

Current Biology

Real-Time Value Integration during Economic Choice Is Regulated by Orbitofrontal Cortex

Highlights

- Rats show immediate changes in choice behavior following reinforcer revaluation
- Direction of satiety-specific revaluation depends on the baseline food preference
- Orbitofrontal inactivation disrupts behavior following reinforcer revaluation

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In Brief

Appropriate decision making depends on up-to-date information about the available offers. Here, Gardner et al. show that immediate adjustments in choice behavior following revaluation of an offer require the orbitofrontal cortex to be online at the time of the choice.



Real-Time Value Integration during Economic Choice Is Regulated by Orbitofrontal Cortex

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SUMMARY

Neural correlates implicate the orbitofrontal cortex (OFC) in value-based or economic decision making [1–3]. Yet inactivation of OFC in rats performing a rodent version of the standard economic choice task is without effect [4, 5], a finding more in accord with ideas that the OFC is primarily necessary for behavior when new information must be taken into account [6–9]. Neural activity in the OFC spontaneously updates to reflect new information, particularly about outcomes [10–16], and the OFC is necessary for adjustments to learned behavior only under these conditions [4, 16–26]. Here, we merge these two independent lines of research by inactivating lateral OFC during an economic choice that requires new information about the value of the predicted outcomes to be incorporated into an already established choice. Outcome value was changed by pre-feeding the rats one of two food options before testing. In control rats, this pre-feeding resulted in divergent changes in choice behavior that depended on the rats' prior preference for the pre-fed food. Optogenetic inactivation of the OFC disrupted this bi-directional effect of pre-feeding without affecting other measures that describe the underlying choice behavior. This finding unifies the role of the OFC in economic choice with its role in a host of other behaviors, causally demonstrating that the OFC is not necessary for economic choice per se—unless that choice incorporates new information about the outcomes.

RESULTS

Rats were trained on the economic choice task used in previous studies [4, 5]. Briefly, within this task, hungry rats are presented with choices between different amounts of unique food pellets. Two different visual stimuli are presented on each trial, each signaling by shape and number of segmentations, respectively, the availability of a particular type and amount of a unique food pellet (Figures 1A and 1B). Rats choose by touching the screen

with the preferred option after a 1-s viewing period, during which they must maintain a nose poke hold at a central port. Rats learn 6 visual cue → food-type associations, resulting in 15 possible pairs. Standard sessions range from ~100 to 300 trials, over which 11 different offers of a particular pellet pair are randomly presented (see STAR Methods for more detail). The choice behavior across each of the offers in a session is used to construct a psychometric curve through which the relative value of the two food types can be estimated. This estimate is expressed as the indifference point (IP), defined as the ratio of the two pellets at which the subject chooses equally between them.

After reaching proficiency on this task and displaying transitivity in choices between several different pellets, rats in the current study ($n = 13$) underwent surgery, in which a virus containing NpHR was infused into lateral orbitofrontal cortex (OFC) and fibers were implanted bilaterally overlying the area to allow optogenetic inactivation of neurons in the region during task performance (Figure 1D). After ~10–12 weeks for recovery, viral expression, and re-acclimatization to the task while tethered to fiber-optic cables, the rats were tested on one of the pellet pairs across two sessions: a standard “baseline” session, in which the full suite of offers was presented to the rats in their normally deprived state, and a “probe” session, in which several offers around the baseline session IP were presented immediately following pre-feeding on one of the pellet types (Figure 1C). The intent of the pre-feeding was to selectively revalue one of the pellets outside the context of the choice task [27–29]. Light was delivered into the fiber-optic cables during cue presentation on all trials in the probe session; sometimes, the rats wore a patent-fiber cable ($n = 23$ session pairs), which allowed transmission of light into the OFC, although other times the rats wore a blocked-fiber cable ($n = 24$ session pairs), which prevented light from entering the skull. Each rat contributed data to both types of sessions with the order counterbalanced, and each session pair utilized a unique pair of pellets to avoid overtraining and practice effects and any lingering effects of pre-feeding on preference.

Also, because calculating the indifference point requires a substantial number of trials, we were not able to assess the effect of pre-feeding under extinction conditions, as is normally done in revaluation studies. By focusing on offers near the IP from the baseline session, we hoped to maximize our ability to see shifts caused by pre-feeding in the fewest trials possible, thereby minimizing the impact of learning about the new value of the pellet. Additionally, we only delivered light into OFC during the choice phase; light delivery was terminated when the rat



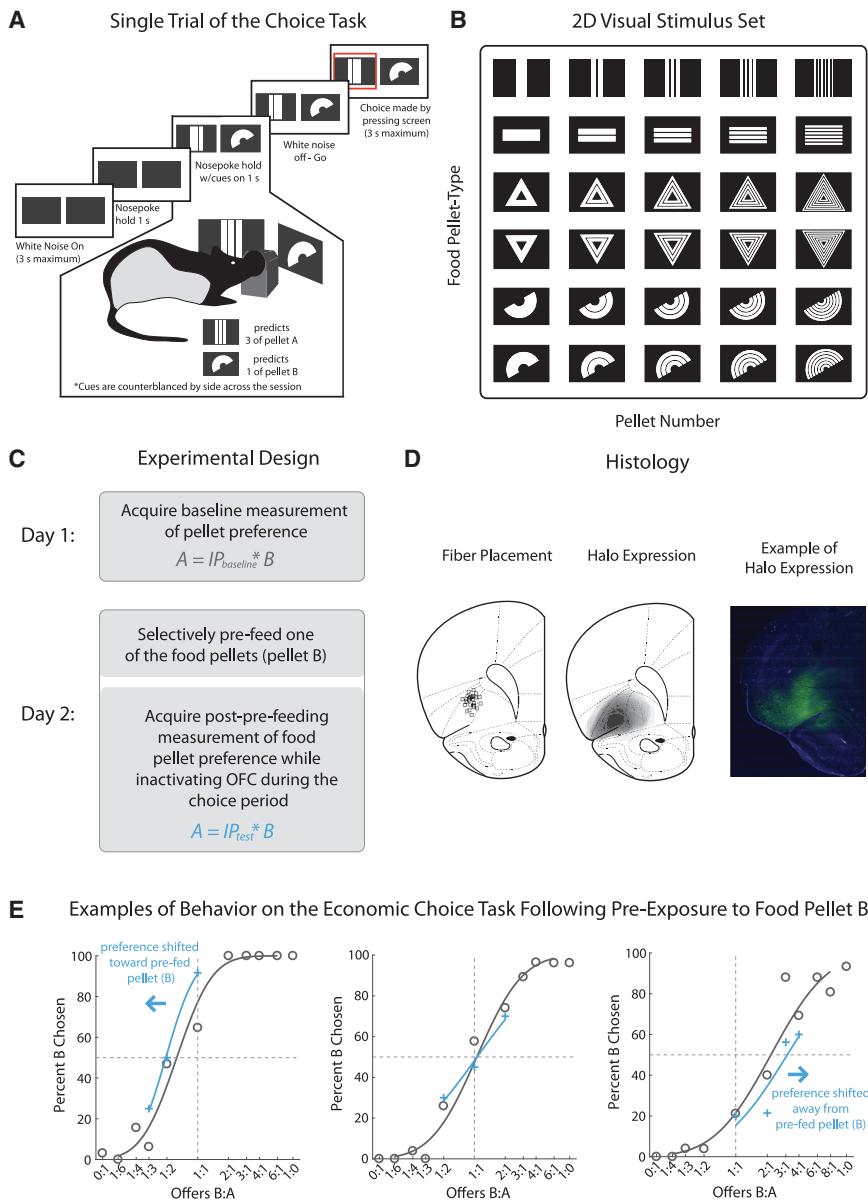


Figure 1. Description of the Economic Choice Task and Design for Optogenetic Inactivation of OFC following Exposure to One of the Pellets

(A) Description of a single trial on the economic choice task. Rats are required to nose poke at a central port following onset of a white noise auditory stimulus. After a 1-s hold, the current offer is presented by displaying the appropriate visual stimuli on either screen. Rats must maintain the nose poke hold for another second before termination of the white noise stimulus, after which the rats can make a decision by pressing one of the screens. An illustrative example of a single trial on the choice task is shown.

(B) All visual stimuli used in the experiment. All rats were trained to associate the shape of each visual stimulus with a specific type of food pellet and the number of segmentations within the visual stimulus with the number of pellets available. Visual symbol \rightarrow food pellet associations were randomly assigned and remained constant throughout the experiment.

(C) Design for the experiment. On the first day, one pair of the 10 possible symbol-pellet pairs was randomly chosen and tested in order to determine a baseline measurement of the indifference point (IP) for the chosen pellets. On the second day, rats were pre-exposed to one of the two pellets that were experienced on the prior day in order to revalue that pellet before being tested on the choice task on a limited set of offers around the IP.

(D) Histological verification of viral expression (middle) and fiber placement (left) for each of the rats at ~ 3.0 mm anterior of bregma. Example of NpHR3.0-eYFP expression (green) and DAPI (blue; right) is shown.

(E) Three representative examples of behavior for the control (blocked fiber) condition. Symbols (black circles, baseline—day 1; blue crosses, probe test—day 2) and lines show choice behavior for each of the 11 offers (x axis) and the generalized linear model (GLM) probit regression, respectively. Percent choice on the y axis is plotted for pellet B, the pellet type that was pre-fed before the probe test on day 2. A shift of behavior to the right from the baseline indicates a devaluation effect for pre-feeding.

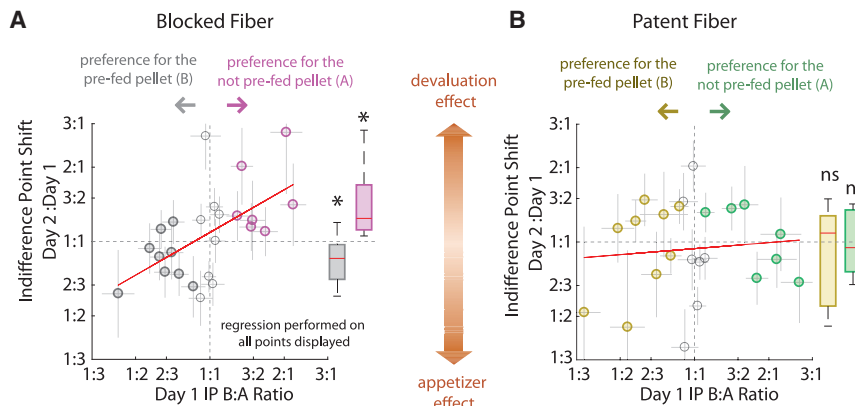
made a choice, well before the pellets were retrieved from the food cup and consumed, which is presumably when learning would occur. Finally, our reading of the literature suggests that any contribution from learning in response to exposure to the re-valued pellet should be insensitive to OFC inactivation, because OFC is typically unnecessary for shifts in behavior caused by directly experienced changes in reward, as occurs in discrimination learning [30, 31], Pavlovian conditioning [17], and extinction by reward omission [32], or even after reward revaluation, as long as the reward is presented [33].

Established Economic Choice Is Sensitive to Outcome Revaluation

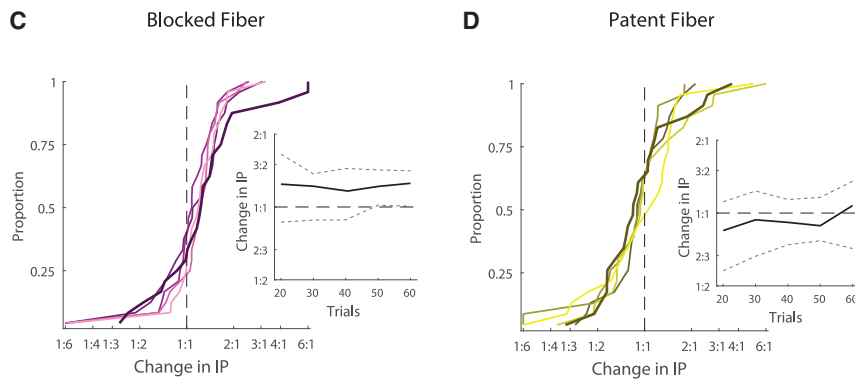
This approach identified clear, if subtle, shifts in economic choice behavior after pre-feeding of one of the pellets in the blocked-fiber control sessions; interestingly, the degree of

the effect was variable, such that sometimes the shift was substantial, sometimes trivial, and in some cases seemed to be toward rather than away from the pre-fed pellet (Figure 1E, example sessions). To better determine the source of this variability, we plotted the change in the IP between the baseline and probe sessions against each rats' preference for the pre-fed pellet, determined in the baseline session. This analysis revealed an inverse correlation between preference for the pre-fed pellet and the IP shift (Figure 2A; $R = 0.56$; $p = 4.3 \times 10^{-3}$), with the direction of shift reversing close to the point of equivalence or 1:1 preference (x-intercept of the regression = 0.93 B:A ratio). In other words, if the rats were pre-fed on the non-preferred pellet, they exhibited a classic devaluation effect [28], shifting their IP away from that pellet in the subsequent probe test (10 of 11 sessions; points right of the 1:1), whereas if they were pre-fed on the preferred

Scatter Plots of the Relationship between the Change in Preference and the Baseline Preference



Moving Window Cumulative Distribution of the Indifference Point (All Data Points)

**Figure 2. OFC Inactivation Disrupts the Dependence of Pellet Revaluation Induced by Pre-feeding on Baseline Preference**

(A) Scatterplots of the IP shift from day 1 to day 2 (y axis, log ratio of IP day 2:day 1) plotted against the IP measured during the baseline session (x axis) for the control (blocked-fiber) sessions. Filled circles represent significant preferences (IPs) determined from the GLM regression either for the pre-fed pellet (gray) or for the non-pre-fed pellet (magenta). Boxplots (indicating the median, 25% and 75% percentiles, and the range) of the change in IP for each of the groups are shown to the right of the scatterplots. Red line, linear regression of the IP shift as a function of the baseline preference.

(B) Same as in (A) but for the inactivation (patent-fiber) sessions. Yellow, pre-fed pellet; green, non-pre-fed pellet. See Figure S1 for scatterplots identifying individual subjects. A linear regression comparing the two conditions revealed a significant coefficient for the interaction of fiber type \times baseline preference ($\beta = 0.66$; $t_{37} = 2.10$; $p = 0.043$) and no other significant coefficients (preference: $\beta = -0.11$, $t_{37} = 1.07$, $p = 0.29$; fiber: $\beta = 0.13$, $t_{37} = 1.07$, $p = 0.29$; y-intercept: $\beta = 0.011$, $t_{37} = 0.23$, $p = 0.96$; subjects: $t_{37} \leq 1.34$, $p \geq 0.19$). The estimated variance of the shifts in preference was similar across the two conditions; see Figure S2A.

(C) Cumulative distributions of the change in IPs (blocked-fiber sessions) determined using a moving window (20 trials) beginning at trial 20 (thick line) over 10 trial intervals until trial 60 (dark to light violet indicates early to late trials). Inset: the median change in IP (solid line) for each of the 20 trial steps plotted with the 25% and 75% percentiles (dotted lines) is shown.

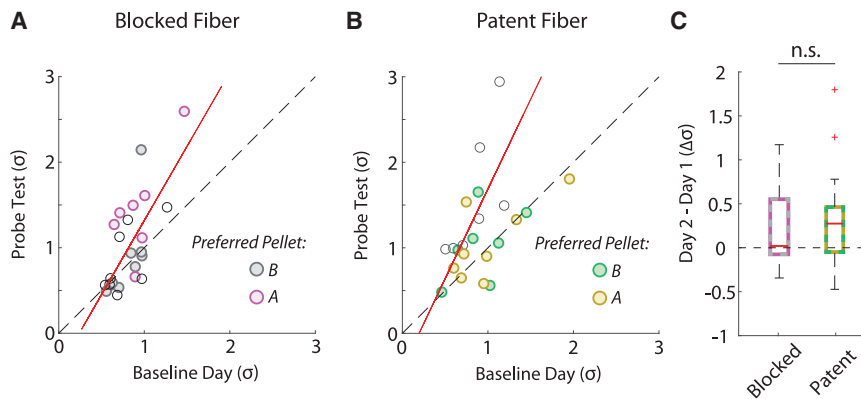
(D) Same as in (C) for the patent-fiber sessions. * $p < 0.05$; n.s., not significant.

pellet, they exhibited priming, or what has been referred to as a “potato chip” or appetizer effect (P. Holland, personal communication), shifting their IP toward that pellet (9 of 13 sessions; points left of 1:1; chi-square test for independence, $\chi^2_1 = 8.86$; $p = 2.9 \times 10^{-3}$). Isolating baseline sessions according to whether the pre-fed pellet was preferred or non-preferred (Figures 2A, filled circles, and S1A for individual rats) revealed that the IP shifted toward the pre-fed pellet when it was preferred (gray whisker plot; one-sided t test; $t_{10} = 2.20$; $p = 0.030$) and away from the pre-fed pellet when it was non-preferred (magenta whisker plot; one-sided t test; $t = -3.01$; $n = 7$; $p = 0.012$). Importantly, this effect was present as early as it was possible to reliably estimate the IP (20 trials; $p = 0.048$; one-sided Kolmogorov-Smirnov test—all data; $p = 0.014$ for sessions with significant baseline preferences) and did not appear to increase over time. This was evident in an analysis of IP across a moving 20-trial window (Figures 2C and S2A), in which the IPs estimated using the first 20 trials (median IP shift = 24.3%) were not significantly different than any other 20-trial interval over the subsequent 40 trials (maximum median IP shift = 25.3%; one-sided two-sample Kolmogorov-Smirnov test: $p > 0.19$). This result suggests that the effect was a spontaneous effect of pre-feeding rather than learning within the probe session.

Revaluation-Sensitive Changes in Established Economic Choice Require Lateral OFC

Consistent with the idea that the OFC would be required for integrating new information about predicted outcomes into an established choice behavior, and not for the established behavior itself, the relationship between pellet preference and IP shift was selectively abolished in the patent-fiber sessions. Rats exhibited the same overall average and range of IPs in the blocked- and patent-fiber baseline sessions (mean IP blocked: 0.98 B:A \pm 0.08%; IP patent: 0.98 B:A \pm 0.11%; range IP blocked: [0.43, 2.17] B:A; range IP patent: [0.36, 2.67] B:A) and consumed the same amounts of both the preferred and non-preferred pellets during pre-feeding before the respective probe sessions (blocked fiber, $n = 24$: 15.3 \pm 0.8 g; patent fiber, $n = 23$: 15.7 \pm 3.4 g; 2-sample t test; $p > 0.05$; $t_{25} = -0.11$); however, when OFC was inactivated in the probe test, the changes in IP from baseline were no longer related to the rats' preference for the pre-fed pellet (Figure 2B; $R = 0.095$; $p = 0.67$). A comparison of the residuals of both regressions revealed a significant reduction in correlation in the patent-fiber condition (one-sided z-test; $p = 0.042$; $z = 1.73$; sessions with significant IPs: $p = 5.2 \times 10^{-3}$; $z = 2.56$). This conclusion was also supported by a within-subjects regression analysis, including fiber type and baseline preference as predictors and subjects as a blocking factor.

Scatter Plots of the Inverse Slope Comparing Baseline and Test Days



(C) Boxplots (indicating the median, 25% and 75% percentiles, and the range) of the change in σ from the baseline to test day. A two-way repeated-measures ANOVA (day \times fiber) revealed a significant main effect of day ($F_{1,78} = 4.34$; $p = 0.041$) but no other significant effect (fiber: $F_{1,78} = 0.78$, $p = 0.38$; fiber \times day: $F_{1,78} = 1.19$, $p = 0.28$; subject: $F_{12,78} = 1.37$, $p = 0.20$).

See Table S2 for linear regression including preference as a factor.

This analysis showed a significant interaction between fiber type and baseline preference ($\beta = 0.66$; $t_{31} = 2.10$; $p = 0.043$), with no effects of any of the other predictors ($t_{31} \leq 1.34$; $p \geq 0.19$; see Figure 2 legend for details). This interaction was due to the aforementioned loss of coupling between the IP shift and preference that had been observed in the blocked-fiber condition. Importantly, this loss was present even in the earliest part of the probe session; a comparison of the cumulative distribution of IP shifts in the blocked- and patent-fiber sessions at 20 trials (Figures 2C and 2D) revealed a significant difference ($p = 0.031$; one-sided two-sample Kolmogorov-Smirnov test).

To affirm the robustness of the above effects based on the IP, we also examined the choice behavior directly by analyzing the percentage of trials in which pellet B (the pre-fed pellet) was chosen in the probe test (Figures 4A and 4B). We ran a linear regression with predictors of offer, baseline preference, fiber type, and subjects as a blocking factor. Consistent with the effects of pre-feeding and OFC inactivation on IP described above, this analysis showed a significant interaction between preference \times fiber type ($\beta = 0.39$; $t_{148} = 3.20$; $p = 1.6 \times 10^{-3}$; see Table S1 for full results).

OFC inactivation affected the relationship between changes in IP and pellet preference despite having no impact on general motivational changes in response latency and the inverse slope of the psychometric curve induced by pre-feeding (Figures 3 and 4C and 4D, respectively). Two-way repeated-measures ANOVAs (fiber \times day) comparing changes in response latency or inverse slope from baseline to the probe session showed that, although rats had shallower slopes in their choice behavior as a result of pre-feeding (main effect of day for inverse slope: $F_{1,78} = 4.04$; $p = 0.041$), response latencies were not affected by pre-feeding (main effect of day for latency: $F_{1,78} = 0.18$; $p = 0.67$), and critically, these effects were independent of OFC inactivation (effect of fiber \times day for inverse slope: $F_{1,78} = 1.19$, $p = 0.28$; effect for latency: fiber \times day: $F_{1,78} = 1.8 \times 10^{-4}$, $p = 0.98$; see legends for Figures 3 and 4, respectively, for full results). Unlike the IPs, these effects did not interact with the baseline preference as revealed by linear regressions identical to those performed for the

Figure 3. OFC Inactivation Does Not Affect the Inverse Slope of the Choice Curve

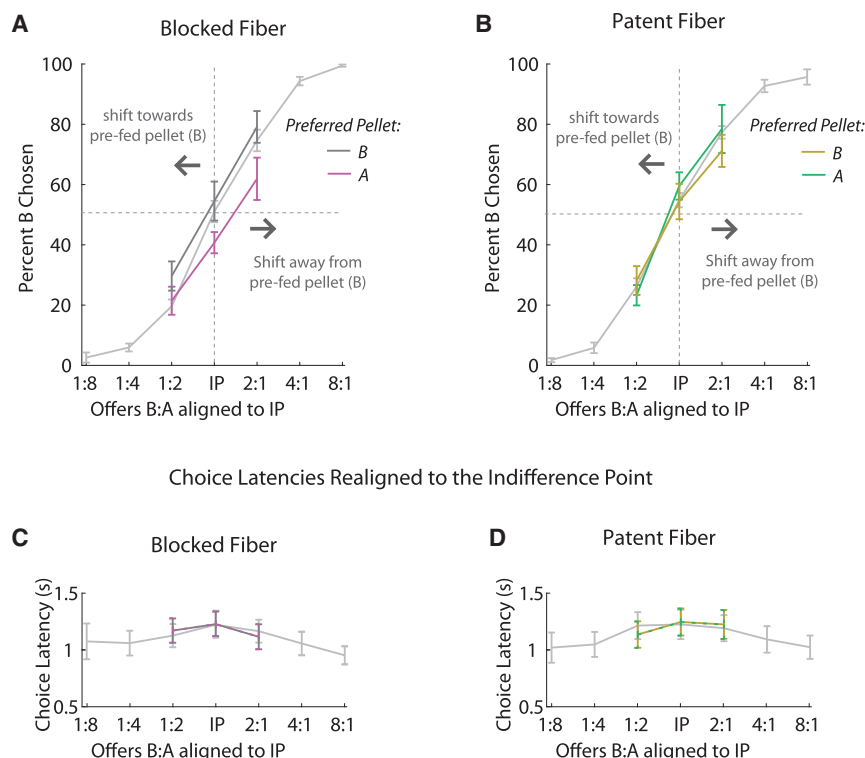
(A and B) Scatterplot showing the inverse slope (σ , probit regression) on the baseline day (x axis) and test day (y axis) for the blocked fiber sessions. Red line, linear regression of the test day σ as a function of the baseline σ is shown (y-intercept: $\beta = -0.42$, $t_{22} = 1.33$, $p = 0.20$; baseline: $\beta = 1.73$, $t_{22} = 2.02$, $p = 0.055$ —tested against the identity line; $R = 0.71$). Filled circles represent significant preferences (IPs) determined from the GLM regression either for the pre-fed pellet (B; gray) or for the non-pre-fed pellet (A; magenta). (B) Same as in (A) for the inactivation (patent fiber) sessions. Sessions with significant baseline preferences for the pre-fed pellet (B; yellow) and for the non-pre-fed pellets (A; green) are shown. Linear regression results are as follows: y-intercept: $\beta = -0.41$, $t_{21} = 1.07$, $p = 0.71$; baseline: $\beta = 2.10$, $t_{21} = 1.06$, $p = 0.31$ —tested against the identity line; $R = 0.40$.

IP (fiber \times preference for the inverse slope: $\beta = -0.28$, $t_{31} = 0.42$, $p = 0.67$; fiber \times preference for the latency: $\beta = 0.28$, $t_{31} = 1.37$, $p = 0.18$; see Tables S2 and S3 for full results).

The impact of pre-feeding was disrupted despite a similar distribution of shifts in IP for the two conditions at test (Figures 2A and S2A; two-sample Kolmogorov-Smirnov test; $p = 0.51$; $D = 0.22$). Thus, the patent-fiber condition showed variance in the IP difference across the two sessions similar to that of controls, but that variance was decoupled from the normal effect of pre-feeding; the IP shifted toward the pre-fed pellet in about half the sessions, regardless of whether it was preferred (6 of 13 sessions) or non-preferred (6 of 10 sessions; chi-square test for independence, $\chi^2_1 = 0.43$; $p = 0.51$), and although the IP followed the baseline preference in 19 of 24 sessions in the blocked-fiber control condition, it did so in only 10 of 23 sessions in the patent-fiber condition (chi-square test for independence, $\chi^2_1 = 6.33$; $p = 0.011$). Consequently, there were no significant changes in choice behavior in the probe test in the patent-fiber condition, whether we isolated sessions in which the preferred (Figure 2B, gold whisker plot; one-sided t test; $t_8 = 0.45$; $p = 0.67$) or non-preferred pellet was pre-fed (green whisker plot; one-sided t test; $t_6 = -0.16$; $p = 0.88$) or analyzed all the sessions together (one-sided t test; $t_{15} = 0.48$; $p = 0.64$).

Finally, to better visualize these divergent effects of pre-feeding in controls and their disappearance in the experimental condition, we plotted the choice behavior from the baseline and probe tests contingent on whether the preferred or non-preferred pellet had been pre-fed (Figures 4A and 4B). This consideration of the baseline preference as a binary factor (preferred/non-preferred) was consistent with previous analyses treating baseline preference as a continuous factor (regression analysis of choice behavior). A three-way repeated-measures ANOVA (fiber type \times offers \times baseline preference) comparing changes in choice behavior across days revealed a significant interaction of fiber type \times baseline preference ($F_{1,43} = 6.64$; $p = 0.013$; see Table S4 for the full results). Tests of the simple effects for the blocked- and patent-fiber conditions revealed a

Average Choice Behavior Realigned to the Indifference Point

**Figure 4. Effects of OFC Inactivation on Choice Behavior and Choice Latencies following Pre-feeding**

(A) Average behavior for the first (light gray, preferred and non-preferred conditions combined) and second day of the test for both the preferred (gray) and non-preferred (magenta) pre-feeding conditions of the control (blocked-fiber) sessions. Behavior was realigned to the IP for each session to allow for appropriate alignment of the psychometric curves. A subset of offers around the IP on the second day was experienced by the rats in order to minimize the number of trials for the test session. An ANOVA performed on the choice behavior treating preference as a categorical factor revealed a significant interaction of fiber \times preference ($F_{1,43} = 6.64$; $p = 0.013$); see Table S4 for full results. (C) Average choice latencies for each of the offers for day 1 (light gray) and test day (gray/magenta). (B and D) Same as in (A) and (C), respectively, for the inactivation (patent-fiber) sessions (preferred pre-fed, yellow; non-preferred pre-fed, green). A two-way repeated-measures ANOVA (day \times fiber) revealed no significant effects (day: $F_{1,78} = 0.18$; $p = 0.67$; fiber: $F_{1,78} = 0.32$; $p = 0.57$; fiber \times day: $F_{1,78} = 1.8 \times 10^{-4}$; $p = 0.98$). There was a significant effect of subject: $F_{12,78} = 34.3$; $p < 10^{-5}$. See Table S3 for linear regression including preference as a factor. All data are plotted in log scale. Error bars represent SE. * $p < 0.05$.

strong main effect of preference for the blocked-fiber and a non-significant main effect of preference in the patent-fiber conditions. The resultant average psychometric curves in Figure 4 provide a concise illustration of these preference-related effects of revaluation on economic choice behavior and their dependence upon lateral OFC.

DISCUSSION

Here, we have shown that established economic choice behavior, tested in rats in an experimental setting, is sensitive to changes in the current value of one of the outcomes on offer. Revaluing one of the two outcomes prior to a test session via pre-feeding resulted in reliable shifts in the outcomes' relative value as revealed by the rats' choice behavior. Importantly, although our design required us to violate "best practices" for revaluation testing by delivering the food pellets during the critical probe test, we found that the effects of pre-feeding were present in controls in the very earliest block of trials and did not change thereafter. This, along with the subsequent OFC dependence of this behavior, strongly suggests that it was a spontaneous effect of pre-feeding rather than learning within the probe session. Thus, our results provide the first demonstration of which we are aware that behavior in laboratory versions of economic choice, which normally involve substantial training, can remain sensitive to transient changes in the current or real-time value of the goods on offer.

This demonstration is important because, although revaluation-sensitive behavior has been upheld as synonymous with

economic choice behavior [34], experimental studies using tasks such as the one employed here have generally paid little or no attention to whether the behavior is in fact based on this type of value as opposed to simply reflecting ingrained or habitual policies acquired with extensive experience on the task. Our current data suggest that there is a bit of both, because the indifference point was shifted by revaluation, showing that real-time value plays a role in its determination, but the shift was not extreme, averaging $\sim 25\%$ of the IP, consistent with the idea that value "cached" in the cues during prior experience plays a substantial role. We would speculate that the balance between such cached versus real-time values reflects the amount of experience the subject has had operating within a particular goods space; this would be consistent with general ideas regarding the habitization of behavior.

Interestingly, pre-feeding in the context of economic choice did not result in the unitary "devaluation" effect often observed in simple, Pavlovian, or even instrumental settings [26, 27, 28, 35, 36]. Rather than simply avoiding the pre-fed pellet, we found that the rats' behavior interacted with their preference for the pellet. When it was non-preferred, they avoided it, showing the classic devaluation effect, whereas when it was preferred, they sought it out, showing what has been referred to as an appetizer effect (P. Holland, personal communication). Although appetizer effects have been described previously, they tend to be unreliable in experimental settings—an observation that may be due to lack of consideration of the food preference as a predictive factor (P. Holland, personal communication). We would speculate that the robust, bi-directional effect seen here may reflect the use of a highly sensitive choice procedure—the economic choice

task—to derive a precise estimate of the relative value of the preferred and control outcomes. The use of choice combined with the sensitivity of the procedure may bring out the appetizer effect in a way that other simpler procedures do not.

Consistent with the general hypothesis that the OFC is important for behavior when that behavior requires the integration of new information about impending outcomes or events (i.e., inferred or model-based information) [4, 37, 38], we found that optogenetic inactivation of the lateral OFC during the choice period in the task selectively abolished the effects of pre-feeding. Rats in the experimental condition exhibited the same behavior as controls at baseline and ate the same amount of the pre-fed pellets, whether preferred or not. Further they showed similar variance in their raw choice behavior and estimated indifference point between the baseline and probe test after pre-feeding. However, the shifts in their indifference point were uncoupled from the principled relationship to pellet preference that was observed in controls. This was true in both directions—that is, OFC inactivation disrupted both the devaluation effect observed when the non-preferred pellet was pre-fed as well as the appetizer effect observed when the preferred pellet was pre-fed. Combined with our prior negative results [4, 5], these findings indicate that the lateral region in OFC is necessary for economic choice behavior to the extent that behavior requires integration of new information into the model or goods space used to guide the behavior. Notably lateral OFC in rodents is arguably homologous with areas of lateral OFC in primates most closely associated with economic choice as well as revaluation-sensitive behavior [39–41]. Thus, a selective role for this area in economic choice after revaluation is consistent with prior causal work on OFC function in other behavioral contexts [4, 15, 17–21, 24, 38] and with correlative evidence that neural representations in OFC update to reflect such integration [10–16].

Importantly, this framework predicts that economic choice behavior in which the goods space is new or not fully explored should be sensitive to OFC inactivation because under these conditions, the choice behavior requires the subject to infer or estimate the relative values of the new items from prior experience with items of varying similarity. This process of mental simulation is what we would speculate requires OFC-dependent mechanisms, which are engaged by the revaluation in the current experiment. This prediction is consistent with evidence from human studies—most correlative, one causal—indicating OFC's involvement in economic choice when offers are more unique [3, 42] and with data indicating effects of OFC inactivation on slope and other measures of economic choice in mice that have only been trained on a single pellet pair and therefore lack extensive experience generalizing across goods [43]. We would suggest that, as with other behaviors, as economic choices become more a repetition of past actions and less dependent on inference and estimation, they will become less dependent on OFC.

Lastly, these findings provide, to the best our knowledge, one of the first demonstrations that the OFC's contribution to revaluation-sensitive changes in behavior is bi-directional. Previous work generally has only documented a role for OFC in settings when the new value must be used to stop or redirect a previously learned response. For example, in classic OFC-dependent

devaluation designs, the OFC is required to stop responding to the cue when the outcome predicted is no longer desired [4, 15–21, 24, 26]. This sort of deficit is often interpreted as reflecting deficits in response inhibition. The current data join a prior report by Gremel et al. [44] to show that the OFC's role is not simply to inhibit behavior, because the OFC is equally necessary to reduce or increase responding, and instead support the interpretation that what is provided by the OFC is the ability to integrate novel information into the associative framework that is used to guide the behavior [7].

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

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SUPPLEMENTAL INFORMATION

Supplemental Information can be found online at <https://doi.org/10.1016/j.cub.2019.10.058>.

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AUTHOR CONTRIBUTIONS

M.P.H.G. designed the apparatus, task, and experiment, with input from G.S. and J.Z. as well as others in the Schoenbaum lab. M.P.H.G., J.C.C., and D.C.S. collected the data. M.P.H.G. analyzed the data with input from J.Z. M.P.H.G. and G.S. interpreted the data and wrote the manuscript with input from the other authors.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Antibodies		
DAPI-Fluorescent- G	Electron Microscopy Services	Cat No. 17984-24
Triton X-100	Sigma-Aldrich	Cat No. X100-500ML
Bacterial and Virus Strains		
AAV5/CamKIIa-eNpHR3.0-eYFP	UNC Vector Core	N/A
AAV5/CamKIIa-eYFP	UNC Vector Core	N/A
Experimental Models: Organisms/Strains		
Long-Evans Rat	Charles River	RRID: RGD_2308852
Software and Algorithms		
MATLAB	Mathworks	RRID: SCR_001622
Graphic State	Coulbourn Instruments	Cat No. G4.0-UP
Other		
Doric dual optical commutators	Doric Lenses	Cat No. FRJ_1x2i_FC-2FC_0.22
200 micron diameter fiber optic patch cable	Thor Labs	M72L01
Fiber optic cannulae	Thor Labs	Cat No. CFM12U-20
ceramic zirconia ferrule bore 230um	Precision Fiber Products	Cat No MM-FER2002S15-P
FC multimode connector	Precision Fiber Products	Cat No. MM-CON2004-2300-2-BLK
543 nm DPSS Laser	Shanghai Lasers	Cat No. GL543T3-100
Arduino Mega	Adafruit Industries	Cat No. 191
Raspberry Pi 3 B	Adafruit Industries	Cat No. 3055
3.5" Resistive Touch Screen	Adafruit Industries	Cat No. 2050

LEAD CONTACT AND MATERIALS AVAILABILITY

Further information and requests for resources and reagents should be directed to and will be fulfilled by the Lead Contact, Geoffrey Schoenbaum (geoffrey.schoenbaum@nih.gov). See the [Key Resources Table](#) for information about resources.

EXPERIMENTAL MODEL AND SUBJECT DETAILS

Fifteen male Long-Evans rats (275-300 g, Charles River Laboratories), aged approximately 3 months at the start of the experiment, were trained and tested at the National Institute on Drug Abuse Intramural Research Program (Baltimore, MD) in accordance with the National Institute of Health guidelines determined by the Animal Care and Use Committee. All rats had *ad libitum* access to water during the experiment and were fed 16-20 g of food per day, including rat chow and pellets consumed during the behavioral task. Rats were initially food restricted to 85% of their baseline weight to begin training. Behavior was performed during the light phase of the light/dark schedule.

METHOD DETAILS

Apparatus

Rats were trained and tested in modified standard behavioral boxes (12" x 10" x 12," Coulbourn Instruments, Holliston, MA) that were controlled by a Raspberry Pi 3 (Raspberry Pi Foundation, Cambridge, UK) using custom-written code in Python (<https://www.Python.org>) [4, 5]. Both custom-made equipment and Coulbourn components were used in the apparatus. Touchscreens (Adafruit Industries, New York, NY, 2.8" – initial training –and 3.5" – later training and testing) were housed in custom-made walls and were controlled by individual microcontrollers (Arduino Mega, Arduino, <https://www.arduino.cc>), which communicated with the Raspberry Pi 3 to display the current offers and provide screen press feedback. Custom-designed nosepoke ports (1.5" H X 1.25" W X 1.5" D) with infrared photodetectors to determine whether a poke had occurred were fixed to the floor of the box about one inch from the wall and. The primary configuration of the box had touchscreens and accompanying wall mounts oriented at 30° from the plane of the left side wall to facilitate better viewing of the screen while the rats were nosepoking at the central port. A tall recessed food magazine (Med-Associates, Fairfax, VT) was placed on the center of the right wall opposite to the nosepoke and touchscreens. Pellets from two

separate externally mounted feeders were dispensed into the food magazine. The speaker used for playing the white noise cue (75 dB) to indicate the beginning of a trial was placed externally to the conditioning chamber. During the optogenetic inhibition phase of the experiment, solid state lasers (532 nm; Laser Century, Shanghai China) were controlled in analog mode (8 bit depth) by a microcontroller (Arduino Uno, Arduino, <https://www.arduino.cc>)

Choice Task

Each trial started with a white noise cue, which indicated that the rat could nosepoke at the central port. After a 1 s nosepoke at the port, the current offers were displayed on the two screens situated on either side of the nosepoke. After another 1 s period, during which the rats were required to remain in the nosepoke, the white noise ended indicating that a choice could be made by touching either of the screens to receive the offer-type and pellet number displayed. Immediately following the choice, the pellets were delivered into the food magazine on the opposite side of the chamber. Rats then waited 6–16 s before the next trial started which depended on a random component as well as the number of pellets delivered on the prior trial. This was determined empirically such that rats were not waiting for longer periods of time for the next trial to start following trials in which only 1 or 2 pellets were delivered. Failure to hold the nosepoke for the first second restarted the 1 s timer and failure to hold the nosepoke once the screens were displayed resulted in the termination of the trial. Rats performed ~150–350 trials per session.

Food-Pellet Reinforcers

All rats received the same menu of pellet offers arranged in the following average preference order (highly palatable banana flavored pellets, Test-Diet 5-TUL (1813985); bacon flavored pellets containing lactose and 1.4% NaCl, Bio-Serv, custom formulation (F07382); grain flavored pellets, Test-Diet 5-TUM (1811143); grape flavored pellets with 50% sucrose and 50% cellulose, Test-Diet, custom formulation (1817455-371); chocolate flavored pellets with 25% sucrose and 75% cellulose, Test-Diet, custom formulation (1817259-371); and 100% cellulose pellets, Test-Diet 5-TUW (1811557). Visual cues predicting the different offer-types consisted of different shapes, indicating the type of pellet available, and different numbers of segmentations of the symbol, indicating the number of pellets available [4]. Each rat received unique cue-pellet pairings that remained constant throughout testing.

Shaping and Pre-Surgical Training

Initial training on the task lasted 3–4 months before rats experienced any of the tested pairs of pellets and progressed through several stages that introduced different aspects of the task. Before starting, rats were food restricted to ~85% of their body weight, then they were first trained to touch a single illuminated touchscreen to receive unflavored sucrose pellets, after which they began training to discriminate two visual cues which either resulted in an unflavored sucrose pellet or nothing (the images used were not used for any subsequent aspect of the task). After rats showed discriminative behavior to the two visual cues, a central nosepoke was introduced to the box and rats were progressively trained to hold in the port for 2 s (1 s with no cues on and one second with visual cues displayed) when the white noise cue was turned on. Upon acquisition of the nosepoke, rats were introduced to the full task. To learn each of the cue-pellet associations, rats were trained for several days on each of the 5 flavored pellets versus a non-preferred cellulose pellet. After rats showed stable preferences for each of the pellets versus cellulose, they were exposed to other pellet-pairs. In each session, rats were given 11 possible offers including the 1:0 and 0:1 offers. The other 9 offers ranged either from 1:6 to 6:1 or 1:4 to 8:1 (X:Y, Y being the presumed preferred pellet-type) from the offer set [1:8, 1:6, 1:4, 1:3, 1:2, 1:1, 2:1, 3:1, 4:1, 6:1, 8:1] depending on the presumed pair preference.

Surgery

Surgical procedures followed guidelines for aseptic technique. Rats received AAV-CaMKIIa-eNpHR3.0-eYFP (Gene Therapy Center at University of North Carolina at Chapel Hill) bilaterally into the medial OFC under stereotaxic guidance at AP 3.0 mm, ML \pm 3.2 mm, and DV $-$ 4.4 mm from the brain surface. A total 1 μ l of virus (titer $\sim 10^{12}$) per hemisphere was delivered at the rate of ~ 0.1 μ l/min by infusion pump [45]. Immediately following viral infusions, optic fibers (200 μ m in core diameter; Thorlab, Newton, NJ) were implanted bilaterally at A/P: 3.0 mm, M/L: \pm 3.2 mm, and D/V: $-$ 4.2 mm (from dura) at an angle of 10 degrees in the M/L plane. Cephalixin (15 mg/kg p.o.) was administered daily for 10 days post-operatively to prevent infection.

Post-Surgical Testing

Following a 2–3 week recovery from surgery, rats were retrained on the full task and accustomed to performing with two fiber-optic patch cables attached to an optic commutator (Doric Lenses, Quebec Canada). Cables were constructed with blocking covers to reduce leakage of light into the box. However, it is impossible to completely eliminate light leakage. To control for effects of such light leakage during laser-on trials, ‘dummy’ fiber-optic cables were employed during retraining and testing. The ‘dummy’, or blocked, cables were identical to the patent-fiber cables except that the optical fiber was blocked at the end of the cable and permitted no light transmittance into the brain. The blocked-fiber cables were constructed identically to the patent-fiber cables with one exception; the optical fiber was terminated at the ferrule, or ~ 1 cm, from the animal-side terminal of the patch cable. A solid metal wire was inserted into the ferrule and epoxied into place in order to block. All blocked-fiber cables were tested after construction as well as on a periodic basis using a Fiber Optic Power Meter (ThorLabs). After rats were familiarized with the blocked-fiber cables and the laser being turned on, testing was begun.

One of the 10 possible pairs of pellets (not including the cellulose pellet) was randomly chosen and rats performed the full choice task while attached to the blocked-fiber cables with the laser turned on for all trials. This first day of re-exposure to a particular pellet-pair was used to obtain an estimate of the rats' baseline IP for the particular pair. On the second day of the experiment, rats were first exposed to one of the pellet-types counterbalanced by whether the pre-fed pellet was the more, or less, preferred pellet based on the IP acquired from the prior day. Rats had 2 hour access to 20 g of one of the pellet-types which were used on the prior day. Immediately following this pre-exposure, rats were run on the task with a limited offer set of 3-4, offers centered on the IP of the prior day. For example, if the estimated IP on day 1 was 2B:1A, offers [1B:1A, 2B:1A, 3B:1A] were used during the probe test. This limited offer set was used to maximize IP estimates for reduced trial numbers following pre-feeding, and a small subset of the sessions had the forced offers [1B:0A, 0A:1B] included which were not considered for any of the analyses. The first 60 trials of probe sessions were used for analysis in order to minimize the effect of learning the new reinforcer values. Sessions with less than 20 trials were excluded from the analysis due to insubstantial data for estimating the IP (3 sessions). For 6 of the sessions rats completed between 40 and 60 trials. Overall rats completed a median of 102 trials during the probe test and a median of 223 trials during the baseline session. During the probe test, rats were either attached to the blocked-fiber or the patent-fiber cables and the laser was turned on for all trials. If the connection of the cables became loose by then end of the session, the session was discarded from the analysis. The lasers (532 nm, 16-18 mW; Laser Century, Shanghai China) were controlled by a microcontroller (Arduino Uno, Arduino) and were turned on concurrently with the white noise cue to indicate the availability to begin a trial. Lasers were turned off at the time of decision using a linear ramp over 300 ms to avoid the possibility of rebound excitation. To minimize the duration of the laser, the white noise and laser were on for 5 s before a timeout period occurred. Rats also had a maximum of 5 s to make a choice once nosepoke hold was fulfilled. Sessions lasted 2-2.5 hours.

Histology

After completion of the experiment, rats were perfused with phosphate buffer saline followed by 4% PFA. The brains were then immersed in 30% sucrose for at least 24 hr and frozen. The brains were sliced at 40 μm and stained with DAPI (through Vecta-shield-DAPI, Vector Lab, Burlingame, CA). The location of the fiber tip and NpHR-eYFP or eYFP expression was verified using an Olympus confocal microscope.

QUANTIFICATION AND STATISTICAL ANALYSIS

Indifference Point and Inverse Slope Estimation

Raw data was collected using custom written code in Python. All further analysis was performed using MATLAB. As described previously [1], in order to estimate a scalar relative value of two goods from a limited subset of all possible offers, an assumption must be made about the function relating the two goods in offer space. Here we assume a linear indifference curve (within a reasonable set of offer space) which entails that the ratio of the number of each good offered leading to indifferent behavior remains constant as the number of goods offered increases. In order to estimate the relative value of two goods from the choice behavior we performed a probit regression for each session [46], which uses the cumulative distribution function of the normal distribution to predict the choice behavior given the log ratio of the offers. This provides estimated parameters $\hat{\mu}$ and $\hat{\sigma}$ of the fitted normal distribution, which were used as estimates for the log of the indifference point (IP) - the estimated relative value - and inverse slope parameter respectively. This analysis was performed using the *fitglm* function in MATLAB which fits a generalized linear model of the choice data using an inverse normal cumulative distribution, 'probit', function as the link function and assumes a bernoulli distribution for the binary choice response variable resulting in the model

$$\Phi^{-1}(\mu) = \beta_0 + \beta_1 x + \varepsilon$$

in which Φ is the normal cumulative distribution function

$$\Phi(z) = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^z e^{-t^2/2} dt$$

and the predictor, x , is the log of the offer ratios resulting in the estimated parameters $\hat{\mu} = \beta_0/\beta_1$ and $\hat{\sigma} = 1/\beta_1$. Sessions with relative pellet values outside of the offer range tested were not included in the analysis. This was done by excluding sessions ($n = 1$) with estimated indifference points $IP = \exp(\hat{\mu})$ greater than a 6:1 ratio (non-preferred:preferred pellet) during the baseline day of the experiment.

Correlation and Linear Regression

The correlation between the change in IP from day 1 to day 2 to the baseline IP was measured using Pearson's correlation coefficient. The correlation coefficients between the two conditions (Blocked and Patent) were then compared using a one-sided z-test (the primary hypothesis of the experiment was that OFC inactivation would disrupt revaluation effects) following application of Fisher's Z-transformation to normalize the correlation coefficients. An ordinary least-squares regression of the form

$$y = \beta_0 + \beta_1 x + \varepsilon$$

was performed with the baseline IP as the predictor and the change in IP from day 1 to day 2 as the response variable in order to determine the point at which the change in preference reversed, β_0 , the x-intercept.

Average Choice Behavior Alignment

The average choice behavior across sessions (Figures 4A and 4B) was computed by subtracting the estimated IP from the log of the offer ratios for each session. The relative offer ratios were then binned into the intervals shown in Figures 4A and 4B. To visualize the average shift in IP for sessions in which both the preferred and non-preferred pellet was pre-fed, preferred pre-fed sessions were reversed.

DATA AND CODE AVAILABILITY

Scripts and CAD files for the behavioral task and equipment can be found at <https://github.com/mphgardner/RatEconChoiceTask>. Additional code and the dataset will be made available upon request from the lead contact, Geoffrey Schoenbaum (geoffrey.schoenbaum@nih.gov).