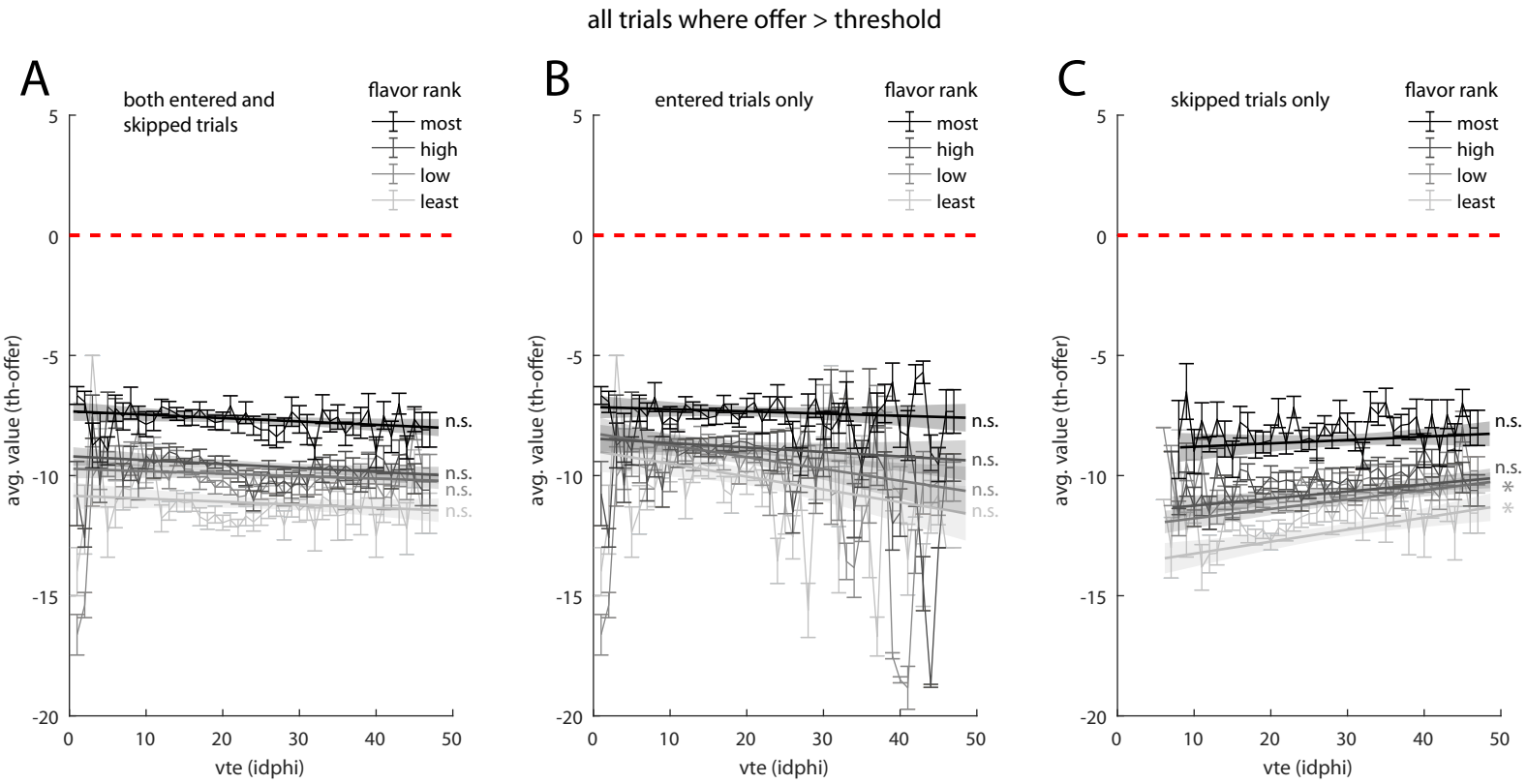
Supplementary Figure 2. Offer discrimination and threshold stability. (A) In the offer-zone, mice accepted (entered) short offers while skipping long offers. (B) In the wait-zone, mice waited for (earned) short offers while quitting long offers. (A-B) Vertical dashed-lines indicates overall threshold collapsed across restaurants (~11.5s in both zones). (C-D) Variability of offer-zone thresholds (C) and wait-zone thresholds (D) was calculated between flavors (x-axis) as well as for a given flavor across 10 days of stable performance (y-axis). Dots represent individual subjects. Space below unity line reflects range of idiosyncratic variability in individual differences in subjective flavor preferences while also reflecting stable preferences within flavor (low relative variability). (E) At baseline, mice assigned to receive either saline, cocaine, or morphine treatments later in the experiment displayed similar trends in offer zone and wait zone thresholds across restaurant rankings. Error bars. ± 1 SEM. Sample size indicated on each plot.



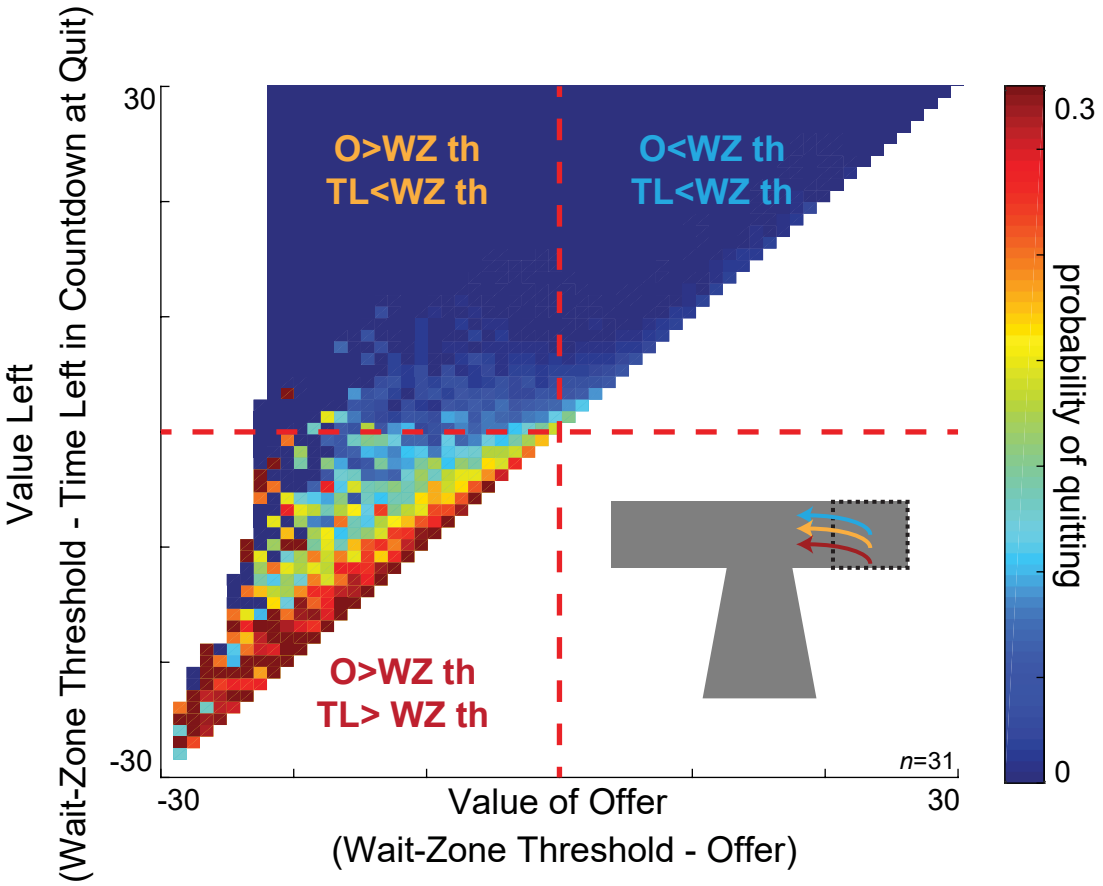
Supplementary Figure 3. Independent and separable valuation metrics across offer-zone, wait-zone, and post-earn lingering behaviors. (A-C) Outside of the ordinal rankings of subjective flavor preferences, no relationships were observed between offer-zone and wait-zone thresholds (A), offer-zone thresholds and post-earn lingering time (B), or wait-zone thresholds and post-earn lingering time. All correlations, correcting for multiple comparisons, resulted in non-significance, P>0.05. (See Fig.1D,1F for agreement that the most-preferred restaurants yielded the highest offer-zone thresholds, wait-zone thresholds, and lingering time). Shaded error region displays 95% CI. N=31.


A
B
C
D
Time (sec)
Time slope
VTE (ldPhi)
VTE slope
O>WZ th.
O<WZ th.
n=31
Value
(WZ threshold - offer)
Relative
Outcome
Probability
skip 100%
quit 100%
earn 100%
flavor rank
least
low
high
most
E
F
Time (s)
VTE (ldPhi)
Value (Wait Zone threshold - offer)
G
H

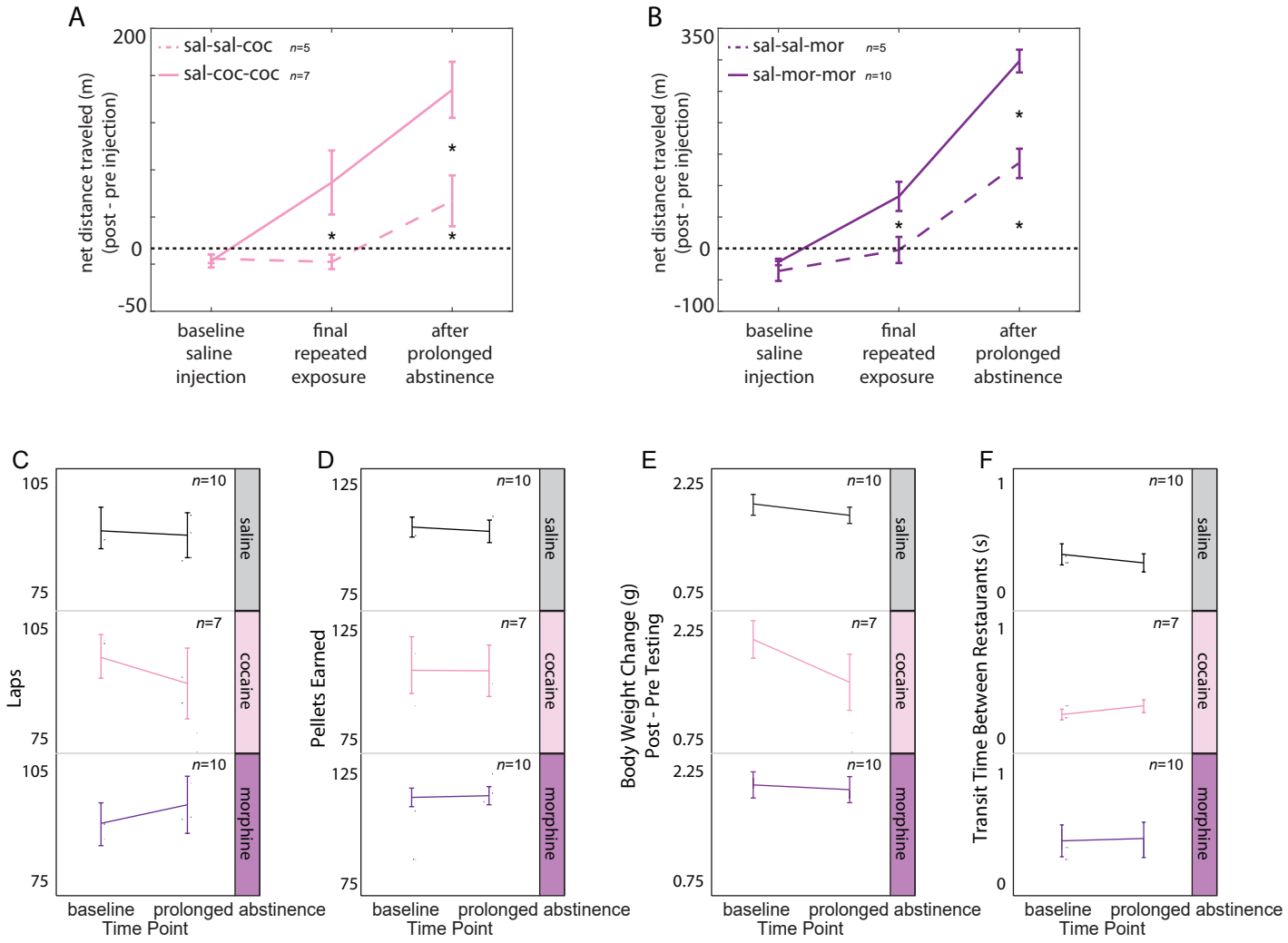
Supplementary Figure 4. Offer-zone deliberation behaviors distributions by value, rank, and trial outcome. (A-D) Linear fits for offer-zone time (A-B) and VTE (C-D) as a function of wait-zone-threshold-derived value revealed decisions got progressively easier (less time and less VTE) when offers were farther away from threshold in either direction (B,D, Sign test slope is significantly different from zero, *P<0.05). That is, offers near threshold (zero value, vertical dashed black line) were toughest. (E-H) Same as A-D split by subjective flavor preference rankings. (E-F) Color scale describes the relative likelihood a trial at a given wait-zone-derived value is to end as either a skip, quit, or earn outcome. Note the increasingly sharper leftward color transition toward red (reflecting skip events) for negatively valued offers in less-preferred restaurants compared to the broader leftward color transition that is predominately green for negatively valued offers in more-preferred restaurants (reflecting enter-then-quit events). (G-H) Slopes for both time (G) and VTE (H) for positively valued offers are significantly different (less) than zero in all ranks, while slopes for negatively valued offers only in less-preferred restaurants are significantly different (greater) than zero. This indicates that decisions for worse deals in more-preferred restaurants, unlike in less-preferred restaurants, were not any easier to make. (*P<0.05). Error bars. ± 1 SEM. N=31.



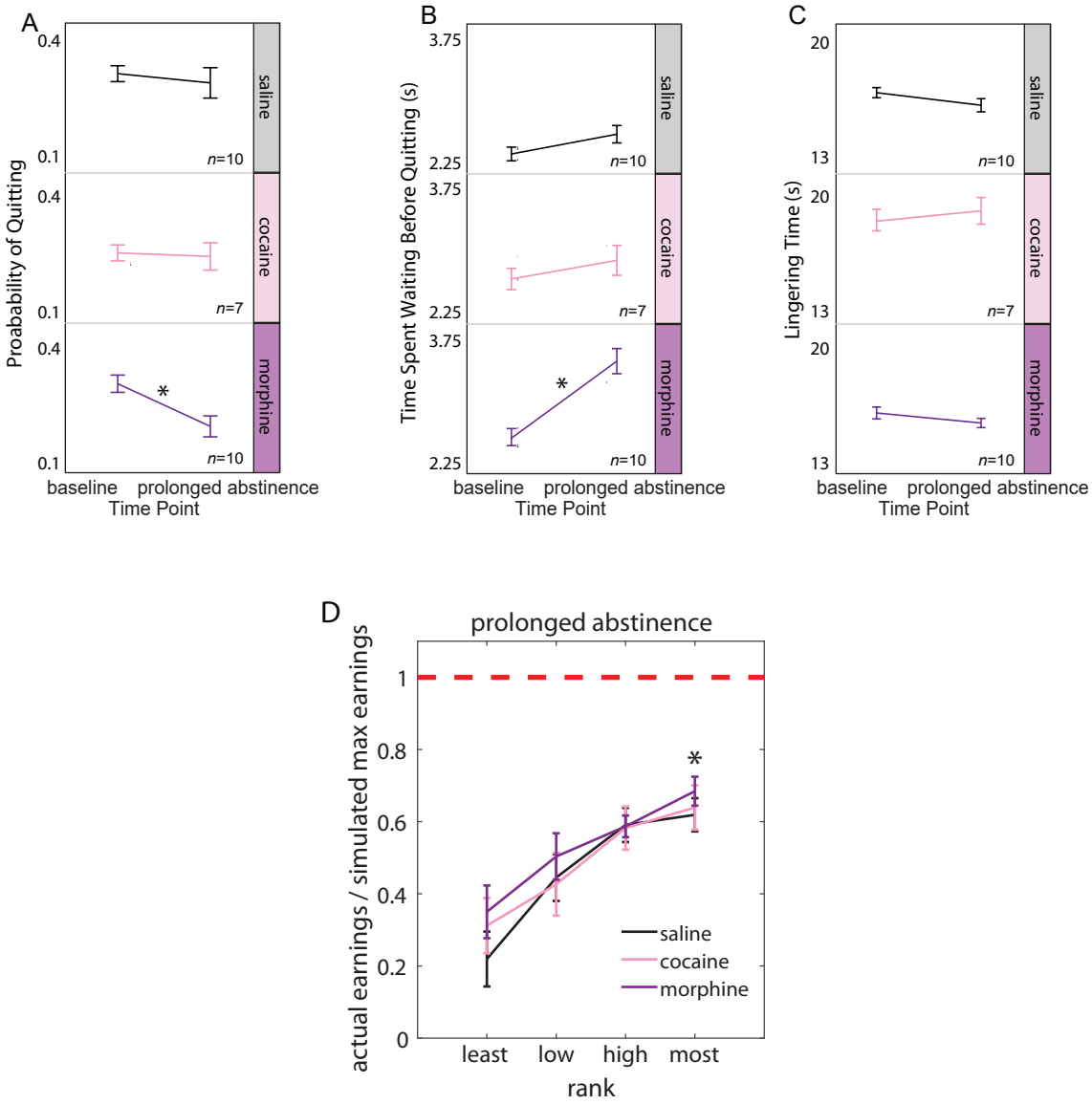
Supplementary Figure 5. Controlling for value as a function of VTE. The average value of offers encountered as a function of VTE measured on that trial are plotted split by restaurant ranking as well as decision outcome on that trial (A: skips and enters grouped together, B: enters only, C: skips only). Data presented here are derived from trials where offer > wait zone thresholds, representing bad deal trials. Thus, average values for all offers plotted here are <0 (horizontal dashed red line). As a function of VTE, offer value could explain some but not all changes in VTE. Correlation significance controlling for 12 multiple comparisons, Bonferroni corrected alpha level 0.05, *P<0.004, not significant (n.s.) P>0.004. Error bars. ± 1 SEM. Shaded error region displays 95% CI. N=31.



Supplementary Figure 6. Economic efficiency of quit events in the wait-zone. Accepted offers greater than wait-zone threshold are negatively valued offers (wait-zone threshold greater than offer). This is separated on the x-axis to the left of the vertical dashed red line indicating zero value (offers at wait-zone threshold). Additionally, the time remaining in the countdown at the time of quit was measured and value left was calculated by subtracting wait-zone threshold minus time left. Thus, negative value left in the countdown at quit is separated on the y-axis below the horizontal dashed red line indicating zero value left (time left in countdown at quit at wait-zone threshold). Majority of quits took place in the lower left quadrant (summarized in Fig.2L), indicating that the majority of quits occurred after mice had taken offers greater than their typical threshold (i.e. economically unfavorable), and the quit was a form of self-correction.

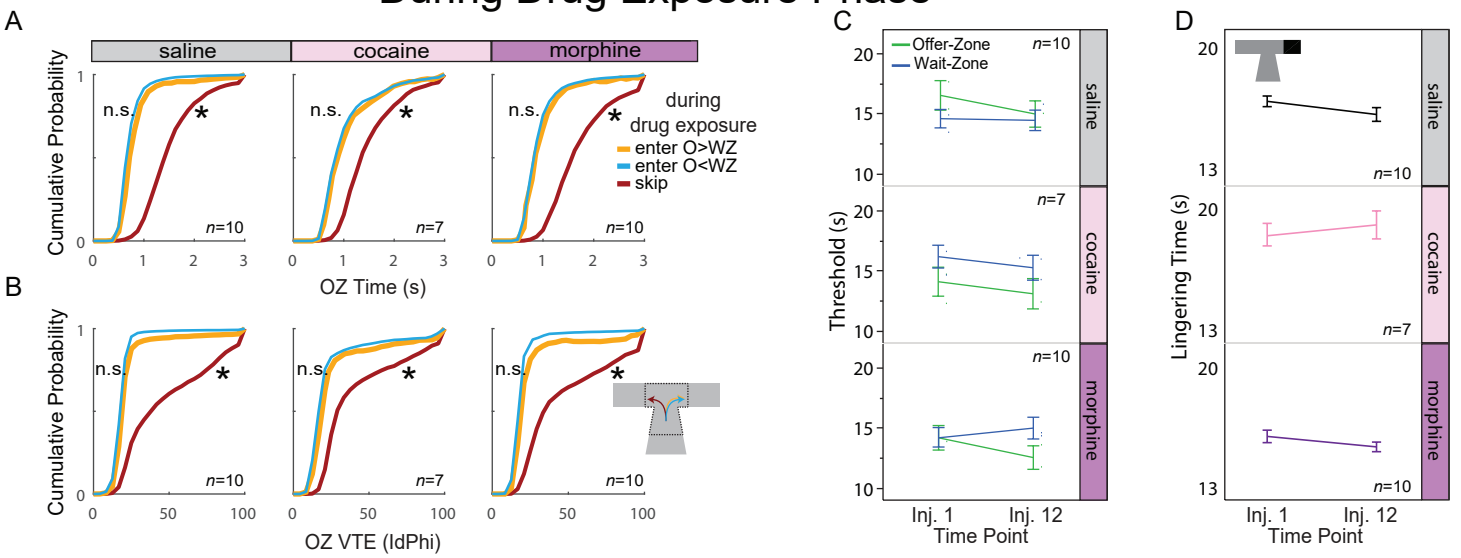


Supplementary Figure 7. Psychomotor sensitization and controlling for non-specific drug effects. (A-B) Locomotor activity immediately (measured in meters, m) before and after injections were measured in cocaine- (A) and morphine- (B) treated animals. All animals were injected with saline initially, then mice in the drug groups received repeated respective drug injections while control mice received repeated saline injections (locomotor response to final injection shown). Lastly, following 14 days of prolonged abstinence, enhanced psychomotor sensitization is expressed in mice with a history of drug use, not first-time drug-exposure in saline pre-treated mice. (Friedman, $P<0.05$, post-hoc Mann-Whitney locomotion comparisons between drug groups at time points, $^*P<0.05$). (C-F) There were no lasting off-target effects on Restaurant Row Performance (C: Laps, D: Pellets Earned, E: Weight Change, F: Transit Speed). All four measures remained constant even after our drug and prolonged abstinence manipulation, implying that these off-target effects did not drive decision-making changes (Friedman, $P>0.05$). Error bars. ± 1 SEM. N per group listed on respective plots.

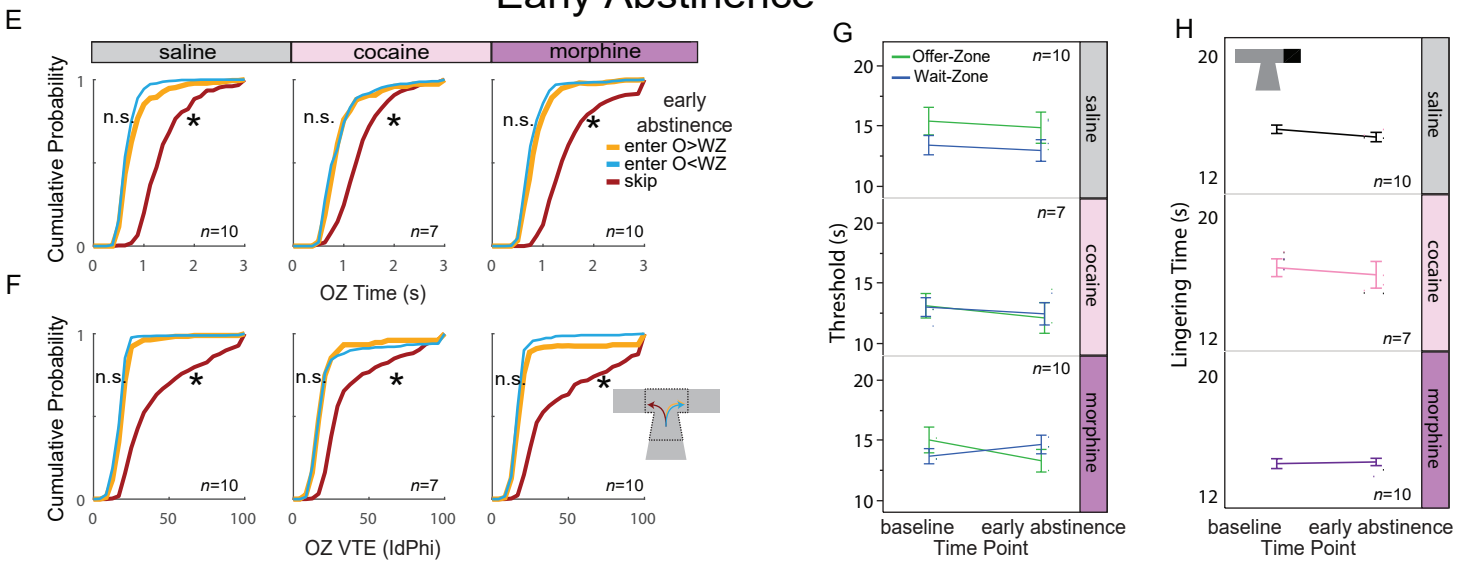


Supplementary Figure 8. Effects of prolonged abstinence on additional decision-making metrics. (A) Probability of quitting accepted offers in the wait-zone. (Friedman, morphine *P<0.05, saline/cocaine P>0.05) (B) Amount of time invested in the wait-zone before quitting. (Friedman, morphine *P<0.05, saline/cocaine P>0.05) (C) Amount of time spent consuming and lingering at the reward-site post-earning. (Friedman, all groups P>0.05) (D) Degree of optimal earnings. Sub-optimality was calculated by simulating Restaurant Row sessions and number of max potential earnable pellets using individual thresholds and running speeds, but removing wasteful behaviors (i.e., no quits, no excess time deliberating in offer-zone nor lingering post-earning beyond the minimum showed by the animal). Horizontal dashed red line indicated optimal performance as determined by simulations. (Sign test, P<0.05, all ranks below 1. Kruskal-Wallis-Dunn tests, most-preferred vs. least-preferred *P<0.05). Error bars. ± 1 SEM. N per group listed on respective plots.

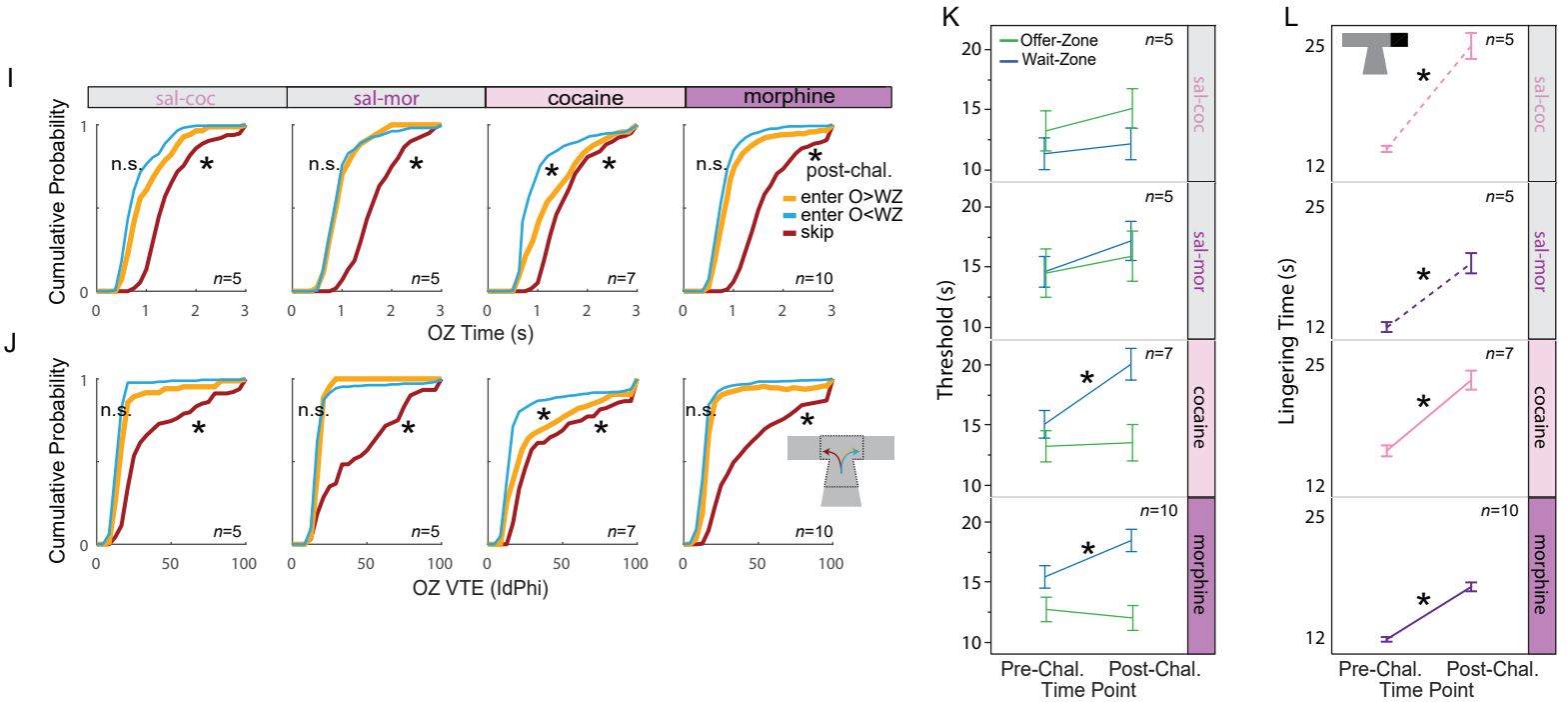
During Drug Exposure Phase



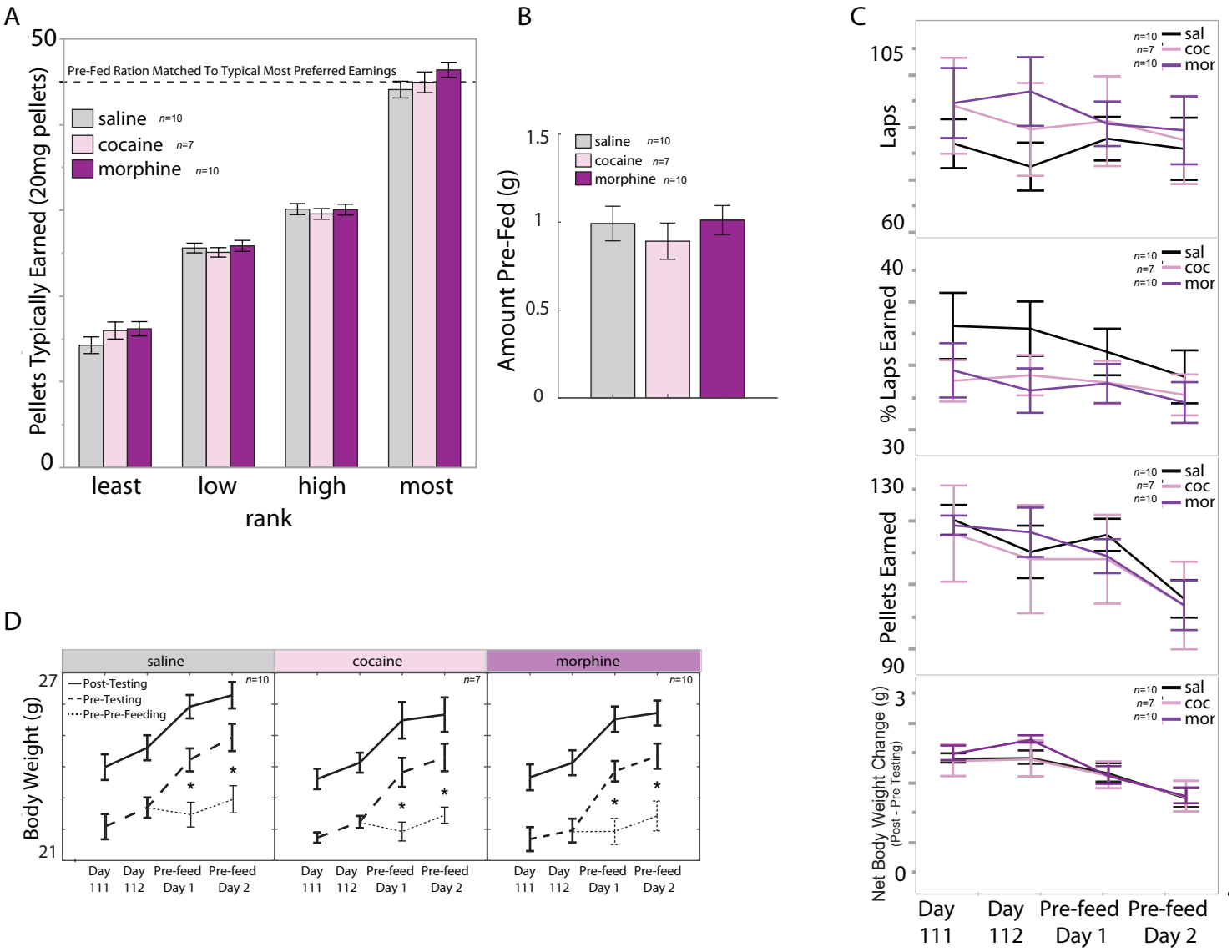
Early Abstinence

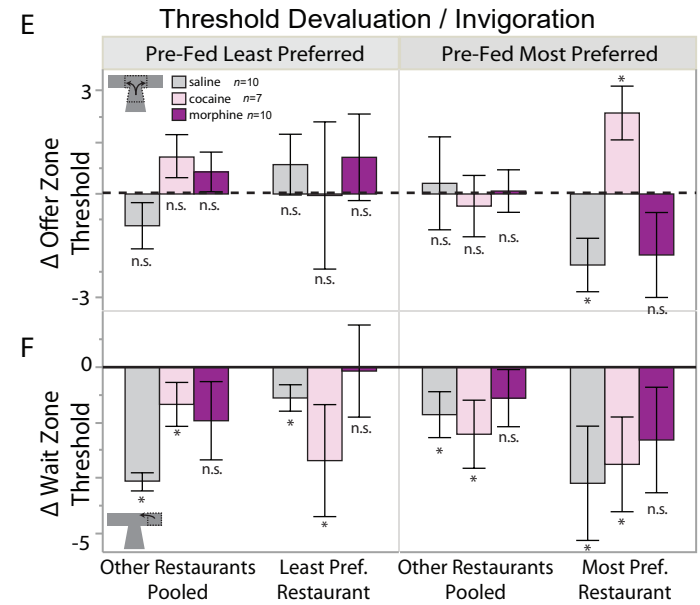


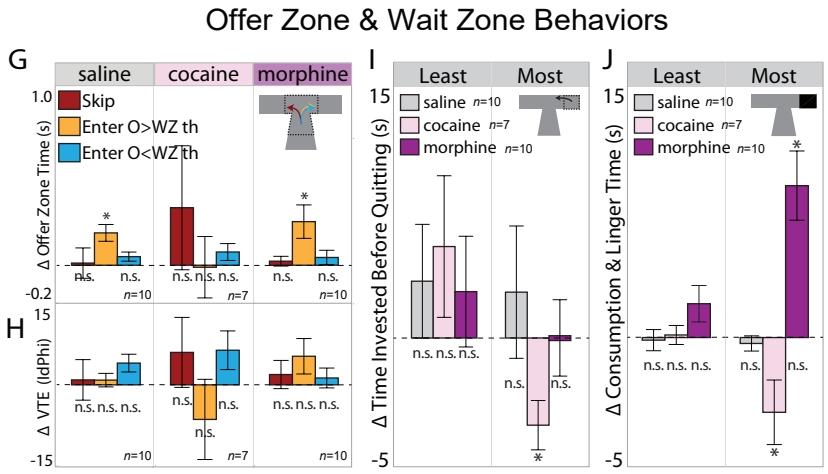
Post-Abstinence Drug-Re-Exposure Challenge



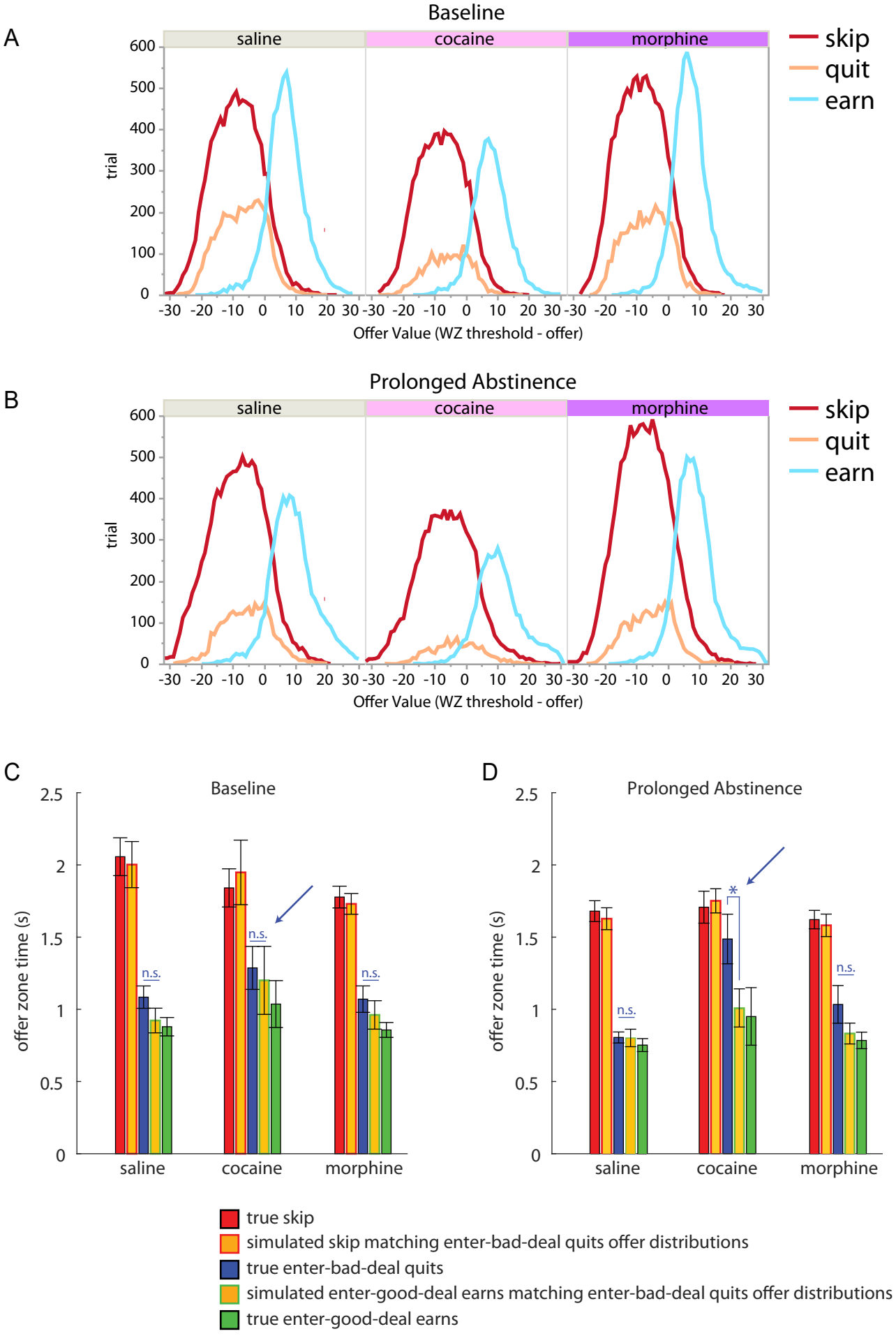
Supplementary Figure 9. Secondary drug-related timepoints (cyan timepoints 1-3). Outside of the primary timepoints of comparison in this study (yellow timepoints in Fig.1A), we also examined behavior of multiple valuation parameters (offer-zone deliberations, offer- and wait-zone thresholds, and post-earn lingering) during the drug exposure phase (A-D), during early abstinence (E-H), and after the drug-re-exposure challenge intended to assess incubation of psychomotor sensitization (I-L) where mice were either re-exposed to the same drug previously administered or saline-pre-treated mice received either cocaine or morphine for the first time. (A-B) Cumulative probability distributions of offer-zone time (A) and VTE (B) for skips as well enters split by offer value separated by drug-treatment conditions collapsed across the drug exposure sequence. Both types of enter decisions were rapid compared to skip decisions (KS tests, *P<0.05) and indistinguishable from each other (KS tests, not significant, n.s., P>0.05) in all three drug conditions, similar to baseline findings. (C) Friedman tests revealed no changes in offer-zone and wait-zone thresholds across first and last injection of the repeated drug exposure sequence separated by drug-treatment conditions (P>0.05). (D) Similarly, no changes were found in time spent lingering at the reward site after earning across first and last injection of the repeated drug exposure sequence (P>0.05). (E-H) During early abstinence, no changes from baseline were observed in any of the valuation parameters. (E-F) Offer-zone time (E) and VTE (F) for enter decisions were both faster than skips (KS tests, *P<0.05) and indistinguishable from each other (KS tests, not significant, n.s., P>0.05) in all three drug conditions, similar to baseline findings. (G-H) Offer-zone and wait-zone thresholds (G) and lingering behavior (H) did not change over time (Friedman, P>0.05). (I-L) After the drug-re-exposure challenge, although cocaine-treated animals still displayed their main effect (following prolonged abstinence) of increase deliberation time (I) and VTE (J) for offers above wait-zone thresholds, no further changes were seen in any drug condition (KS tests, *P<0.05, not significant, n.s. P>0.05). (K) Only animals with a history of repeated drug exposure (both cocaine and morphine pre-treated groups) displayed increased wait-zone thresholds in response to an acute drug-re-exposure challenge while first-time-exposed mice did not (Friedman, *P<0.05). (L) All mice displayed an increase in lingering behavior following an acute drug challenge (Friedman, *P<0.05). Error bars. ± 1 SEM. N per group listed on respective plots.


A
Pre-Fed Ration Matched To Typical Most Preferred Earnings
saline n=10
cocaine n=7
morphine n=10
Pellets Typically Earned (20mg pellets)
least
low
high
most
rank
B
Amount Pre-Fed (g)
C
Laps
% Laps Earned
Pellets Earned
Net Body Weight Change (g) (Post - Pre Testing)
sal
coc
mor
Day 111
Day 112
Pre-feed Day 1
Pre-feed Day 2
D
saline
cocaine
morphine
Post-Testing
Pre-Testing
Pre-Pre-Feeding
Body Weight (g)


E
Threshold Devaluation / Invigoration
Pre-Fed Least Preferred
Pre-Fed Most Preferred
Δ Offer Zone Threshold
F
Δ Wait Zone Threshold
Other Restaurants Pooled
Least Pref. Restaurant
Most Pref. Restaurant


Offer Zone & Wait Zone Behaviors
G
saline
cocaine
morphine
Skip
Enter O>WZ th
Enter O<WZ th
Δ Offer Zone Time (s)
H
Δ VTE (IdPhi)
I
Least
Most
Δ Time Invested Before Quitting (s)
J
Δ Consumption & Linger Time (s)

Supplementary Figure 10. Pre-feeding probe session (cyan timepoint 4). (A-B) Average number of pellets typically earned in each ranked restaurant. Dashed horizontal black line indicates the approximate number of pellets earned in a single session in most-preferred restaurants (A, ~45 pellets, 20mg each). This number was used to determine how much to pre-feed mice before devaluation probe sessions with the intention to partially satiate mice while preserving motivation to run the task following pre-feeding (B, ~0.9g). The same number was also used in both pre-feeding probe sessions regardless if pre-feeding with either the most- or least-preferred flavor. (C) Pre-feeding had no effect on laps run, % laps earned, pellets earned, or net-body-weight-change comparing pre-testing weights to post-testing weights (Friedman, $P>0.05$). (D) Pre-feeding however did increase body-weight when comparing pre-pre-feeding weights to post-pre-feeding weights measured before Restaurant Row testing (Friedman, $^*P<0.05$). Pre-feeding plus additional weight gained during Restaurant Row did not significantly change starting pre-pre-feeding weight on the second probe session (Friedman, $P>0.05$). (E-J) We measured changes in behavior of multiple valuation parameters (offer- and wait-zone thresholds, offer-zone deliberations, wait-zone quits, and post-earn lingering) by calculating changes relative to 5d of average behavior preceding the first pre-feeding session (Sign tests, $^*P<0.05$, not significant, n.s., $P>0.05$). (F) Mice with a history of repeated saline or cocaine exposure showed decreased wait-zone thresholds in all restaurants in response to pre-feeding regardless of the identity of the pre-fed flavor. Morphine pre-treated mice displayed no changes in wait-zone thresholds. (E) In the offer-zone, thresholds of only the most-preferred flavor only when pre-fed that flavor decreased in saline mice, increased in cocaine mice, and did not change in morphine mice. No other offer-zone thresholds changed in all mice. (G-H) Only saline- and morphine-mice showed increased offer-zone reaction times when accepting offers above wait-zone threshold (G) in the most-preferred restaurant when pre-fed that flavor, however these changes were not accompanied with changes in vicarious trial and error (VTE) behavior (H). (I-J) Cocaine-mice showed a decrease in time invested before quitting (I) and a decrease in time spent lingering (J) in the most-preferred restaurant when pre-fed that flavor while morphine mice only showed an increase in lingering time. Saline mice displayed no changes in wait-zone quit time or post-earn lingering after pre-feeding. Error bars. ± 1 SEM. N per group listed on respective plots.


A
Baseline
saline
cocaine
morphine
skip
quit
earn
trial
Offer Value (WZ threshold - offer)
B
Prolonged Abstinence
C
Baseline
offer zone time (s)
n.s.
D
Prolonged Abstinence
*
true skip
simulated skip matching enter-bad-deal quits offer distributions
true enter-bad-deal quits
simulated enter-good-deal earns matching enter-bad-deal quits offer distributions
true enter-good-deal earns

Supplementary Figure 11. Controlling for offer distribution differences in decision outcomes. (A-B) Decision types sorted by trial outcome as a function of offer value (wait zone threshold minus offer) across all animals split by treatment group at baseline (A) or prolonged abstinence (B) intended to illustrate different decision outcomes occur on trials with very different offer distributions, particularly the two types of enter decisions (enter then earn, enter then quit). (C-D) We ran single trial simulation analyses during baseline (C) or prolonged abstinence (D) to control for unequal distributions of offers based on trial type (skipping bad deal, entering bad deal then quitting, or entering good deal) that could confound interpretations of offer zone behaviors when making initial enter or skip decisions. We generated simulated shuffled data sets of both skipping a bad deal and entering a good deal then earning matching the same trial-by-trial distributions of offer lengths as those subsets of trials where mice entered a bad deal then quit. That is, simulations were performed by using the offer length distributions that belong to the enter-bad-deal scenario and then averaging only those offer-zone reaction times that matched this offer distribution where the outcomes were instead skips (for the skip simulation) or enter-good-deals (for the enter simulation). We found that after running these analyses on baseline days 66-70, we do not see any significant differences in any treatment group between our conditions of interest (how mice deliberated before accepting bad deals in the offer-zone), comparing entering bad offers that leads to quits to the shuffled control entering that leads to earns simulated to match offer distribution of entering bad deals before quitting, ($P>0.05$). This comparison of interest does change even when matched against simulated shuffled data sets only in the cocaine group after prolonged abstinence ($*P<0.05$). Thus, offer-zone behavior when entering-bad-deals looks like entering-good-deals (both are rapid snap judgments even if the former is a mistake) for all mice at both time points except the cocaine-treated animals at the prolonged abstinence time point. Error bars. ± 1 SEM. N per group listed on respective plots.

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