Distinct forms of regret linked to resilience versus susceptibility to stress are regulated by region-specific CREB function in mice

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Regret describes recognizing alternative actions could have led to better outcomes. It remains unclear whether regret derives from generalized mistake appraisal or instead comprises dissociable, action-specific processes. Using a neuroeconmic task, we found that mice were sensitive to fundamentally distinct types of regret following exposure to chronic social defeat stress or manipulations of CREB, a transcription factor implicated in stress action. Bias to make compensatory decisions after rejecting high-value offers (regret type I) was unique to stress-susceptible mice. Bias following the converse operation, accepting low-value offers (regret type II), was enhanced in stress-resilient mice and absent in stress-susceptible mice. CREB function in either the prefrontal cortex or nucleus accumbens was required to suppress regret type I but bidirectionally regulated regret type II. We provide insight into how maladaptive stress response traits relate to distinct forms of counterfactual thinking, which could steer therapy for mood disorders, such as depression, toward circuit-specific computations through a careful description of decision narrative.

INTRODUCTION

Mistakes are an essential component of reinforcement learning (1). However, acknowledging the error of one’s own agency separates the more complex experience of regret from the mere disappointment of rewards that do not meet expectations (2). Counterfactual thinking, or imagining unselected actions, lies at the core of how regret is processed (3, 4). Appreciating that an alternative action could have led to a better outcome serves as the computational basis of regret that can alter mood and may detract from one’s emotional well-being, potentially promoting psychiatric syndromes such as depression (2). Consideration of regret can influence subsequentvaluations, often in a compensatory manner and even sometimes at the expense of making optimal decisions (5). This has been postulated in the psychology and economics literature, nonetheless, to serve to increase the salience of realized losses, which may be useful for mitigating cognitive dissonance and avoiding future regret (1, 2, 6, 7).

Stress-related disorders such as depression are debilitating illnesses in which individuals struggle with severe emotional dysregulation (8). It is widely accepted that regret contributes to disease burden and may be linked to symptoms including emotional reactivity and negative rumination (8–10). On the other hand, a decreased sensitivity to regret may also appear in depression as individuals often suffer from generalized numbness related to anhedonia, a key symptom of this disorder (8, 9). Thus, no aspect of regret appears pathognomonic for depression, with differences seen across subtypes of this heterogeneous syndrome. Furthermore, little is known about the neurobiology of what might make this process maladaptive and what aspects of regret, if any, carry utility that is worth preserving to restore healthy emotional processing and adaptive coping. Therefore, a more thorough understanding of the computational underpinnings of regret and its link to the underlying neurobiology of stress and decision-making is needed.

Animal models used for the study of depression and other stress-related disorders have made substantial contributions to the field. These include identifying key molecular mediators, such as cyclic adenosine monophosphate response element–binding protein (CREB), which regulates the transcription of stress-sensitive genes that control responses to rewarding and stressful stimuli in a brain region–specific manner (11–13). CREB serves as a central point of convergence among several molecular pathways, transducing the action of many neurotransmitters at the cell membrane level into genetic and epigenetic changes (e.g., histone modifications), ultimately altering circuit function (11). CREB is among the best-characterized transcription factors shown to control stress susceptibility to date. CREB mediates opposing behavioral effects in the nucleus accumbens (NAc) versus medial prefrontal cortex (mPFC) (11). CREB overexpression in the NAc promotes susceptibility to stress and produces an emotional numbing state marked by an increase in depressive-like behaviors and concomitant alteration in anxiety-like behaviors in rodents (14–17). Furthermore, expression of a dominant negative mutant, mCREB (CREBS133A), in the NAc induces the opposite phenotype (14–17). On the other hand, CREB activation in the mPFC promotes resilience to stress (13, 14, 18), and analysis of human postmortem tissue from the mPFC supports a similar region-specific role in depression (13). While elucidating functions of CREB in mediating differential stress responses has begun to make headway, much of the existing interpretations have been based solely on simple behavioral assays, sometimes with conflicting findings. Furthermore, animal models have been limited in their ability to capture the complexity of affective processes in decision-making observed in human patients with stress-related disorders. The role of CREB in decision-making, let alone how this molecular player influences more complex computations such as the processing of the negative consequences of one’s choices, is far less understood. To shed light on this translational gap, we combined the well-established chronic social defeat stress (CSDS)
model in mice with molecular manipulations and approaches in neuroeconomics. The latter have been validated for use in both rodents and humans and used recently to demonstrate behavioral and neurophysiological correlates of regret-related processes in rodents (5, 7, 11, 14, 19).

How can one ascertain if rodents are capable of experiencing regret? How can such a phenomenon be measured nonverbally? In 2014, Steiner and Redish (5) developed a neuroeconomic decision-making task, termed “Restaurant Row,” for use in rats. Animals foraged for food rewards while on a limited time budget, making accept or reject decisions for offers of varying costs in the form of delays signaled by the pitch of a tone. Choices were accompanied by behavioral and neurophysiological evidence of “deliberation” during tone presentation, suggesting that animals were comparing competing alternatives before making informed decisions (20). Steiner and Redish (5) found that in the specific situation in which rats atypically rejected a short delay offer only to encounter a long delay offer on the next trial, animals physically looked back at the previous reward site (as measured by head direction reorientation) with concurrent “replay” events in frontal and striatal ensembles representing the previous decision point location leading to the forgone reward. These events served as correlates of regret-related processes and thus biased animals to be more likely to overcompensate and accept long delay offers on the second trial compared to sequences in which animals did not make economic violations.

Building off of this work, in 2018, Sweis et al. (7) translated this task for use in mice and examined the sequelae of the converse economic violation: atypically accepting long delay offers (7). The task design was modified such that mice had an opportunity to correct these putative mistakes within the same trial. In this modified version of Restaurant Row, decisions were physically separated into two distinct stages: tones presented in an offer zone that indicated the delay of the current trial whose countdown did not begin until mice explicitly entered a separate wait zone during which mice could quit at any point. This allowed for a more thorough interrogation of how decisions to enter the wait zone for long delay offers might be erroneous. Most decisions to enter long delay offers occurred on trials in which mice displayed high-velocity behavioral trajectories, or ballistic journeys, through the offer zone. These events signaled a failure to “deliberate” and produced the most change-of-mind quit decisions in the wait zone. Sweis et al. (7) found behavioral evidence of compensatory valuations on subsequent trials compared to non-violation sequences (“skipped first instead”) much like Steiner and Redish (5), suggesting that change-of-mind decisions, too, can contribute to a post-decision regret-like phenomenon (21, 22).

Until now, it had been unexamined whether these different operational definitions of regret published by Steiner and Redish (5) (regret type I defined by displaying altered decisions after skipping high-value offers) versus Sweis et al. (7) (regret type II defined by displaying altered decisions after accepting low-value offers) are related and share a common computational basis for generalized “mistake appraisal” or rather reflect fundamentally distinct types of counterfactual processing that may be biologically separable or clinically relevant. To this end, we test here whether sensitivity to regret might be linked to individual differences in stress response traits. We directly compare both operational definitions of regret head-to-head in mice following one of two experimental manipulations: (i) challenging mice in a well-validated animal model used to study depression (CSDS) capable of categorizing individuals into two classes of different stress response phenotypes, stress susceptible and stress resilient, and (ii) virally knocking down the transcription factor CREB, a known regulator of stress-sensitive genes, in either the mPFC or NAc—regions important for decision-making and also in which CREB function is known to promote differing stress response phenotypes on simple tasks (11, 18). In this effort, we thereby investigated to what degree stress-related regret profiles might be mimicked or blocked by CREB manipulations. We report that neither social defeat stress nor viral CREB manipulations altered the ability to acquire the Restaurant Row task and had no effect on gross locomotor or feeding behavior. However, we found an increase in sensitivity to regret type I and a decrease in sensitivity to regret type II in stress-susceptible mice only. On the other hand, stress-resilient mice, like nondefeated controls, never displayed regret type I and instead displayed enhanced sensitivity to regret type II over that of nondefeated controls. CREB expression levels in the mPFC versus NAc uniquely covaried with sensitivity to each type of regret. Dissociable alterations in sensitivity to regret types could be induced by perturbing the function of CREB in the mPFC versus NAc of stress-naïve mice, which, in response to future stress, also precipitated differential changes in regret sensitivity. Together, we demonstrate that (i) the effects of mistake history on influencing future decisions differentially depend on the nature of the erroneous choices made, (ii) these differences arise from dissociable brain structures, and (iii) distinct regret profiles can be extracted from mice with unique stress-response predispositions.

RESULTS
Restaurant Row task
C57BL/6 male mice were trained on the Restaurant Row task variant previously described by Sweis et al. (7). Mice had a limited daily time budget (60 min) to forage for their sole source of food by running counterclockwise around a square maze (Fig. 1A). Each corner “restaurant” was decorated with unique contextual cues and contained the reward site of a single, fixed flavor (chocolate, banana, grape, or plain). Flavors were used to modulate subjective value determined by revealed preferences without assuming reward value (as opposed to varying pellet number in each restaurant, as this would come with added complexity of opportunity cost because of increased handling time per pellet). Flavor preferences for individual animals were determined by summing the end-of-session total pellets earned in each restaurant and ranking flavors from most preferred to least preferred (Fig. 1B). Upon entry into a restaurant’s T-shaped intersection (offer zone), a reward offer of a particular delay was randomly selected from a uniform distribution of 1 to 30 s. The corresponding tone frequency associated with the selected delay sounded repeatedly until mice made an explicit decision to enter a separate wait zone within the restaurant. If mice chose to enter the wait zone, tones descended stepwise with decreasing pitch counting down progress toward obtaining the reward. Alternatively, in the offer zone, mice could choose to skip the wait zone and instead advance down the hallway to the next restaurant, as mice were required to encounter restaurants serially.

Thresholds of willingness to wait were calculated in each restaurant by fitting whether mice earned rewards to a sigmoid as a function of cued offer cost and identifying the inflection point of each curve (Fig. 1C). This metric reflects the cost of an offer below which mice typically earn and above which mice typically forgo. Thus, the value

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of an offer on a given trial can be calculated by subtracting the delay from one’s threshold derived from that day’s session. This allows offers across mice with individual differences in subjective flavor preferences and across days to be normalized to one’s own indifference point. Economic violations on this task were defined here as atypical choices that violate one’s own stable decision policies. Skipping an offer below threshold (offer value > 0) constitutes what we define here as “economic violation type I” and captures the events investigated by Steiner and Redish (5) (Fig. 1D). Accepting an offer above threshold (offer value < 0) constitutes what we define here as “economic violation type II” and captures the events investigated by Sweis et al. (7) (Fig. 1E). Because time is a limited commodity on this task, decisions are interdependent across trials. Thus, sensitivity to the consequences of having made these distinct types of economic violations were analyzed on the subsequent trial using the behavioral readout previously published: bias to accept a low-value offer on the subsequent trial (Fig. 1, D and E) (5, 7). This metric captures how mistake history can bias individuals to subsequently make atypical or compensatory reward-seeking decisions. To test whether distinct regret-related computations are independently manipulable, we examined these behaviors in mice following one of two experimental procedures: (i) following CSDS or (ii) following brain region–specific molecular manipulations.

**Fig. 1. Restaurant Row task.** (A) Task schematic. Mice had 60 min to forage for their only food for the day by making serial decisions in each uniquely flavored restaurant. Reward delays were randomly selected from a range of 1 to 30 s and signaled by the pitch of a tone. Trials ended if mice skipped in the offer zone, quit during the tone countdown in the wait zone, or earned a pellet before being required to advance to the next restaurant. (B) Pellets earned in each restaurant determine daily flavor rankings. Example session from a single mouse. (C) Economic thresholds of willingness to wait were calculated by fitting a logistic regression to whether food was earned as a function of cued offer cost and identifying the inflection point of each curve. Example session from a single mouse. (D and E) Two types of economic violations in the offer zone are defined by atypical decisions to skip a high-value offer (D) (type I) or enter a low-value offer (E) (type II). Both types of violations have been previously demonstrated to bias animals to make compensatory decisions on subsequent low-value trials relative to nonviolation decisions—a behavioral readout of sensitivity to regret-related processes.

**Chronic social defeat stress**

In the first cohort of mice, we subjected animals to the CSDS protocol that effectively distinguishes between stress-susceptible (SUS) and stress-resilient (RES) animals—based on a simple behavioral screening test—alongside nonstressed controls (CON; Fig. 2A) (18). C57BL/6J mice were exposed to aggressive CD-1 male mice daily for 10 consecutive days. Animals were allowed to physically interact for approximately 5 min before being separated by a mesh partition. They then remained cohoused for the rest of the day to allow for continuous sensory interaction before repeating defeat with a different CD-1 mouse. Following the final defeat, C57BL/6J mice were tested in a rapid social interaction screening assay measuring approach versus avoidance behavior toward an unfamiliar CD-1 mouse. Social avoidance induced by this protocol defines SUS mice (Fig. 2B) (18). CON and RES mice on the other hand typically approach the unfamiliar CD-1 mouse during the social interaction screen. This approach versus avoidance dichotomy thereby subdivides defeated mice into RES (i.e., CON-like) versus SUS groups, respectively, and is consistent with
Previous reports using this rapid social interaction screen–based categorization of RES and SUS to predict depressive-like behaviors on several other rapid tests (12, 18).

Following this protocol, all mice were food-restricted for 3 days to approximately 80% body weight and trained on the Restaurant Row task. All mice acquired the basic structure of the task. Mice were well trained until their performance stabilized across several behavioral metrics, including body weight, laps run, and pellets earned. Defeat had no immediately observable effects on overt locomotor or feeding behavior (Fig. 2C). SUS, RES, and CON mice ran an equivalent number of laps and earned the same amount of food, remaining stable at similar body weights. All mice learned to reliably discriminate tones by accepting high-value offers and rejecting low-value offers (Fig. 2D and fig. S1C). Because mice also treated the same tones differently in each restaurant indicates that animals understood the economic structure of the task. That is, mice made informed economical decisions that integrate delay information communicated via auditory cues with flavor information communicated by visuospatial cues to forage effectively while also prioritizing subjective preferences. Mice readily revealed subjective flavor preferences whose ordinal rankings among the four flavors—as indicated by thresholds of willingness to wait (fig. S1A) and by the ability to acquire the structure of the task (fig. S1C)—were matched across SUS, RES, and CON mice.

**Distinct types of economic violations affect future choices**

Next, we examined how each type of economic violation influenced subsequent decisions on this task. The effect of choice history on future decisions is the key behavioral end point in this study. Economic violation type I is defined by situations in which mice skip a positively valued offer (offer below one’s threshold). Scenarios in which mice not only make this decision but then immediately encounter on the next trial a subsequent offer that is negatively valued (offer above one’s threshold) have been previously used to elicit neural representations of counterfactual outcomes and bias future choices (Fig. 3A) (5). This critical distinction separates a mere mistake or atypical choice from one that may be specifically linked to a regret-related process. Thus, this sequence operationalizes an economically disadvantageous skip decision in a foraging task that results in a poor outcome and is highlighted by a missed opportunity when information is provided on the second trial. To simplify the labeling of these trials, we will refer to the first trial, the trial on which the violation occurred, as “trial t-1.” To quantify how mistake history on trial t-1 might bias mice to subsequently make atypical decisions, we calculated the probability of accepting the negative offer on the second trial, offers animals would typically reject. We call this trial, the trial following the violation, the “readout trial.” These specific sequences were not constructed a priori or built into the task design but rather extracted post hoc from an animal’s natural encounters while foraging among random offers that were uniformly distributed. The bias toward or probability of accepting offers on the readout trial is determined by dividing the number of enter choices on this trial by the total number of offers presented on this trial given that the following contingencies are true: (i) the offer on trial t-1 was positively valued, (ii) the choice on trial t-1 was a skip decision, and (iii) the offer on the readout trial was negatively valued (see fig. S2 for visual explanation).
Unexpectedly, in the present study, we found that this is a property unique to SUS mice but not CON or RES mice (Fig. 3B and fig. S3A). The ability to detect this effect required fully leveraging the economic complexity of Restaurant Row separating the value space across the three primary dimensions of the task: offer value, restaurant identity, and choice history. Furthermore, violation rates on trial t-1 were not different between restaurants or groups of mice (fig. S1B), indicating that behavioral differences were not due to frequency of scenarios encountered or willingness to “underspend” on trial t-1, but rather reflect how animals weigh choice history differently during subsequent decisions. The fact that type I regret measured in rats by Steiner and Redish (5) tracks only with SUS mice here suggests that attention should be paid to animals who may have baseline elevated levels of stress either as a result of a species or strain difference or as a result of stressful laboratory experiences such as maintaining chronically implanted tetrodes as used in their study.

Economic violation type II is defined by situations in which mice enter a negatively valued offer (offer above one’s threshold) on trial t-1. Similar to the above analysis, we calculated the probability of accepting a negatively valued offer on the readout trial following this type of violation (Fig. 3C). Thus, the bias toward or probability of accepting offers on the readout trial is determined by dividing the number of enter choices on this trial by the total number of offers presented on this trial given that (i) the offer on trial t-1 was negatively valued, (ii) the choice on trial t-1 was an enter decision, and (iii) the offer on the readout trial was negatively valued. Here, the nonviolation decision on trial t-1 would have been to skip such trials instead and thus serves as the control sequence to compare how choice history in this economic scenario can influence subsequent decisions. We found that mice displayed an increase in the probability of entering negatively valued offers on the readout trial following...
mid-journey in the offer zone, suggesting that VTE incorporates a skip decisions chiefly comprise near-enter trajectories that are rerouted choice point. On the basis of the initial heading direction of skip paths, low VTE events that are typified by ballistic journeys through the hesitation (32), suggesting that offer-skipping behaviors on this task invoke more thinking (28). Restaurant Row task shows signs of planning and episodic future (during VTE) and in humans tested on translated versions of the IdPhi was made as in angle,

dx and dy. From these vectors, we calculated the instantaneous change in angle, Phi, as dPhi that is then integrated over the pass through the offer zone from offer onset until either a skip or enter decision was made as IdPhi. Neural activity in the offer zone in rodents (during VTE) and in humans tested on translated versions of the Restaurant Row task shows signs of planning and episodic future thinking (28–31).

We found that VTE was significantly higher for skip decisions than enter decisions (Fig. 4, A and B), consistent with previous reports suggesting that offer-skipping behaviors on this task invoke more hesitation (7, 32). Conversely, enter decisions instead are generally low VTE events that are typified by ballistic journeys through the choice point. On the basis of the initial heading direction of skip paths, skip decisions chiefly comprise near-enter trajectories that are rerouted mid-journey in the offer zone, suggesting that VTE incorporates a delayed valuation to override prepotent or habit-like offer-taking responses on this task. As a function of offer value, VTE generally displays an inverted U-shaped curve with a left-shifted peak such that negatively valued offers just above one’s thresholds elicit the most VTE (Fig. 4C). This suggests that the most difficult to process decisions are for offers that are just more expensive than one is willing to wait, consistent with previous reports (7, 32). The probability of appropriately skipping negatively valued offers increases as a function of the amount of VTE displayed in the offer zone (Fig. 4D). This indicates that the outcome of such a deliberative process is more likely to result in an economically advantageous decision the more an animal engages in VTE. Furthermore, the amount of VTE required to reliably skip negatively valued offers is higher in more preferred restaurants (Fig. 4D). Together, these data indicate that choices in the offer zone can use a flexible decision-making process that integrates conflict between expensive, though desirable, rewards. These data also indicate that a failure to engage in VTE—what we term “snap judgments”—can contribute to type II violations, unlike type I violations that follow from high VTE events. Unexpectedly, SUS mice displayed less of an inverted U-shaped VTE curve with higher VTE when encountering positively valued offers compared to RES and CON mice (Fig. 4C). In addition, RES mice displayed less VTE when encountering negatively valued offers and required less VTE to skip negatively valued offers compared to SUS and CON mice (Fig. 4, C and D). These findings suggest that SUS and RES mice may be attending to or integrating information throughout their offer zone decision process differentially depending on the value of the offer, which could differentially affect the weight each type of economic violation carries into future choices.

Next, we examined how mice executed decisions in the wait zone on trial t-1 to better understand the behavioral sequela following economic violation type II: accepting negatively valued offers. In the wait zone, mice were tasked with remaining near the feeding site during the tone countdown after making an enter decision to earn a reward but were free to quit at any moment. We found that the vast majority of quits occurred following enter decisions for negatively valued offers (Fig. 5A). Furthermore, we found that the point at which mice quit negatively valued offers occurred most frequently with an amount of time remaining in the countdown that was above one’s threshold (Fig. 5A). That is, the value of the time left required to obtain the reward of a negatively valued offer, too, was likely still negative at the time of quitting. This indicates that many type II violations in the offer zone resulted in wait zone quit decisions and that most of these quit decisions in the wait zone were economically advantageous choices that effectively corrected offer zone violations—decisions that were the product of a failure to engage in VTE. This allows us to confidently label enter decisions for negatively valued offers as “mistakes.” Consistent with previous reports, these data highlight how reevaluating recent mistakes via change-of-mind decisions following ballistic events can contribute to post-decisional regret (3, 7, 21, 22, 33–35). This is in part because the initial choice was an error of one’s agency and because the counterfactual alternative (“should have skipped first”) is mapped onto the action that is ultimately selected following this correction (7, 20–24). SUS, RES, and CON mice all executed quit decisions in this manner and to similar degrees (Fig. 5B), suggesting that not overall quit frequency but rather how animals weigh the value of choice history following these violations is altered. Previous reports have shown that a closer examination of the quitting process can reveal hidden costs during.
change-of-mind decisions and could shed light on how animals may be differently valuing future reward-seeking behavior following type II violations (22, 36).

Following economic violation type II—atypically accepting a low-value offer—one is faced with the dilemma to change one’s mind during continued investment. This is related to a well-studied cognitive bias known as the sunk cost fallacy (36). This describes the phenomenon during which irrecoverable losses that should be ignored can escalate the commitment of an ongoing endeavor, and is thought to generate cognitive dissonance on some level (36–38). In the present task, quit decisions capture the continuous reevaluation of an ongoing investment paid toward earning a reward. We developed a dynamic analysis capable of extracting the hidden effects of time already spent in the wait zone, or sunk costs, on the likelihood of quitting—a phenomenon that has been previously published in rodents and humans tested on translated versions of the Restaurant Row task (36). This analysis separates the time already waited during a given countdown in the wait zone from future time left required to obtain a reward on that trial and measures how these two dimensions of time independently augment the value that promotes staying in the wait zone. Each quit trial was parsed into bins of [time spent, time left] pairs at the moment of quitting from which many permutations arise based on various starting offers (fig. S6A). The probability of earning a reward in the wait zone was dynamically calculated along a continuum using a sliding window survival analysis as both a function of time left in the countdown and time already waited (Fig. 5C).

Consistent with previous reports across species, we found that time already waited (resources spent that should be ignored) increases the likelihood of continuing to wait to earn a reward independent of the temporal distance to the goal (Fig. 5, C to E) (36). In addition, the more time that was already waited, the stronger this effect, a critical tenant of the sunk cost phenomenon (Fig. 5, C to E). This effect is driven by time spent waiting only after accepting negatively valued offers compared to equivalent time spent waiting after accepting positively valued offers (Fig. 5C). This means that the escalation of commitment due to sunk costs drove mice to earn rewards that, economically speaking, should have been quit, consistent with the classic notion that sunk costs can drive suboptimal behavior. While all mice were sensitive to the effects of time already waited on the value of staying, unexpectedly, this phenomenon was much more robust in RES compared to SUS or CON mice (Fig. 5E). Neither the amount of time spent in a restaurant’s offer zone before making type II violations nor time spent since the last reward was earned influenced the likelihood of waiting once in the wait zone for all mice (fig. S6, B to D). These data indicate that the time spent considering quitting negatively valued offers, the same trials that contribute to sensitivity to type II regret, carries additional weight that is uniquely enhanced in RES mice. Together, these data suggest that how type I and type II violations influence future decisions for SUS, RES, and CON mice may be linked to valuation differences in the decision-making processes of the mistakes themselves.

**Brain region–specific role of CREB in mediating sensitivity to distinct types of regret**

We demonstrated that different operational definitions of regret as described by Steiner and Redish (5) and Sweis et al. (7) do not always covary but, rather, following a social stress manipulation, are separable in a manner that may be clinically relevant. Next, we aimed to better understand the neurobiology underlying susceptibility to stress and its link to regret-related computational processes. To date, there
are no studies linking molecular neuroscience at the level of gene regulation to neuroeconomics. We therefore focused our studies on CREB, a well-characterized transcription factor extensively implicated in mediating chronic stress action (11). CREB function has been shown to promote, in opposing directions, stress susceptibility versus stress resilience when studied in either the NAc or mPFC, respectively. These regions are critically important for value-based decision-making, and have been shown to be engaged by the Restaurant Row task in both rodents and humans, and have been shown to be involved in some of the decision processes related to type I and type II economic violations (5, 28–30). To date, most behavioral studies investigating CREB function have been performed on relatively simple screening assays, with little focus on decision-making.

To establish a role for CREB in mediating such complex decision-making processes, we molecularly profiled CREB activation in the NAc and mPFC. Despite the extensive literature on CREB and stress, CREB activation in the NAc and mPFC following social defeat stress has never been directly associated with social interaction score–based behavioral definitions of SUS and RES mice. CREB activation can be measured by quantifying expression levels of phosphorylated CREB (pCREB), its active form. Western blot analyses revealed a significant increase in pCREB in the NAc of SUS mice and a decrease in the mPFC of RES mice (fig. S7, A to C). These data reflect a region-specific double dissociation role of CREB activation that is linked to unique stress-related phenotypes. Next, to better link CREB function with stress-related phenotypes of sensitivity to regret, we investigated expression levels of CREB-targeted genes in the NAc and mPFC from animals tested on the Restaurant Row task. Quantitative polymerase chain reaction (qPCR) analysis of a cluster of genes that are known to be targeted by CREB (including the Creb1 gene...
itself, as well as *Fos* and *Zfp189* in the NAc and mPFC of mice tested on Restaurant Row was performed. We found that the expression levels of this cluster of genes correlated with each other within each brain region but not between brain regions (fig. S7, D to F). We also found that individual differences in gene cluster expression levels in the NAc, but not mPFC, correlated positively with individual differences in sensitivity to regret type I, while gene cluster expression in mPFC (but not NAc) correlated with regret type II (fig. S7, G to L). Together, our data suggest differential CREB activation in two models with behavioral phenotypes associated with increased sensitivity to type I and type II regret.

To test causality, we next perturbed CREB function in the NAc or mPFC. Here, we inhibited CREB function in NAc or mPFC neurons via adeno-associated virus 2 (AAV2)–mediated overexpression of a dominant negative CREB mutant (mCREB; fig. S8) in stress-naïve mice and then trained these animals in Restaurant Row (fig. 6A and figs. S1, D to F, and S9). Control animals were transfected with a green fluorescent protein (GFP)–only virus in either region. The rationale

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**Fig. 6.** CREB function in the mPFC and NAc differentially influences sensitivity to distinct types of economic violations with associated changes in offer zone VTE and wait zone sunk cost behavior. (A) Mice were transfected in mPFC (*n* = 10) or NAc (*n* = 10) with a neurotropic adeno-associated virus (AAV2) encoding either GFP (*n* = 20) or a dominant-negative mutant form of CREB (CREBS133A; mCREB). Representative image taken from sectioned NAc tissue. See fig. S8 for targeting. (B) Pretask percentage baseline body weight (top) (ANOVA: *F*₂,₃₁ = 12.169, *P* < 0.0001). Dots represent individual animals. Error bars ± 1 SEM. (C) Probability of offer zone choice by restaurant. (D to G) Sequence schematics (D and F) and decision bias on the readout trial (E and G) as described in Fig. 3 for type I (D and E) and II (F and G) economic violations with respective nonviolation control sequences. See fig. S2 for a visual explanation of this analysis. See fig. S3 (C and D) for quantification of the difference score in the decision bias on the readout trial between violation and nonviolation sequences. (H) VTE behavior as a function of offer value. Vertical dashed lines indicate threshold of willingness to wait. AIC weights: NAc, linear: 4.102 × 10⁻²⁴, quadratic: 0.999; mPFC, linear: 2.855 × 10⁻¹⁹, quadratic: 0.999; GFP, linear: 2.155 × 10⁻⁹, quadratic: 0.999. NAc mice displayed an increase in the amount of VTE required to skip at least 50% of trials, while *V*_off < 0 (VTE cutoff, inset) split by preferences (*F*₂,₃₉ = 12.169, *P* < 0.0001). (I) Relative proportion of quit types across the three categories represented by icon (top) defined in Fig. 5A split by groups of mice. All quit trials (left, pie) versus relative to each restaurant (right, bars) ranked from least preferred to most preferred flavors from left to right. (J) Sensitivity to sunk costs as described in Fig. 5E (*F*₂,₃₉ = 30.249, *P* < 0.0001). Dots represent individual animals. Error bars ± 1 SEM.
for choosing this manipulation approach is threefold: (i) We found differential pCREB levels in the NAc and mPFC from SUS and RES mice (fig. S7), (ii) viral-mediated mCREB expression in the NAc has been previously used to experimentally promote RES versus SUS phenotypes on simple behavioral assays such that this approach is rooted in an expansive understanding of the molecular biology of chronic stress action, and (iii) alternative methods to manipulate these brain regions, for instance, via lesion procedures, would likely involve gross behavioral impairments. Inhibitory designer receptors exclusively activated by designer drugs (DREADDs) in the mPFC of rodents tested on Restaurant Row significantly altered animal travel speed, consumption speed, willingness to wait for a reward, and reinforcement rate (30, 31). These confounds would significantly shift multiple factors influencing one’s value estimates of the environment and would severely limit the ability to make interpretations regarding regret-related behavioral processes that require a much more delicate preservation of multiple behavioral controls. In the present study, following viral transfection surgeries, mice were allowed to recover and then were food-restricted for 3 days to approximately 80% body weight before being trained on the Restaurant Row task. The trained mice ran an equivalent number of laps and earned the same amount of food while maintaining stable and similar body weights (Fig. 6B). All mice were capable of reliably discriminating tones as a function of cued offer cost and revealed subjective flavor preferences whose ordinal rankings among the four restaurants were matched across groups (Fig. 6C and fig. S1, D and F).

We found that, compared to GFP controls, expression of mCREB in the mPFC or NAc increased sensitivity to type I economic violations (Fig. 6, D and E, and fig. S3C): Following skip decisions for positively valued offers (violation) compared to enter decisions for similar offers (nonviolation) on trial t-1, these animals displayed an increased likelihood of accepting negatively valued offers on the readout trial. These data suggest that normal CREB function in either region is required to suppress regret-related processes associated with this type of economic violation. Compared to GFP controls, we also found that expression of mCREB in the mPFC increased sensitivity to type II economic violations (Fig. 6, F and G, and fig. S3D): Following enter decisions for negatively valued offers (violation) compared to skip decisions for similar offers (nonviolation) on trial t-1, these animals displayed an increased likelihood of accepting negatively valued offers on the readout trial. In contrast, expression of mCREB in the NAc decreased sensitivity to type II economic violations. Groups did not differ in their frequency of type I or type II violations (fig. S1E) or if a positively valued offer was instead presented on the readout trial (fig. S5, E to H). These data reveal that sensitivity to different types of economic violations are capable of being modulated independently depending on the brain region perturbed and rather than share a generalized basis for mistake appraisal capture separable, fundamentally distinct action-specific computational processes.

When examining how mice executed decisions on trial t-1, we found that mCREB expression caused several changes in both offer zone and wait zone behaviors. In the offer zone, all mice displayed an inverted U-shaped curve of VTE behavior as a function of offer value (Fig. 6H). However, compared to GFP controls, mCREB expression in either the mPFC or NAc decreased the amount of VTE mice displayed for positively valued offers. mCREB expression bidirectionally altered VTE for negatively valued offers in the mPFC versus NAc. mCREB expression in the mPFC decreased VTE for negatively valued offers, consistent with previous reports whereby chemogenetic disruption of mPFC activity can decrease VTE, decouple mPFC and hippocampus interactions, and indirectly alter hippocampal sequences, causing animals to become more decisive (30, 31, 39). Conversely, mCREB expression in the NAc increased VTE. In addition, NAc-treated animals required a higher amount of VTE to appropriately skip negatively valued offers. Overall, the brain region–specific effects of mCREB expression on VTE resulted in asymmetric changes in the offer zone depending on the value of the offer presented [i.e., (i) shared direction of change for positively valued offers (covarying with changes in regret type I) versus (ii) opposing direction of change for negatively valued offers (covarying with changes in regret type II)]. In the wait zone, all mice engaged in change-of-mind decisions most frequently following enter choices for negatively valued offers and when the value of the amount of time left in the countdown was still negative (Fig. 6I). In addition, all mice were sensitive to how the amount of time already spent waiting for a reward, or sunk costs, increased the likelihood of staying in the wait zone independent of temporal distance to the goal (Fig. 6I). However, mCREB expression bidirectionally altered sensitivity to sunk costs. mCREB expression in the mPFC increased sensitivity, consistent with previous reports demonstrating that mPFC disruption can increase sunk costs (29). Conversely, mCREB expression in the NAc decreased sensitivity to sunk costs. The opposing direction of these changes between mPFC and NAc mCREB treatment in wait zone sunk cost behavior is aligned with the opposing direction of changes in offer zone VTE behavior for negatively valued offers as well as sensitivity to the effect of type II violations on subsequent trials. This is in contrast to the shared direction of changes in VTE behavior for positively valued offers and sensitivity to the effect of type I violations on subsequent trials following mCREB treatment in either the mPFC or NAc. Groups did not differ in the way they valued other time spent on this task (fig. S9). These data suggest that there are dissociable, region-specific changes in decision processes linked to CREB function that are value dependent and augment the way in which attention, value, planning, and decisiveness may evolve throughout the choice process to affect future decisions. These findings shed light on different computational processes that may be at play in SUS and RES mice (29, 40-43).

Much of the existing literature examining CREB function involves a combination of CREB manipulation and some sort of stressor (11). Thus, we next aimed to characterize not only what role region-specific basal CREB function plays in regret-related processes of stress-naïve mice but also how altered CREB function affects the way in which future stress precipitates changes in regret sensitivity. To test this, we exposed mCREB-treated mice trained on the Restaurant Row task to a subthreshold (“micro”) social defeat stress protocol (i.e., 1 day of defeat exposure) typically used to reveal heightened sensitivity to stress-related effects. Following this micro-defeat experience, mice were subsequently tested again on Restaurant Row for 1 day. We found that subthreshold social defeat caused a change in regret-related behavior only in mCREB-expressing compared to GFP-expressing control mice (fig. S10). When mCREB was targeted to the NAc, stress induced a pro-resilient regret profile (i.e., decrease in type I sensitivity and increase in type II sensitivity), whereas when mCREB was targeted to the mPFC, stress induced a pro-susceptible regret profile (fig. S10). These findings are consistent with known literature on CREB manipulations and stress responses, albeit on tests of much simpler behaviors (15). These data reveal how a pro-resilient phenotype can be unmasked by a subthreshold defeat. Typically, a subthreshold defeat protocol is intended to reveal heightened susceptibility.
to stress, not stress resilience. Rather, we show here how more nuanced behavioral approaches can reveal unique behavioral phenotypes in individuals whose stress response profiles may be part of underlying computational traits specific to resilient individuals. Together, these data provide a rich neuroeconomic framework to dissect differential region-specific roles of CREB in regulating complex decision-making computations across the mPFC and NAc that suggest a link between the value-based processing of offer zone and wait zone choices to sensitivity to distinct types of economic violations on future choices.

Modeling the economic utility of sensitivity to distinct violations
To better understand the contribution of sensitivity to distinct economic violations on the overall ability of the individual to forage effectively for rewards, we generated a computer model of the Restaurant Row task that could accurately simulate mouse performance (Fig. 7, A and B, and fig. S11, A and B). Because the Restaurant Row task involves multiple, complex interacting decision steps, it can be hard to predict how one decision variable affects the way animals forage throughout the rest of the session. By considering each animal’s average decision speed, travel speed, reward consumption speed, and thresholds reflecting subjective flavor preferences, we could reliably simulate sessions of the task after presenting randomly generated sequences of offers. Thus, this Restaurant Row simulation offers the ability to systematically manipulate key decision variables and observe their downstream effects on performance outcome measures such as total number of end-of-session rewards earned. This simulation incorporated two regret terms called “type I bias” and “type II bias” that carried added value promoting the acceptance of negatively valued offers during subsequent decisions following each type of economic violation. This regret term alters not the frequency with which mice make economic violations but rather to what degree violations influence the subsequent trial. These two regret terms, as well as violation rates, were systematically varied and revealed complex interactions influencing the relative number of total rewards earned (Fig. 7C and fig. S11, C to G). We found that increasing sensitivity to type I bias resulted in an overall relative decrease in the number of rewards earned on this task simulation (Fig. 7C). This was true across several variations of threshold violation rates (fig. S11C), even if violation rates were different in each restaurant (fig. S11D). Increasing sensitivity to type II bias affected earning potential to a much lesser degree (Fig. 7C and fig. S11, C and D).

We next examined at a deeper level whether differences in regret terms among each restaurant could result in relative changes in flavor-specific reward earnings. We set sensitivity to each type of regret separated by either the least preferred (LP) or most preferred (MP) restaurants to match the profiles of CON, SUS, and RES mice (Fig. 7D and fig. S11, E to G). These simulations were compared against 1000 shuffled control simulations that randomized the bias weight assignment from 0 to 1 across both types of regret and the different restaurants (fig. S11, E and F). Sensitivity to type II bias in the LP restaurant, reminiscent of CON, RES, and GFP-only–treated mice, resulted in no net change in reward intake in either LP or MP restaurants (Fig. 7D and fig. S11G). Conversely, sensitivity to type I bias in the MP restaurant—the economic phenotype reminiscent of SUS and NAc-mCREB–treated mice—resulted in the greatest change in reward intake (Fig. 7D and fig. S11G). Furthermore, this economic phenotype resulted in a net positive gain in reward intake for LP flavors and a net negative loss in reward intake for MP flavors. These data suggest that distinct regret-related processes may have different downstream consequences on net foraging behavior. These data also suggest that the pattern of how mistake history of SUS mice influences future decisions that may contribute to a redistribution of reward value shifted away from preferred rewards.

DISCUSSION
The way an individual experiences regret may be altered in stress-related disorders such as depression (8). However, this is often described clinically using plain language that, without attention to neuroeconomic principles, may miss fundamentally distinct computations derived from separable brain functions (8, 10). Here, we reveal two dissociable forms of regret-related behaviors in mice that are differentially associated with unique stress response traits and with CREB function across two brain regions (Fig. 8). Our findings suggest that the ability to appraise one’s own mistakes is composed of multiple processes that can be altered independently. These data have important implications for better understanding how different behavioral responses to poor decisions may be linked to adaptive versus maladaptive responses to stress.

This study extended upon Steiner and Redish (5) and Sweis et al. (7) by looking at discrete action selection processes involved in distinct economic violations compared to what an individual could have done differently (i.e., counterfactual outcome). Two dimensions along which to classify a counterfactual outcome include (i) direction and (ii) operation (44, 45). The direction of a counterfactual outcome may be either upward or downward. An upward counterfactual comprises one that would have been better than the actual outcome, whereas a downward counterfactual comprises one that would have been worse than the actual outcome. Regret stems from unselected actions that derive from upward counterfactuals and is what separates regret from simpler outcome evaluation or reward prediction error processes. The operation of a counterfactual outcome may be either additive or subtractive (44, 45). An additive counterfactual describes the unselected option that an individual recognizes is something one could have acted upon and added to reality but did not. Conversely, a subtractive counterfactual describes the unselected option that an individual recognizes is something one could have forgone and subtracted from reality but instead was chosen. In this study, economic violation type I would most likely evoke representations of an additive counterfactual, while violation type II would most likely evoke representations of a subtractive counterfactual. While this is just one interpretation of the computations at play, it is nonetheless a useful framework for describing the distinctions between subcategories of regret and for making explicit predictions of the neural representations underlying different forms of counterfactual thinking.

Several examples of neural representations of counterfactual processing have been previously demonstrated across species. In humans, activation in mPFC correlates with negative discrepancies between actual and counterfactual outcomes on gambling tasks and with self-report of the experience of regret only when information is provided about the outcome of unselected actions (46). Patients with damage to these brain regions reveal an inability to process and consider anticipated regret during decision-making (47). In nonhuman primates, PFC neurons can encode hypothetical outcomes and reward signals that contribute to fictive learning with sustained changes in activity, which lead into subsequent decisions depending on whether
information about the optimal choice is provided to the animal (3, 48). More recently, PFC and striatal neurons in nonhuman primates have been shown to encode the value of counterfactual outcomes of unselected actions when presented with the opportunity to select one of two reward offers presented serially regardless whether the first or second of these two options were selected (49, 50). Other PFC regions, including orbitofrontal cortex and anterior cingulate cortex, as well as subthalamic nucleus have also been implicated in representing counterfactual outcomes and multiple forms of error monitoring during executive functioning, including neurons tuned to post-error choices that may augment attention, previous outcome appraisal, or the value of upcoming opportunities (3, 46, 47, 51, 52). Both the orbitofrontal cortex and NAc recorded in rodents tested on Restaurant Row encode additive counterfactuals of missed opportunities from trial t-1 during regret type I sequences (4, 5), but little is known about change-of-mind representations during regret type II sequences. While such studies have begun to lay the foundation for how counterfactuals may be encoded in the brain and how they depend on access to information about the outcome of one’s actions, the neural underpinnings of both the direction and multiple operations of regret-related processes and how this could map on to individual stress-response traits have not yet been explored before the present study. Reward prediction error signals seen in depressed patients can be dissociated from other mood symptoms (53), and thus, how individuals with stress-related disorders monitor and understand errors of one’s own agency during counterfactual thinking may be multifactorial.

Reward- and stress-related phenotypes of SUS and RES mice have been well-characterized across several simple behavioral screening tests (18). We found that endogenous CREB activation levels in the NAc versus mPFC bidirectionally maps onto the social interaction profiles of SUS and RES mice and could explain individual stress-related differences in sensitivity to distinct types of regret. We also found unique alterations in regret sensitivity before and after exposure to stress in CREB-manipulated mice. This wealth of complex decision-making behavioral data can help guide often counterintuitive
and conflicting findings in the stress literature that, to date, is based largely on rapid behavioral end points. Stress-induced increases in NAc CREB activity are known to increase neuronal excitability in this region (54) and drive depressive-like behaviors (16, 17, 55), while mPFC CREB activity protects against stress-induced depressive-like behaviors, in both rodents and postmortem mPFC tissue harvested from depressed humans (13). Furthermore, experimentally decreasing CREB function in either region decreases local neuronal excitability and induces opposite behavioral profiles in simple assays (11, 14, 15, 54, 55). Thus, it would appear that CREB function across these two regions has a similar, though inverted, role along a singular, shared behavioral axis (11). Our data argue that this simplified picture is far more complex in reality, with multiple dimensions rooted in decision-making information processing that are either undetectable or markedly reduced when using simple tasks. Because animals may use different circuits to achieve seemingly similar computations when tested on simple tasks, previous studies may have been unable to attribute which computations unique to a given brain region might be differentially perturbed in these mice (56). For example, knocking down CREB in the NAc is known to promote stress-resilient phenotypes on social interaction—and other simple reward-based tasks but can paradoxically increase anxiety-like behavior in these animals with little computational explanation as to how this might occur (14, 15, 54). We find that the neuroeconomic profile of RES mice is much more computationally complex, where future choices are hypersensitive to only certain types of economic violations but not others. This framework reveals a region-specific role for CREB in regulating distinct aspects of decision-making information processing both at baseline and following stress. We found that mCREB NAc treatment in stress-naive mice enhances type I regret and blunts type II regret, but following stress shifts animals toward the regret profile of RES mice. These data highlight how stress exposure interacts with underlying molecular function to switch the computational processes of a given brain region, contributing to one’s stress response traits. These changes could be influencing why RES mice approach unfamiliar CD-1 target animals during the social interaction test following CSDS, given their increased propensity toward repeating previous low-value actions on the Restaurant Row task. These decisions on the one hand may appear maladaptive in the face of potential threat. On the other hand, such valuations may facilitate increased willingness to engage with potentially rewarding stimuli over that of SUS mice, whether appetitive or social, so as not to generalize avoidance or miss out on future rewards, even if costly and despite past experiences.

Although SUS and RES phenotypes on simple screening tests are generally considered to be maladaptive and adaptive stress response traits, respectively (57–59), it remains unclear whether sensitivity to regret type I or type II comprises maladaptive versus adaptive decision-making processes themselves. Using an economic model of the task, we found that the regret-related phenotype unique to SUS mice produced the greatest change in food intake. This change did not result in less overall food earned but rather a redistribution of yield shifted away from most preferred flavors and toward least preferred flavors that may suggest a more nuanced manifestation of anhedonia-related behavioral changes in SUS mice. We found that individual differences in sensitivity to type I versus type II regret both correlate but in opposing directions with social interaction score, which is known to covary with many stress-related phenotypes (18). We also found that regret sensitivity, agnostic of social interaction score, was capable of revealing distinct clusters of animals that, on the one hand, nicely recapitulate canonical social interaction–based definitions of CON and SUS groups, while on the other hand only partially recapitulate the RES group. Therefore, future animal studies should compare whether individual differences in sensitivity to each type of regret can predict other complex reward- and affect-related processes as well as add more complex dimensions of behavior with which to stratify subgroups of individuals that would otherwise be classified together. Furthermore, whether each type of regret differentially affects emotional burden in an adaptive or maladaptive

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**Fig. 8. Summary schematic of sensitivity to distinct types of economic violations.** Two types of economic violations in the offer zone are defined by atypical decisions to skip a high-value offer (left) (type I) or enter a low-value offer (right) (type II). Both types of violations can bias animals to make compensatory decisions on subsequent trials relative to nonviolation decisions—a behavioral readout of sensitivity to regret-related processes. Nondefeated and GFP control mice display type II sensitivity only. Stress-resilient mice display enhanced sensitivity to type II regret over that of controls. Stress-susceptible and NAc-CREB knockdown mice display a loss of function in type II regret with a unique gain of function in type I regret. mPFC-CREB knockdown mice display a mixed phenotype, with enhanced sensitivity to both types of regret. Sensitivity to regret in stress-naive NAc-CREB and mPFC-CREB knockdown mice shifts toward pro-resilient and pro-susceptible regret profiles, respectively, following subsequent exposures to stress (fig. S10). How regret-related experiences transform into behavioral consequences following different types of economic violations does not share a common computational basis for generalized mistake appraisal but instead is made up of multiple action-specific processes that can be altered independently.
way is more difficult to address here and may be unrelated to food intake altogether. Because this task has been translated for use in humans, correlating regret- and risk-related sensitivity to distinct personality traits (28, 36, 60–62), and assessing emotional states immediately after each decision step in relation to mistake processing and overall emotional toll, would be useful in better approximating individual differences in these neuroeconomic constructs across species and in unique patient populations (63).

Notably, we report here two unique categories of behavioral differences following CSDS where (i) all three groups of animals (RES, SUS, and CON) differ from one another (i.e., sensitivity to type II regret) and (ii) a behavioral profile that is exclusive to RES mice (i.e., sensitivity to sunk costs). Sensitivity to sunk costs in particular has historically been thought to be a suboptimal decision-making bias, which brings into question why such a phenomenon has been conserved across evolution (36, 64–66). A rational agent, in theory, should ignore sunk costs when making economic decisions. Economic stress, budget constraints, and limited reward availability can drive individuals to make suboptimal choices, for example, in the form of overly perseverative behaviors that can reallocate finite resources sometimes with diminishing returns (38, 67). Sensitivity to sunk costs is known to be heightened under such circumstances (36, 37). However, it has been postulated that sensitivity to sunk costs may have hidden utility (36). For instance, valuations calculated from predictions of future outcomes can be difficult and so basing decisions instead on past information may sometimes be a better predictor of future returns, which can serve as a useful heuristic when foraging (29, 38, 65, 66, 68). Alternatively, a sunk cost bias may emerge as a by-product of regret related to change-of-mind decisions, which we found was typified by an associated gain in regret type II in both RES mice and mCREB-treated animals in the mPFC, reduced by mCREB expression in the NAc. Chemogenetic disruption of mPFC activity has been shown to increase sensitivity to sunk costs in Restaurant Row concurrent with changes in neural ensembles that represent more local and less forward-oriented information (29–31). Optogenetically depotentiating mPFC outputs to the NAc can also decrease the frequency of change-of-mind decisions (39). Collectively, these data suggest that RES animals may have evolved circuit-specific processes that rely on sunk costs and change-of-mind–related regret to sharpen decisions and increase attention paid toward realized losses that may be more costly (69). It may also be possible that animals better suited to cope with stress-induced pathology, which also happen to engage decision valuations in this way even if unrelated to a stress response itself, may have indirectly contributed to why decision phenomena such as type II regret and sensitivity to sunk costs have been conserved across evolution (70, 71).

While this body of work represents a unique combination of elements from several different fields including stress models, molecular manipulations of transcription factors, and complex neuroeconomics, there are several limitations to this study. First, there are many different stress paradigms known to elicit heterogeneous responses in animals (72). Here, mice were only tested in the CSDS paradigm. Other stress protocols beyond social defeat, including chronic variable stress, early life stress, and chemical stress, should be explored in future studies. It is known that chronic stress induces sex-specific changes in the neurophysiology of brain regions critical for reward sensitivity and learning (73–75). Moreover, recent work carefully investigating covert decision strategies find that male and female animals diverge in how they learn complex tasks (76). Given the twofold greater prevalence of depression and other stress-related disorders in females (8), more work is needed to define how stress affects changes in their counterfactual processing. A common issue in stress-related research is understanding whether the neuroeconomic profiles of SUS and RES mice stem from a set of preexisting traits, are accentuated by stress, or are induced de novo following a stress exposure. How much one’s sensitivity to each type of regret may serve as a predictive tool for susceptibility versus resilience to stress is an interesting, though separate, question. Nonetheless, one piece of evidence suggesting that regret sensitivity is not a preexisting characteristic of stress-naïve animals is the fact that the presence of regret type I does not exist at baseline in nondefeated CON mice or GFP-only–treated mice. Baseline sensitivity to regret type II, on the other hand, in theory could be used in a future experiment to predict behaviors on a rapid social interaction screening test following defeat. In addition, future studies should investigate the degree to which these regret-related processes may be reversible in defeated animals either through CREB manipulations similar to those presented here or following other treatments, with classic antidepressant medications, for instance. Last, as is the case with all stress-related research, consideration of circadian rhythms and potential shifts in hypothalamic-pituitary-adrenal axis function should be kept in mind as these animals were tested during their light phase. These procedures were consistent with all previous studies using Restaurant Row and the vast majority of work with CSDS and CREB manipulations in stress models. Nonetheless, extensive measures have been taken to ensure that all conditions were counterbalanced across testing throughout the day. Last, although the role of CREB in mediating SUS and RES phenotypes as measured on simpler behavioral assays has been well studied at a mechanistic level, CREB function itself is influenced by many upstream effectors and exerts its downstream effects on numerous targets (77–79). Thus, it may be difficult to interpret precisely how the present CREB data specifically translate into stress-related changes in neural processing that drive the behavioral effects observed here.

Future experiments, together with in vivo physiology and an investigation of more specific downstream molecular consequences of CREB function, would help link gene expression changes to the electrophysiological signatures of counterfactual thinking and help broaden the scope and complexity of stress and depression research.

In summary, we operationalized value across several dimensions and revealed how choice history affects future decisions not only based on the framing of one’s past mistakes but also based on what the individual could have done differently. We provide a refined lens through which to stratify more complex decision-making computations and identify two fundamentally distinct forms of regret-related processes that may evoke different additive or subtractive counterfactuals linked to susceptibility versus resilience to chronic stress. We provide insight toward identifying molecular therapeutic targets for further investigation as to which regret-related processes may need to be potentially restored (type II) versus ameliorated (type I) in the treatment of stress-related disorders like depression. These data highlight how two separate regret-related processes—one blunted while another hyperreactive—can simultaneously coexist within the same individual and may serve as a signature for stress susceptibility. Our neuroeconomic approach to computational psychiatry has been validated in a set of tasks translated for use across species and affords a rich pipeline to directly apply discoveries from animal behavior to human psychology in ways that could provide new structure to how patients are interviewed clinically, asking specific questions about the
nature of one’s counterfactual thinking to home in on separable circuits involved (80). This work demonstrates how circuit computation-specific processes can be extracted on the basis of a careful description of one’s decision-making processes and, in the case of the complexities of regret, about how not all mistakes are created equally and about the different roads not traveled.

**MATERIALS AND METHODS**

**Animals and husbandry**

Ten-week-old wild-type male C57BL/6J mice were purchased from The Jackson Laboratory for the experiments in this study. In addition, 16- to 24-week-old male CD-1 (ICR) mice (sexually experienced retired breeders purchased from Charles River Laboratories) were used as aggressors for the CSDS protocol. All C57BL/6J mice were initially randomly group-housed (three to five mice per cage) and allowed a 1-week period to acclimate to the housing facilities before the start of experiments. CD-1 mice were singly housed. During the CSDS protocol, a single C57BL/6J mouse was randomly cohoused with a single CD-1 mouse as part of the CSDS protocol described in detail below. Before and during the CSDS protocol, mice had access to regular chow ad libitum. Following the CSDS protocol, C57BL/6J mice were individually housed and switched to a full-nutrition flavored pellet diet (BioServe products; 20 mg of dustless precision pellets; a ~3-g mixture of chocolate-, banana-, grape-, and plain-flavored pellets as a daily ration) and food-restricted to approach 80 to 85% of their free-feeding body weight over the next 3 days before starting training on the neuroeconomic operant decision-making paradigm termed Restaurant Row described in detail below, where mice work for these very same 20-mg rewards as their sole source of food. Mice were weighed daily before and during the CSDS protocol and twice daily (before and after testing) on the Restaurant Row task. Mice were placed daily in Restaurant Row 7 days a week from the beginning to the end of the experiment to maintain the closed-economy contingency wherein task performance each day provided full nutrition. Animals were randomized in all experiments. Mice were behaviorally tested by separate blinded experimenters different from those who handled the social defeat or CREB manipulations. For data analyses, generic MATLAB code was written and applied to all treatment conditions, simultaneously looping across blinded coded conditions. The investigators who performed the end point analyses were blinded to the animal groups. Sample size for behavioral studies (~N = 10 per condition) was determined on the basis of previous studies conducted in mice from the same genetic background strain (7, 32, 36, 39). The social defeat social interaction profiles (Fig. 2B), as well as the basic economic profiles demonstrating understanding of the task structure (Figs. 2D and 6C) obtained for all animals, are consistent with the findings observed in previous studies (7, 32, 36, 39), thus demonstrating reproducibility. All mice were maintained on a 12-hour light/12-hour dark cycle with ad libitum access to water. Experiments were conducted during the light phase, consistent with most previous research performed with the behavioral and experimental interventions detailed below. In addition, because of the duration of the Restaurant Row procedure, experiments were performed across a ~12-hour period, and circadian factors were counterbalanced across groups and analyses. In the rare instance (<5%) that mice could not independently support their own body weight by foraging for rewards on the task, small rations of post-task supplementary feeding were offered to the animals that they readily consumed before fasting again for 23 hours until the next Restaurant Row testing session to remain in concordance with animal safety regulations. Data from all mice run on the Restaurant Row task were included. Experiments were approved by the Mount Sinai Institutional Animal Care and Use Committee (protocol number LA12-00051) and adhered to the National Institutes of Health (NIH) guidelines.

**Chronic social defeat stress**

Mice underwent CSDS, a well-established animal model of psychosocial stress that is capable of inducing a depressive- and anxiety-like phenotype (28). CD-1 mice were screened for aggressive behaviors before use. During CSDS, a single C57BL/6J mouse was cohoused with a single CD-1 mouse and allowed to physically interact and experience aggression behavior for 5 to 10 min of attacking before being separated for the remainder of the day. Both the C57BL/6J and CD-1 mice remained cohoused in the same cage but were separated by a mesh divider so they no longer had direct physical contact but continued to have visual, olfactory, and auditory contact. This procedure was repeated for 10 consecutive days with 10 different CD-1 mice. As a control to this stressor, nonstressed (nondefeated) C57BL/6J mice were handled equally without exposure to CD-1 mice but were exposed to other domiciled C57BL/6J mice of the same size and age. By the end of this protocol, mice are typically assayed on a social interaction test that captures social avoidance, which has been shown to be highly predictive of several other depressive-like behavioral and neurobiological abnormalities (28). This assay is a short behavioral screen where a single C57BL/6J mouse is placed in a large open-field arena with an unfamiliar CD-1 mouse enclosed in a small chamber. EthoVision software was used to track the location of the C57BL/6J mouse during this social interaction assay. Time spent near (interaction zone) versus away from the CD-1 mouse was used to quantify a social interaction score calculated from time in the interaction zone with the CD-1 mouse present in the chamber (2.5-min trial) relative to a preceding 2.5-min baseline trial without the target CD-1 mouse present.

**Neuroeconomic decision-making paradigm: Restaurant Row task**

Mice were trained to forage in a square maze for food rewards of varying cost (delays ranging from 1 to 30 s) and subjective value (unique flavors tied to four separate and uniquely spatially cued locations, or “restaurants,” located in each corner of the maze) while on a daily limited time budget (60 min). Each restaurant consisted of two separate decision zones: (i) an offer zone (T-shaped intersection) and (ii) a wait zone (small chamber with a reward receptacle). Upon entry into a restaurant’s initial offer zone, a tone sounded whose pitch indicated the delay mice would have to wait to earn food if they chose to enter the wait zone (higher tone pitch equates to a longer delay randomly selected upon offer zone entry; pitch identities were shared across restaurants). If a mouse chose to enter the wait zone, a countdown began during which tones descend stepwise every second either until the reward was earned or the mouse decided to quit and leave the wait zone. There is no penalty to quitting other than the offer was rescinded and the mouse must advance to the next restaurant. Thus, a trial was terminated if a mouse made (i) a skip decision in the offer zone and advanced down the hallway or (ii) a quit decision in the wait zone or (iii) earned a reward, after which the mouse must progress to the next restaurant in a serial order. Rewards earned on this task served as the only source of food (full nutrition flavored.
BioServe 20-mg pellets), making this task closed-economic in nature with time as a limited commodity. This means that decisions made on this task were interdependent both across trials and across days. This also means that any time spent engaged in a given behavior was at the expense of spending from the time budget engaged in other behaviors or exploring alternative options, a concept known as opportunity cost in the foraging literature. Thus, how value is calculated can be operationalized in many forms depending on available actions to choose from, choice history, and current economic situation. Different animals preferred the unique flavors differently, and these idiosyncratic differences in flavor preferences were harnessed to operationalize value subjectively as a function of offer cost relative to indifference points in decision thresholds within a given restaurant and across the ordinal rankings of each restaurant’s flavor. Flavor preferences developed early in training and were stable across days—roughly equal fractions of mice displayed preferences for each of the flavors. Each restaurant remained spatially fixed in the maze, with patterns on the wall to signify the restaurant identity (chocolate, vertical stripes; banana, checkers; grape, triangles; plain, horizontal stripes). Rewards were delivered using a three-dimensional printed automated pellet dispenser that was triggered by a computer running the behavioral task programmed in the ANY-maze software made by the Stoelting Company. Behavioral events were triggered by spatial movements through the maze tracked by ANY-maze. The receptacle of the pellet dispenser also featured a custom-built trap door that would discard an uneaten pellet triggered upon exit from the wait zone if mice did not immediately consume food off of the pedestal. This prevented mice from hoarding rewards and quickly trained animals to adhere to the structure of the task to make meaningful and intentional foraging decisions. Small wall-mounted speakers (MakerHawk 3 Watt 8 Ohm Single Cavity Mini Speakers driven by a DROK 5W+5W Mini Amplifier Board PAM8406 DC 5V Dual Channel Class D) were fixed to the wall of each restaurant that played a 500-ms tone upon entry into the offer zone and repeated every second until either an enter or skip decision was made. The pitch of the tone varied depending on the randomly selected offer of that trial (1 s = 4000 Hz and each second above that was an additional 387 Hz; e.g., 5 s = 5548 Hz, 15 s = 9418 Hz, and 30 s = 15,223 Hz). Upon entry into the wait zone, the tones descended in a countdown fashion, stepping down 387 Hz each second until mice either quit the wait zone or waited out the full countdown. ELP USB camera with a Xenocam 1/2.7” 3.6-mm lens was used for video tracking. Restaurant Row testing took place in dim lighting conditions. Channel Class D) were fixed to the wall of each restaurant that played a 500-ms tone upon entry into the offer zone and repeated every second until either an enter or skip decision was made. The pitch of the tone varied depending on the randomly selected offer of that trial (1 s = 4000 Hz and each second above that was an additional 387 Hz; e.g., 5 s = 5548 Hz, 15 s = 9418 Hz, and 30 s = 15,223 Hz). Upon entry into the wait zone, the tones descended in a countdown fashion, stepping down 387 Hz each second until mice either quit the wait zone or waited out the full countdown. ELP USB camera with a Xenocam 1/2.7” 3.6-mm lens was used for video tracking. Restaurant Row testing took place in dim lighting conditions.

Stereocteal surgery and viral gene transfer
In a separate cohort, an additional 40 C57BL/6J mice (10 weeks old from The Jackson Laboratory) were anesthetized by intraperitoneal injection with a mixture of ketamine-HCl (100 mg/kg) and xylazine (10 mg/kg) and were positioned on a stereotaxic instrument (David Kopf Instruments). In the NAC (from bregma with an angle of 10°: anterior-posterior (AP), +1.6 mm; medial-lateral (ML), ±1.5 mm; dorsal-ventral (DV), −4.4 mm) or mPFC (from bregma with an angle of 10°: AP, +1.8 mm; ML, ±0.75 mm; DV, −2.7 mm), 0.7 to 1 μl of virus (1 × 1012 AAV2-CMV-mCreb, Addgene, plasmid #68551 or 1 × 1012 AAV2-CMV-eGFP, UNC GTC Vector Core) was bilaterally infused using 33-gauge Hamilton needles over 5 min, and the needle was left in place for 5 to 10 min after the injection. Mice were allotted 2 weeks to recover before beginning food restriction in preparation for testing on Restaurant Row to match the timeline of the CSDS cohort. At the end of the behavioral testing, animals were euthanized and viral transfection was visually inspected using a fluorescence microscope. Brain tissue used for histological quantification of virus transfection levels and cell type specificity was collected in a separate set of test mice 3 weeks after surgery. At time of collection, animals were deeply anesthetized with peritoneal injections of Fatal-Plus (500 mg/kg) (Vortech, catalog no. 9373) and intracardially perfused with 15 ml of 4% paraformaldehyde (Electron Microscopy Science, catalog no. 15713-S). Brains were postfixed for 24 to 72 hours and subsequently sliced on a Leica VT1000 S vibratome at 40- to 50-μm sections. Sections were blocked for 1 hour in blocking buffer [10% donkey serum (Jackson ImmunoResearch, catalog no. 017-000-121) and 0.3% Triton X-100 (Sigma-Aldrich, catalog no. 9284) in phosphate-buffered saline (PBS)], followed by overnight incubation with primary antibody (1:1000 Ch-NeuN; MilliporeSigma, catalog no. ABN91) in diluted blocking buffer (1:3 dilution in PBS). Sections were washed three times with diluted blocking buffer (15 min each) prior to incubation with secondary antibodies (Ch-647; Jackson ImmunoResearch, catalog no. 703-605-155) for 1 hour. Wash three additional times (twice for 15 min in diluted blocking buffer and once for 10 min in PBS). Last, sections were incubated with 1:10,000 DAPI (4′,6-diamidino-2-phenylindole) (Thermo Fisher Scientific, catalog no. 62248) for 5 min. Sections were mounted with Prolong Diamond Antifade Mountant (Thermo Fisher Scientific, catalog no. P36970). Images were acquired on a Zeiss LSM 780 confocal microscope using Zen software with 40× oil immersion lens at 1.1 digital zoom. Three images per region and animal were acquired. Quantification of transfection was performed using CellProfiler. Cells were first identified to be DAPI+, and neurons were subsequently identified if both DAPI and NeuN positive. Similarly, virally transfected cells were identified if both DAPI and GFP positive. Virally transfected neurons were identified if DAPI, NeuN, and GFP positive.

Serum corticosterone measurement
Mice were sacrificed immediately after behavioral testing, and trunk blood was collected into EDTA-containing tubes (Fisher Scientific, #NC9954576). The blood was centrifuged for 15 min at 1500 relative centrifugal force, and plasma was separated and stored at −80°C. Corticosterone levels were measured in duplicates using an enzyme-linked immunosorbent assay (Enzo Life Sciences, #ADI-900-097) according to the manufacturer’s instructions. The plate was read on a SpectraMax 340PC384 microplate reader (Molecular Devices), and corticosterone levels were calculated from a serial dilution curve using SoftMax Pro 5 software (Molecular Devices).

Protein extraction and immunoblotting
Brains were removed and blocked into coronal sections, from which tissue punches were obtained from the mPFC and NAC. Proteins were extracted by homogenizing brain tissue samples in radioimmunoprecipitation assay lysis buffer [150 mM NaCl, 1% NP-40, 1% sodium deoxycholate, 0.1% SDS, and 50 mM tris (pH 8)], followed by a 30-min incubation at 4°C with agitation. Samples were sonicated for five cycles (20 s ON; 20 s OFF, 50% amplitude) at 4°C and then centrifuged for 15 min at 14,000 rcf at 4°C. Thermo Fisher Scientific’s Pierce BCA assay was used to determine protein concentrations. Proteins were heated to 60°C for 15 min with 4x Laemmli sample buffer (Bio-Rad; supplemented with β-mercaptoethanol). Equal amounts of protein (10 μg) were loaded into a 4 to 20% gradient precast midi-Criterion TGX gel (Bio-Rad), and proteins were separated...
with 200 V in 1x tris/glycine/SDS buffer (Bio-Rad). Proteins were transferred to a nitrocellulose membrane using the Trans-Blot Turbo system (Bio-Rad), mixed molecular weight protocol. Membranes were blocked for 1 hour at room temperature in 3% milk in tris-buffered saline. Primary antibodies were incubated overnight at 4°C (ms-blocked for 1 hour at room temperature in 3% milk in tris-buffered system (Bio-Rad), mixed molecular weight protocol. Membranes were transferred to a nitrocellulose membrane using the Trans-Blot Turbo with 200 V in 1× tris/glycine/SDS buffer (Bio-Rad). Proteins were carried out using JMP Pro 16 Statistical Discovery software package.

RNA isolation and qPCR
Total RNA was isolated from tissue punches taken from the mPFC and NAc using Zymo’s Direct-zol MiniPrep according to the manufacturer’s instructions. RNA samples were eluted in deoxyribonuclease/ribonuclease-free water, and 40 ng was reverse-transcribed into cDNA using Bio-Rad’s iScript SuperMix. All cDNA was diluted 1:4 following conversion. The relative mRNA expression levels of duplicates were determined using real-time qPCR by TaqMan Fast Advanced PCR master mix and TaqMan specific probes. Relative mRNA expression levels were determined by the ddCt method, with normalization to Gapdh endogenous control followed by normalization to control animal samples. The following solutions/reagents were used: Direct-zol MiniPrep (Zymo, #R2052), iScript SuperMix cDNA kit (Bio-Rad, #1708841), Taqman Fast Advanced Master Mix (Thermo Fisher Scientific, #4444557), qPCR probe Gapdh (VIC) (Thermo Fisher Scientific, #4352339E), qPCR probe Creb1 (FAM) (Thermo Fisher Scientific, #Mm00501607_m1), qPCR probe Fos (FAM) (Thermo Fisher Scientific, #Mm00487425_m1), and qPCR probe Zfp189(FAM) (Thermo Fisher Scientific, #Mm00523810_m1).

Statistical analyses
All data were processed in MATLAB, and statistical analyses were carried out using JMP Pro 16 Statistical Discovery software package from SAS. All data are expressed as means ± 1 SE. Sample size is included in each figure. Statistical significance was assessed using Student’s t tests, one-way, two-way, and repeated-measures analysis of variance (ANOVA), with post hoc Tukey t tests correcting for multiple comparisons. Correlations were reported using Pearson correlation r coefficients. No data were excluded as outliers. Asterisks used in figures are intended to direct attention to comparisons of interest.

SUPPLEMENTARY MATERIALS
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View/request a protocol for this protocol from Bio-protocol.

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