

A Double Hit of Social and Economic Stress in Mice Precipitates Changes in Decision-Making Strategies

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ABSTRACT

BACKGROUND: Economic stress can serve as a second hit for people who have already accumulated a history of adverse life experiences. How one recovers from a setback is a core feature of resilience but is seldom captured in animal studies.

METHODS: We challenged mice in a novel 2-hit stress model by first exposing them to chronic social defeat stress and then testing adaptations to increasing reward scarcity on a neuroeconomic task. Mice were tested across months on the Restaurant Row task, during which they foraged daily for their primary source of food while on a limited time budget in a closed-economy system. An abrupt transition into a reward-scarce environment elicits an economic challenge, precipitating a drop in food intake and body weight to which mice must respond to survive.

RESULTS: We found that mice with a history of social stress mounted a robust behavioral response to this economic challenge that was achieved through a complex redistribution of time allocation among competing opportunities. Interestingly, we found that mice with a history of social defeat displayed changes in the development of decision-making policies during the recovery process that are important not only for ensuring food security necessary for survival but also prioritizing subjective value and that these changes emerged only for certain types of choices.

CONCLUSIONS: These findings indicate that an individual's capacity to recover from economic challenges depends on that person's prior history of stress and can affect multiple decision-making aspects of subjective well-being, thus highlighting a motivational balance that may be altered in stress-related disorders such as depression.

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Repeated exposure to stress can drive maladaptive behaviors and contribute to mental illness (1). How one recovers back to baseline following stress is critical for generating healthy coping strategies and can separate individuals who are resilient from those who may be susceptible to developing psychiatric sequelae (2–4). In the animal stress literature, studies of the behavioral and neurobiological underpinnings of resilience have gained traction in recent years (5,6). However, relatively few studies of resilience have focused on characterizing the behavioral and cognitive processes involved in one's recovery to baseline levels, partly because developing and operationalizing a model capable of capturing a stress-inducing setback and associated signatures of recovery in animals has been difficult.

A unique way to formalize this problem in a translationally relevant manner involves turning to the neuroeconomics decision-making field. Neuroeconomics describes the study of how the physical limits of the brain give rise to cognitive mechanisms involved in decision making and how advanced behavioral methods can dissociate biologically distinct choice processes (7,8). This field focuses on understanding complex interactions between choice parameters including reward

value, price, effort, energetic demand, competing actions, and opportunity costs (9). These factors can differentially influence fundamentally distinct valuation algorithms in physically separable circuits in the brain (10). In this context, an example of economic stress can be defined as a change in one's budget constraints, (e.g., in humans, the financial burden of losing one's job or following market inflation), which can take a cognitive, affective, and physiological toll on an individual in addition to the practical ramifications that a stricter budget can have, including limiting access to basic survival needs (11,12). A challenge such as this can precipitate behavioral reactions to one's environment that may be adaptive or maladaptive. For instance, economic stress and budget constraints can drive one to pursue higher quantity and perhaps less expensive but poorer nutritional quality food, which results in increased risk of developing psychological and metabolic problems. Furthermore, imposing metabolic demand on an individual by increasing the overall scarcity of rewards available in the environment may alter the motivational balance between pursuing rewards that are of high subjective value and maintaining adequate food security. By studying stress in this way, robust measures of decision making–related behavior can be gleaned

from how one responds to different economic challenges. Modeling this type of stressor has received far less attention in the animal stress literature and opens doors to multiple lines of inquiry. This includes asking how budget constraints and economic demand of reward scarcity in the environment interact with one's stress history so as to alter the way that an individual makes future decisions. Approaches in neuroeconomics offer a novel framework with which to operationalize these concepts in ways that may be useful for understanding stress-related pathologies with richer behavioral end points (13). We previously demonstrated that behavioral changes in fundamentally distinct types of value-based choices could capture circuit-specific decision-making vulnerabilities in a manner that is readily translatable across species from mice and rats to monkeys and humans (14–20).

Here, we set out to examine how an individual's prior history of stress influences their future responses to stress manifested in the form of behavioral changes in neuroeconomic decision making. We investigated exposure to 2 distinct but commonly interacting types of stress that have often been highlighted in human but not animal work: social and economic (21–23). Here, we developed a novel 2-hit stress model by combining the well-established chronic social defeat stress protocol (24) (first hit) with a longitudinal neuroeconomic decision-making paradigm, Restaurant Row (18,25,26). This complex task, during which mice must forage for their primary source of food for a limited period of time, comprises a changing economic landscape that embeds an acute and severe economic challenge (second hit). This economic challenge precipitates a drop in food availability that mice must respond to for survival. This approach enabled us to rapidly extract individual differences in response to social stress and investigate how these different profiles affect how subsequent economic challenges alter the balance of multiple decision-making strategies during the recovery process. We focused on the behavioral characterization of how motivation for maximizing subjective value competes with reestablishing and maintaining food security when economic demand increases. This novel 2-hit stress paradigm facilitates studying how one's previous adverse life experiences interact with behavioral adaptations to a changing environment. We characterized neuroeconomic behavior by balancing multiple decision-making processes that may be altered in stress-related disorders such as depression.

METHODS AND MATERIALS

Subjects

Adult male C57BL/6J mice (10 weeks, $n = 32$; Jackson) and CD-1 mice (20 weeks, $n = 22$; Charles River) were used. After social defeat, mice were individually housed and maintained on a 12-hour light/dark cycle with ad libitum water and were only food restricted during Restaurant Row testing, conducted during their light phase. Experiments were approved by the Mount Sinai Institutional Animal Care and Use Committee (protocol No. LA12-00051) and adhered to National Institutes of Health guidelines.

Chronic Social Defeat Stress

Twenty-two C57BL/6J mice underwent chronic social defeat (Figure 1A; Figure S1A). Each mouse was paired with a CD-1

aggressor for 5 minutes before remaining cohoused separated by a mesh divider for the rest of the day. This was repeated with a novel CD-1 mouse for 10 days. Ten C57BL/6J nondefeated mice were paired instead with other, domiciled C57BL/6J mice. Mice were then screened on a brief, rapid social interaction (SI) test. Time that was spent near (interaction zone) versus away from the CD-1 mouse compared to when no CD-1 mouse was present was used to calculate an SI score to divide mice into resilient and susceptible subgroups.

Neuroeconomic Task

Then, we characterized defeated and nondefeated mice longitudinally in Restaurant Row (25). Mice had a limited period of time each day to forage for their primary source of food by navigating a maze with 4 uniquely flavored and contextualized feeding sites or "restaurants" (Figure 1B). Each restaurant had a separate offer zone (OZ) and wait zone (WZ). Upon entry into the OZ, a tone sounded, the pitch of which indicated how long mice would have to wait in a cued countdown if they entered the WZ. Mice were tested for 55 consecutive days in a changing economic landscape. During the first 5 days of testing (block 1, green epoch), all trials consisted of 1-second offers only. During the next 5 days of testing (block 2, yellow epoch), offers ranged from 1 to 5 seconds randomly selected from a uniform distribution. Block 3 (5 days, orange epoch) consisted of a 1- to 15-second range. The fourth and final block (red epoch) consisted of offers ranging from 1 to 30 seconds and continued for 40 days. Data were processed in MATLAB (version 2022a; The MathWorks, Inc.) with statistical analyses in JMP Pro 16 (see Supplemental Methods). All data are expressed as mean $\pm$ 1 standard error. Statistical significance was assessed using Student's *t* tests and 1-way, 2-way, and repeated measures analyses of variance. Correlations were reported using Pearson correlation coefficients (*r*). The Akaike information criterion was used to compare model fits between linear and cubic functions. No data were excluded as outliers.

RESULTS

Mice Were Exposed to Social Defeat Stress Before Undergoing Longitudinal Neuroeconomic Testing

Social avoidance induced by chronic defeat has served as a well-validated predictor of several depression-related phenotypes on other rapid screening tests (24). We induced social avoidance in defeated mice compared with nondefeated mice ($F_{1,31} = 10.793$, $p < .01$) (Figure S1A, B). We observed no changes in body weight across the defeat protocol while mice remained on ad libitum food ($F_{9,31} = 0.061$, $p = .81$) (Figure S1C, D) and no correlation between body weight and social avoidance scores ($r = 0.244$, $R^2 = 0.06$, $p = .18$) (Figure S1E, F). Following defeat, mice were food restricted, singly housed, and tested longitudinally on the Restaurant Row task (Figure 1A).

Reward Scarcity Unmasks Different Foraging Patterns in Mice With a History of Social Stress

Food Intake Renormalization. Social defeat had no immediately observable effect on task acquisition, feeding

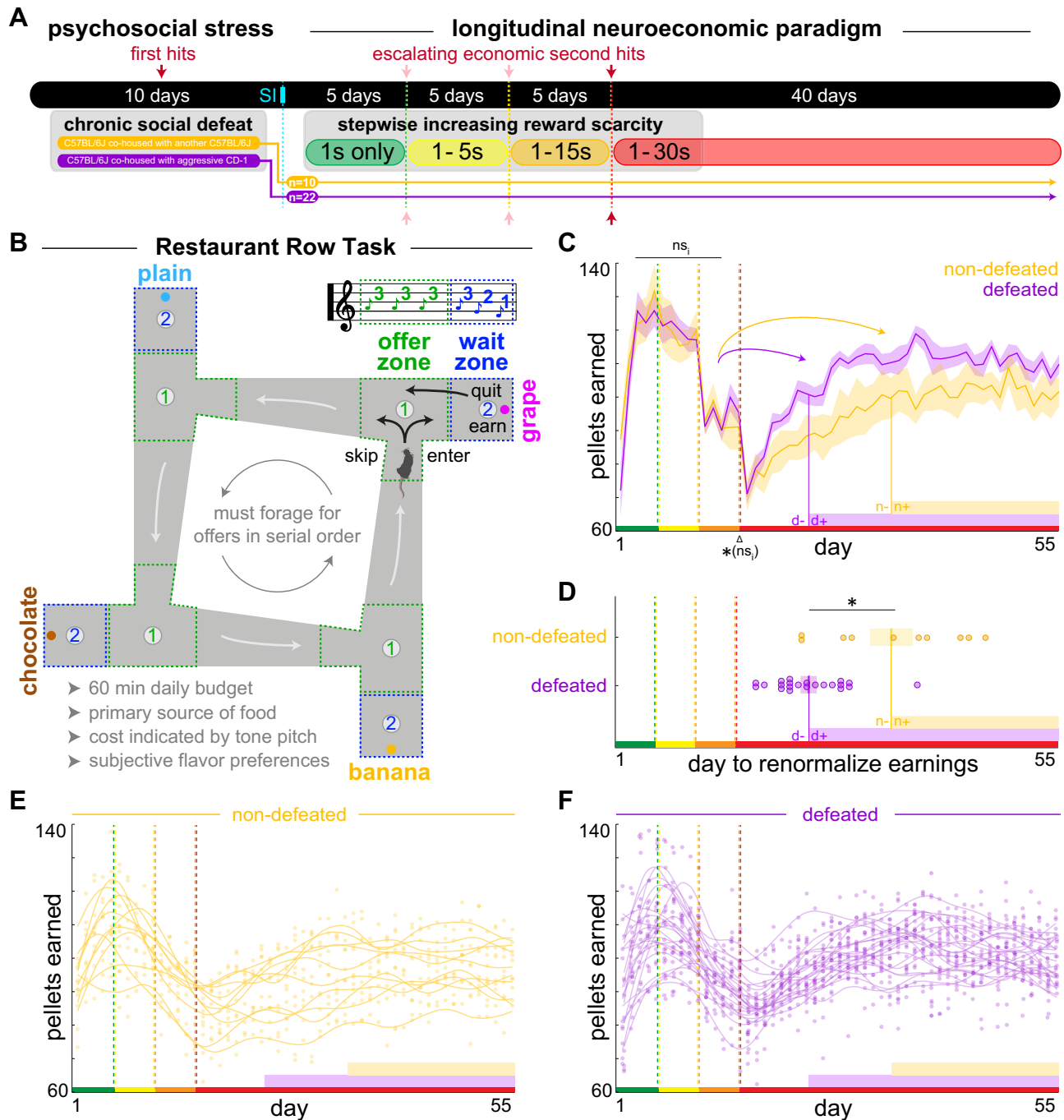


Figure 1. Novel 2-hit social and economic stress model. **(A)** Experimental timeline. Mice were exposed to chronic social defeat stress (first hits, dark red arrow) followed by a brief SI screening assay before being tested longitudinally (55 days) in a spatial neuroeconomic decision-making paradigm with a changing value landscape that grew increasingly scarce stepwise every 5 days (pink arrows). After 15 days, mice experienced the largest change in reward scarcity (final dark red arrow), during which they abruptly transitioned into an environment where offers ranged from 1 to 30 seconds. **(B)** Restaurant Row task schematic. Mice were required to forage for their sole source of food while on a limited 60-minute daily time budget for rewards of varying costs (delays) and flavors (4 uniquely contextualized locations or “restaurants”). In this closed-economy system, mice learned to run counterclockwise in a single direction and encountered an offer zone in each restaurant in which a tone was presented on each trial whose pitch indicated the amount of time mice would have to wait for a reward if they chose to enter the wait zone, after which a pitch signaled that countdown would begin. **(C)** Average total number of daily pellets earned across the entire 55 days of testing, first in reward-rich environments where all offers were 1 second only (low pitch, green epoch), advancing stepwise into increasingly reward-scarce environments where offers could range from 1 to 5 seconds (yellow epoch), 1 to 15 seconds (orange epoch), or 1 to 30 seconds (red epoch). All mice experienced a loss in food intake immediately upon transitioning into the 1- to 30-second reward-scarce environment (Δ symbol). Recovery back to near-baseline levels of food intake (curved arrows, number of days to equate earnings with average yellow and orange epochs) for each group is

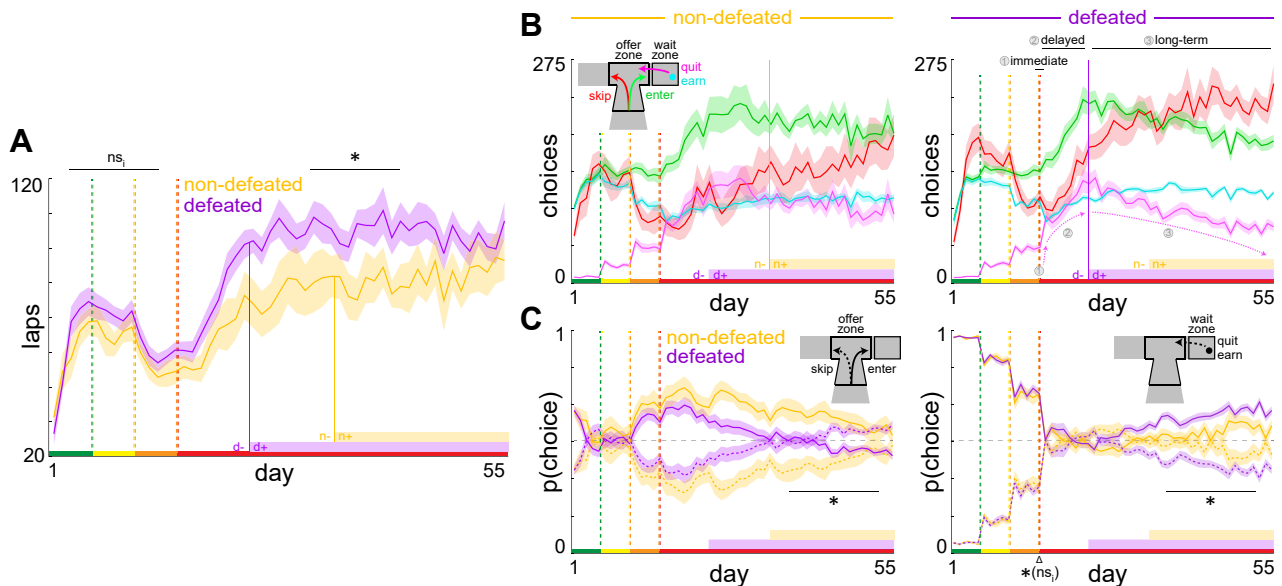


Figure 2. Increased activity and simple choice breakdown reveal multiple stages of a food-scarcity response profile. **(A)** Average number of laps run in the correct direction. Note that the “–” and “+” annotations along the purple (defeated) and gold (nondefeated) bars on the x-axis demarcate food intake renormalization windows separated by vertical solid purple and gold lines as defined by earnings in Figure 1C, D. **(B)** Average number of enter or skip choices made when in the offer zone as well as quit or earn choices in the wait zone for nondefeated and defeated mice. In addition to the “–” and “+” food intake renormalization window annotations, note additional annotations numbered [1] immediate phase (day 15–16 transition to 1- to 30-second offers, red epoch); [2] delayed phase (during the “–” renormalization window for each group of mice); and [3] long-term phase (after the “+” renormalization window for each group of mice). The magenta dashed arrow markings use quit behavior for defeated mice as an example to summarize and illustrate changes in quit behavior associated with these 3 distinct phases (i.e., [1]—immediate sharp rise, [2]—delayed gradual rise, and [3]—long-term direction change with a gradual decline in quitting behavior). Note that these changes in quits during these phases while considering changes in food intake, laps run, and enter vs. skip choices. **(C)** The probability of making a choice in the offer zone relative to the total number of offers or a choice in the wait zone relative to the total number of enter decisions. Note that $p(\text{skip})$ and $p(\text{quit})$ here (dashed lines) are 1 minus $p(\text{enter})$ and $p(\text{earn})$ (solid lines), respectively, reflected at about the 0.5 chance line (horizontal dashed gray line). Reflection is intended to highlight the major crossover inversion points in behavioral strategy across training. Shaded error bars ± 1 SEM. Change relative to the transition into the 1- to 30-second reward-scarce environment (Δ symbol). * $p < .05$. d, defeated; n, nondefeated; ns, nonsignificant interaction.

behavior, or body weight during early testing in relatively reward-rich environments when offer costs remained low (blocks 1–3, green-yellow-orange epochs, 1 second/1–5 seconds/1–15 seconds offers) (Figure 1C) (first 15 days: $F_{1,14} = 1.802$, $p = .180$) (Figure S2). These data highlight that there were no overt changes in motivated food intake that could be attributable to hunger or metabolism differences induced by social defeat given low economic demands. Each 5-day block increase in reward scarcity was marked by an abrupt transition into an environment with a larger offer range. Block 4 (red epoch) marked a critical point when mice encountered the greatest increase in offer range, up to 30 seconds, and experienced a sharp loss in food intake to extremely low levels of earnings with a concurrent drop in body weight, observed equally among defeated and nondefeated mice (Figure 1C) (reward-scarce transition: $F_{1,1} = 24.714$, $p < .0001$; no group interaction: $F_{1,31} = 0.227$, $p = .635$) (Figure S2A–C, E). Differences between defeated and

nondefeated mice in total pellets earned by the end of each session were only observable in the weeks after mice transitioned to the fourth block of testing. Over weeks, mice recovered overall food intake back to levels near those observed in reward-rich environments. Mice with a prior history of defeat renormalized their food intake in fewer days than nondefeated mice (Figure 1C–F) ($F_{1,31} = 20.046$, $p < .0001$) (Figure S2D). Renormalization rates were not correlated with body weight ($r = 0.025$, $R^2 = 0.00$, $p = .89$) (Figure S2F) or number of pellets earned ($r = 0.016$, $R^2 = 0.00$, $p = .93$) (Figure S2F) on the day following the transition into a reward-scarce environment. These findings demonstrate that an economic challenge is capable of eliciting differences in foraging after delayed time points that interact with relatively distant stress histories.

Choice Breakdown Revealed Multiple Stages of a Food-Scarcity Response Profile. During testing in

indicated by solid, vertical drop lines where “–” indicates the window of testing before vs. “+” after food intake was renormalized, summarized as number of days in (D) for individual animals. Purple and gold shaded bars along the x-axis indicate the “–” to “+” renormalization transition for each group throughout the remainder of figures as a point of reference. (E, F) Food earnings for individual mice across all 55 days of testing. Dots and smoothed lines represent individual animals. Shaded and x-y error bars ± 1 SEM. * $p < .05$. d, defeated; n, nondefeated; ns, nonsignificant interaction; SI, social interaction.

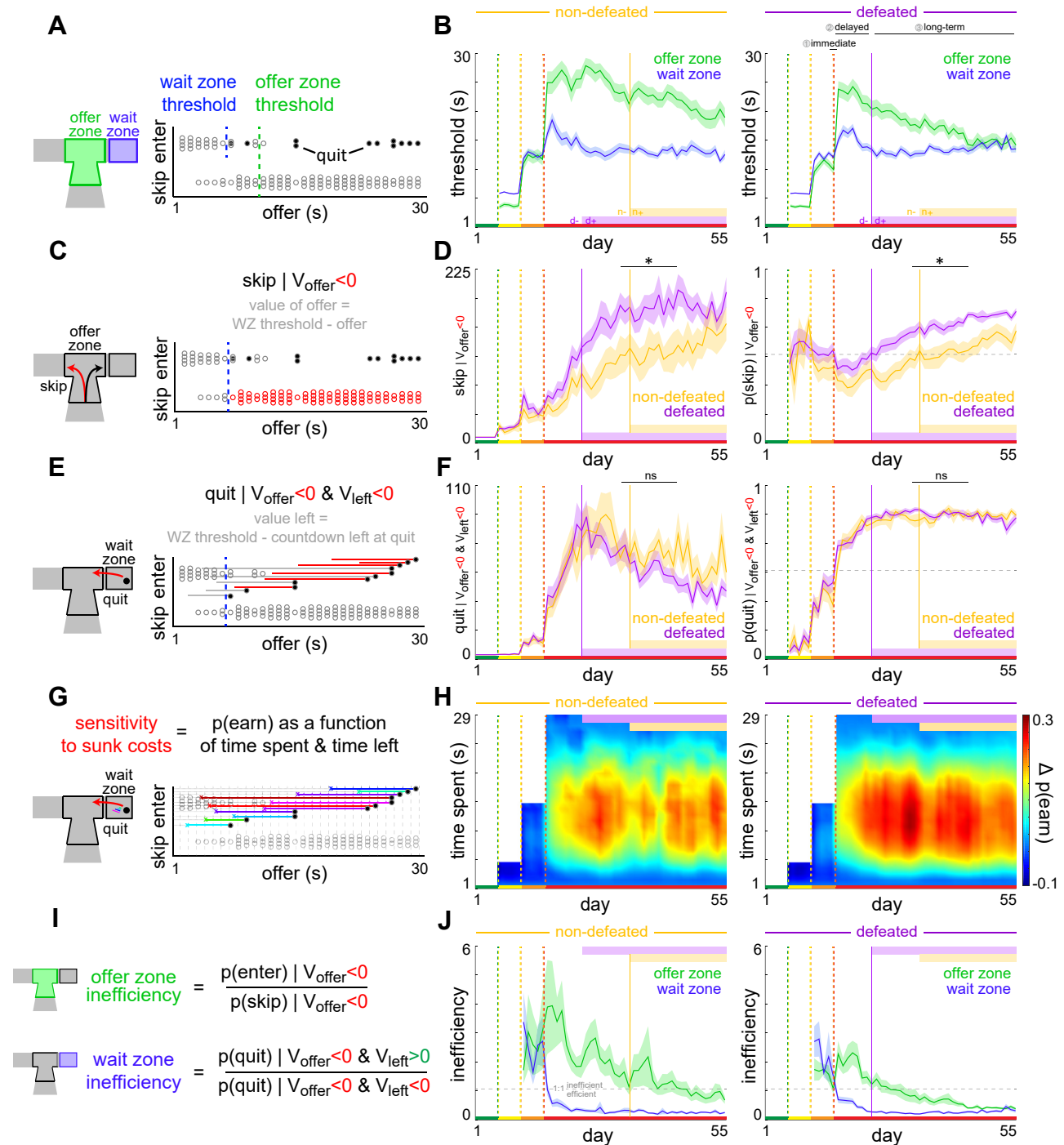


Figure 3. Learning occurs across multiple, economically distinct valuation algorithms. **(A)** Thresholds of willingness to wait are determined by fitting a Heaviside step regression to choose outcome (enter vs. skip in the OZ or earn vs. quit in the WZ) as a function of cued offer cost (Figure S4). Vertical dashed lines reflect example thresholds in the OZ (green) or WZ (blue) for a single restaurant from a single mouse during a single session. Individual trials in this example are represented by dots, with quits as filled black dots. **(B)** Average OZ and WZ thresholds across all 55 days of testing for nondefeated and defeated mice. **(C)** Because WZ thresholds were generally stable across testing for both groups of mice, offer value could be calculated relative to thresholds (gray text). **(D)** The average number of skip decisions and the probability of skipping given the offer is above threshold, where offer value ($V_{offer} < 0$). **(E)** For quit decisions, the value left at the moment of quitting can also be calculated relative to thresholds (gray text). **(F)** The average number of quit decisions and the probability of quitting given the offer is above threshold, where $V_{offer} < 0$, and the time left at the moment of quitting is still above threshold, where value left ($V_{left} < 0$). **(G)** Sensitivity to sunk costs can be calculated by comparing the probability of earning a reward in the WZ as a function of time already spent and amount of time left in the countdown (see Supplemental Results and Figure S5 for a visual explanation and walk-through of quantification steps). **(H)** A heatmap of the change

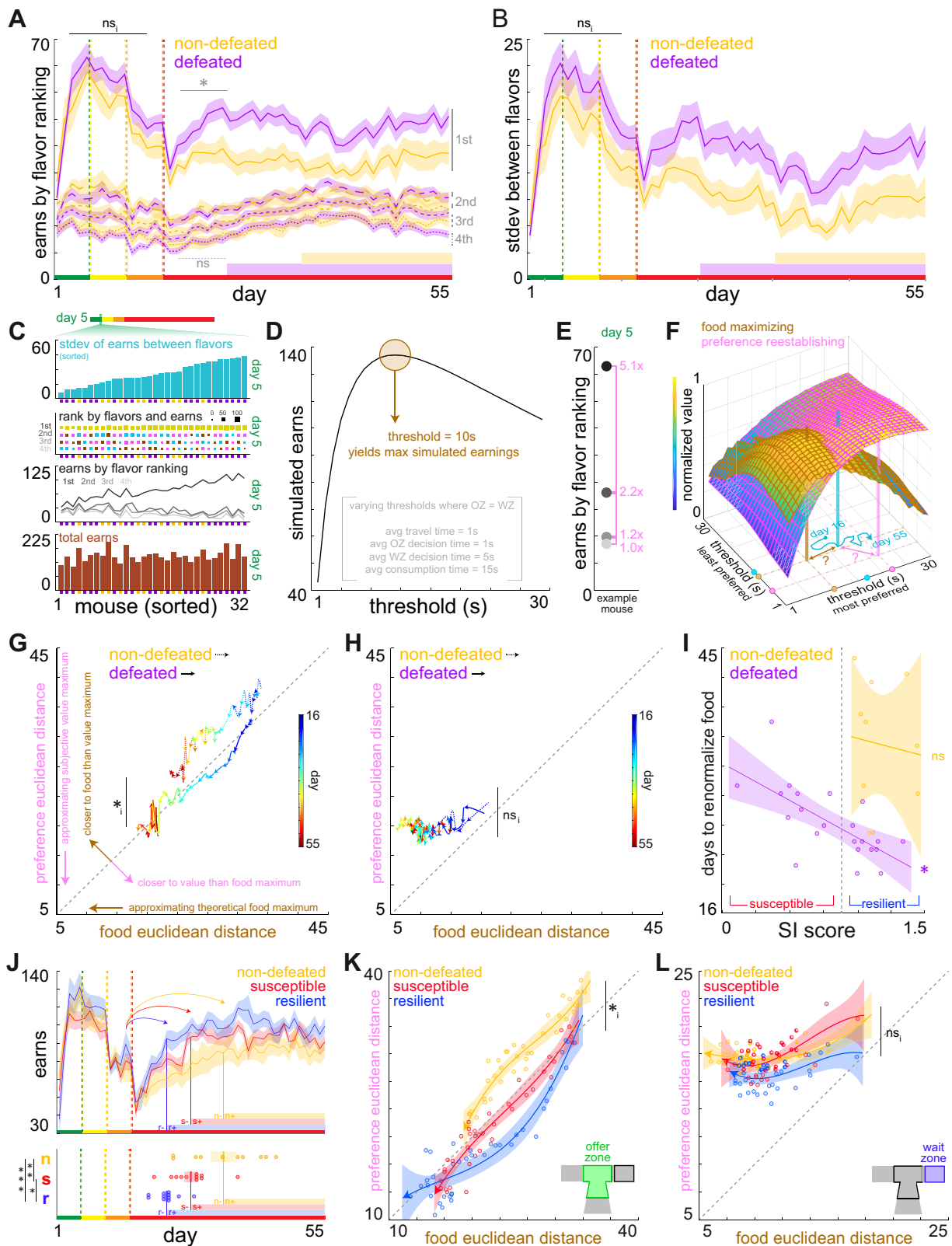
reward-rich environments, defeat had no effect on overt locomotor behavior because all mice were able to learn to run the same number of laps in the correct direction (first 15 days: $F_{1,14} = 0.454, p = .501$) (Figure 2A). Following the transition into a reward-scarce environment, there was a gradual and sustained increase in laps. This effect was larger in defeated mice than nondefeated mice ($F_{1,31} = 94.099, p < .0001$) (Figure 2A). The rise in laps was synchronized with food renormalization, respectively for each group of mice (d- and n- in Figure 1C, D), where laps reached a plateau phase only after food intake renormalized for each group (d+ and n+ in Figure 1C, D). Thus, this time course following the transition into the 1- to 30-second epoch can be divided into 3 distinct phases ([1] immediate, [2] delayed, and [3] long-term) when examining changes in simple choice outcomes (OZ: enter vs. skip; WZ: earn vs. quit). First ([1] immediate), there were no changes in OZ choice outcomes between groups immediately following the transition into a reward-scarce environment (enters: $F_{1,31} = 1.088, p = .298$; skips: $F_{1,31} = 1.024, p = .313$) (Figure 2B). However, there was a sharp, immediate increase in WZ quit outcomes that was equivalent in the 2 groups (reward-scarce transition: $F_{1,31} = 28.360, p < .0001$; no group interaction: $F_{1,1} = 0.090, p = .764$) (Figure 2B). Second ([2] delayed), during the food intake renormalization window for each group (d- and n-), there was a gradual increase in the number of enters, skips, and quits that was greater for defeated mice (3-way group and choice interaction during renormalization: $F_{2,3} = 6.452, p < .01$) (Figure 2B). Third ([3] long-term), following food intake renormalization (d+ and n+) and after laps reached a plateau, choice profiles continued to change despite there being no obvious additional gain in food intake or decrease in the laps run. Skip outcomes continued to rise decoupled from any further changes in the laps run, and unlike before during the delayed phase [2], this rise in skip outcomes was associated with a concomitant decrease in the number of enters and quits. This third-phase effect was greater in defeated animals and, when normalized to laps, was disproportionately more pronounced (interaction between choice probabilities and groups during final 2 weeks: $F_{1,1} = 57.717, p < .001$) (Figure 2B, C). These data highlight how an abrupt transition into a reward-scarce environment, which precipitates a low yield in food, can reveal behavior-environment interactions. Poor performance in a closed-economy system can drive multistage changes in foraging profiles that have previously been linked to distinct circuit-specific computational processes across distinct time scales (17,18,20).

Learning Occurs Across Multiple Economically Distinct Valuation Algorithms. Next, we analyzed how cost and time-related elements informed economic choice behavior. First, we calculated thresholds of willingness to wait in each zone by fitting a Heaviside step regression to choice outcome as a function of cued offer cost on each day (Figure 3A). OZ thresholds reflect willingness to enter initially

presented offers, whereas WZ thresholds reflect willingness to remain committed to an ongoing investment upon entering. A large discrepancy between OZ and WZ thresholds immediately emerged following the transition into a reward-scarce environment, where OZ thresholds increased to nearly 30 seconds (reward-scarce transition: $F_{1,1} = 52.836, p < .0001$; no group interaction: $F_{1,31} = 0.001, p = .970$) (Figure 3B). This indicates that animals were more likely to indiscriminately enter into the OZ regardless of cost (Figure S4A, C), a policy that they had previously adhered to without consequence in reward-rich environments. The large discrepancy with WZ thresholds indicates that mice accepted a large proportion of offers they were not willing to wait for once in the WZ, which precipitated the sharp increase in quit outcomes (Figure 2B, C, immediate phase). This explains why mice experienced an immediate loss in food intake: a significant portion of the limited time budget was allocated to quitting behavior. This also explains why during the delayed phase, as laps increased, entering, skipping, and quitting behavior gradually increased over the subsequent weeks because OZ economic policies remained fixed. This response profile during the delayed phase, although at the expense of running more laps, allowed animals to sample the new range of offers in a reward-scarce environment with greater frequency. This captures the development of a rigorous foraging strategy that ignores offer cost in the OZ during the delayed phase but is sufficient to renormalize food intake following an economic challenge in the short term. Mice with a history of defeat employ this strategy more robustly.

To further quantify economic choices, we converted offers into value terms by normalizing trials to an individual's WZ threshold for each flavor, which is generally stable across testing. For example, if a mouse's threshold on a given day and in a given restaurant is 15 seconds and an offer on a given trial is 20 seconds, $\text{value}_{\text{offer}} = \text{threshold} - \text{offer}$, or -5 in this example trial, reflecting that an offer should be rejected (Figure 3C). This allows individual differences in willingness to wait across mice or between flavors to be normalized into a comparable value term rather than offer delay. We found that skipping negatively valued offers did not begin to increase until late in testing and was more robust in defeated mice (across days: $F_{1,39} = 232.307, p < .0001$; between groups: $F_{1,31} = 148.619, p < .0001$) (Figure 3D). This change underlies the gradual decrease in OZ thresholds observed during the long-term phase as defeated mice more rapidly learned to make cost-informed choices in the OZ by discriminating tones (Figure 3B) (across days: $F_{1,39} = 165.084, p < .0001$; between groups: $F_{1,31} = 168.530, p < .0001$) (Figure S4B, D). We applied a similar analysis to quit choices and included a term that captured the value remaining in the countdown at the moment of quitting. For example, if a mouse's threshold on a given day and in a given restaurant is 15 seconds and an offer on a given trial is 20 seconds, but the animal quit after waiting only 3 seconds with 17 seconds remaining in the countdown,

in p(earn) in the WZ as a function of time spent (sunk cost sensitivity) independent of time left showing an escalation of commitment to waiting that is stronger the more time has already been waited. (I, J) OZ and WZ inefficiency can be summarized by taking the ratio of probabilities of making an economically disadvantageous decision relative to the advantageous choice in the OZ given $V_{\text{offer}} < 0$ or in the WZ given $V_{\text{offer}} < 0$ depending on V_{left} . Horizontal dashed gray line indicates a 1:1 ratio where policies become more efficient and fall below this line across testing. Shaded error bars ± 1 SEM. * $p < .05$. d, defeated; n, nondefeated, ns, nonsignificant; OZ, offer zone; WZ, wait zone.



value_{left} = threshold – time left, or –2 in this example trial, reflecting an accepted offer that was quit in an economically advantageous manner (Figure 3E). We found that these economically efficient quits increased during the delayed phase after transitioning into a reward-scarce environment in parallel with a decreased latency to quit (Figure S3), but with no differences between defeated and nondefeated mice (across days: $F_{1,39} = 233.364$, $p < .0001$; no effect between groups: $F_{1,31} = 3.310$, $p = .069$) (Figure 3F). This early rigorous foraging strategy typified by a high rate of change-of-mind decisions was sufficient to renormalize food intake during the delayed phase. At later long-term time points after food intake had renormalized, quitting behavior decreased as mice learned to effectively trade an enter-then-quit strategy for a skip-first strategy in the OZ (see Supplemental Results and Supplemental Discussion for quantification of sensitivity to sunk costs during quit decisions) (Figure 3G, H; Figure S5). The economic efficiency of these OZ and WZ choices, summarized in Figure 3I, J highlights the separate learning time scales of each decision process. Differences in choice processes between OZ and WZ decisions, which have been shown to reflect distinct circuit-specific computations (17,20), underlie unique adaptations to economic challenges among mice with a history of social defeat stress.

Strategies That Optimize Food Security Can Also Separately Contribute to Subjective Value

During testing in reward-rich environments, defeat had no immediate effects on revealed flavor preferences (first 15 days: no group interaction with earns by flavor: $F_{1,31} = 0.411$,

$p = .745$; standard deviation of flavor: $F_{1,31} = 1.969$, $p = .161$) (Figure 4A, B). In contrast, the transition into a reward-scarce environment had the greatest impact on earnings for the most preferred flavors, with more robust recovery for these flavors in defeated mice than nondefeated mice (most preferred flavor: $F_{1,31} = 180.749$, $p < .0001$; least preferred flavor: $F_{1,31} = 2.177$, $p = .140$) (Figure 4A).

Next, we asked how the decision policies of defeated and nondefeated mice prioritize maximizing food intake versus subjective values across testing following an economic challenge. We calculated the Euclidean distance between the coordinates of observed thresholds and theoretical thresholds that would yield maximal food (empirically determined via simulations) versus maximal subjective value (calculated mouse by mouse based on revealed preferences that were determined on day 5 projected across testing) on each day separately in both the OZ and WZ (Figure 4F; see Supplemental Methods). We found a significant difference in decision-making trajectories across testing in a reward-scarce environment between defeated and nondefeated mice depending on the type of choice being made. In the OZ, all mice decreased Euclidean distances to theoretical maxima for both food intake and the subjective value (Figure 4G) ($F_{1,39} = 438.753$, $p < .0001$) (Figure S6A, B, E, G). However, defeated mice more robustly drove both distances closer to absolute zero ($F_{1,31} = 268.423$, $p < .0001$; group interaction with distance type: $F_{1,31} = 38.699$, $p < .0001$) (Figure S6A, B, E, G). Groups of mice did not differ in distances between observed thresholds and either theoretical maxima early in testing in a reward-scarce environment (Figure S6G). Groups of mice also did not differ in distances between theoretical food or

Figure 4. Decision policies that optimize food security are shared with but can also independently guide strategies that separately promote subjective value depending on the type of choice being made. (A) Average number of pellets earned in each restaurant ranked from most to least preferred across 55 days of testing. (B) Average standard deviation of earns among the 4 flavors. (C) Display of individual mouse behavior (standard deviation of earns across the 4 flavors [used to sort mouse order for all data in this panel], rank order of flavors, and total number of earns split by ranked flavors [square color: chocolate, brown; banana, yellow; grape, magenta; plain, blue; square size: number of pellets earned scaled 0–50–100], and total number of overall earns), extracted only from day 5 of testing, the final day of the green epoch where all offers were 1 second only. These day 5 data were sorted by the standard deviation of earnings across flavors, from similar to dissimilar flavor palettes. Purple and gold squares along the x-axis denote defeated or nondefeated group membership. (D) Computer Restaurant Row simulation of total number of pellets earned. The ideal threshold required to obtain the theoretical maximum number of pellets when ignoring flavor preferences was empirically determined to be 10 seconds. (E) Example session: number of pellets earned across flavors ranked from most (darker) to least preferred from a single mouse extracted from day 5. Pink inset text indicates the relative ratio of earns for this mouse on day 5 between the flavor rankings (i.e., this mouse had a 5.1:2.2:1.2:1 ratio of earns across flavors capturing a summary of idealized relative subjective value for this mouse when all offers were 1 second only). (F) Two intersecting planes of decision policies that yield varying amounts of theoretical value either for maximal food intake (as determined by computer simulations, brown plane) or subjective value (as determined by multiplying day 5 preferences on a mouse-by-mouse basis, pink plane) when in a reward-scarce environment (1- to 30-second offers). Here, only 2 decision policy dimensions (least-preferred and most-preferred restaurants) of the 4 dimensions (all 4 ranked restaurants) are shown. Both planes are normalized to each's minimum and maximum values for the purpose of plotting both in the same space while preserving the threshold coordinate locations that achieve either theoretical maximum (brown [location always fixed at threshold coordinates of 10 seconds] or pink beacons [location of discovered threshold coordinates that vary from mouse-to-mouse]). Actual observed daily decision policies represented by the cyan beacon wander throughout this space from day 16 to day 55 in a reward-scarce environment. Trajectories projected to the floor of this display trace out individual mouse decision-policy paths. Example coordinates of brown, pink, and cyan beacons illustrated as dots on the x-axis and y-axis. Euclidean distance from cyan coordinates to either brown or pink coordinates were calculated (question mark symbols). (G, H) Scatterplot of Euclidean distances from observed decision policies in the OZ (G) or WZ (H) to either food or preference theoretical maximum across testing in a reward-scarce environment (color-coded arrowed line stepping through days, nondefeated mice in dashed arrows, defeated mice in solid arrows). See Figure S6 for more comprehensive and summary data. Data in (G, H) are intended to highlight progression across days while (K, L) highlight trajectory shape. (I) Scatterplot of food intake renormalization rates and SI score. Vertical dashed gray line indicates an SI score of 1. Dots represent individual mice. (J) Food intake renormalization data from Figure 1C, D replotted splitting defeated mice by resilient and susceptible subgroups (as defined by SI score >1 or <1 , respectively). See Figures S7 and S8 for a full characterization of longitudinal Restaurant Row metrics among these subgroups. (K, L) Decision-policy trajectories across testing replotted with resilient and susceptible subgroups. Pointed arrowheads indicate the overall direction across days of testing as shown in (G, H). Dots represent group mean on each day. Diagonal dashed gray lines in (G, H) and (K, L) indicate a slope of 1. Shaded and x-y error bars ± 1 SEM or 95% CI of curve fits. * $p < .05$. n, nondefeated; ns, nonsignificant interaction; OZ, offer zone; r, resilient; s, susceptible; SI, social interaction; WZ, wait zone.

subjective value maxima (Figure S6H), thus not skewing absolute Euclidean distances. By subtracting Euclidean distances for OZ thresholds, we found that the OZ policies of defeated mice were closer to the theoretical maximum for subjective value than for food compared to nondefeated mice (Figure 4G; Figure S6C). In the WZ, decision-making trajectories decreased the Euclidean distance only for theoretical food maximum, with no contribution to maximizing subjective value and no differences between groups of mice (Figure 4H) (interaction with distance type across days: $F_{1,39} = 35.183$, $p < .0001$; no group effect: $F_{1,31} = 1.163$, $p = .281$) (Figure S6A, B, D, F, G). These data indicate that changes in OZ and WZ thresholds can contribute to aspects of food- and value-related motivation that may not be appreciable if not considering how multifactor policies adapt to a reward-scarce environment with regard to an individual's revealed preferences. These data highlight how mice with a prior history of social stress manifest changes in adaptations to a reward-scarce environment only for certain types of choices.

To link unique, traditionally clustered social defeat response profiles to economic response profiles, we correlated SI scores with food intake renormalization rates and found that defeated mice with higher SI scores required fewer days to renormalize following the transition into a reward-scarce environment (Figure 4I) (defeated: $F_{1,20} = 16.43$, $p < .001$; nondefeated: $F_{1,8} = 0.08$, $p = .787$) (Figure S1B). High SI scores following defeat have traditionally been linked to resilient stress-response phenotypes, whereas low SI scores have traditionally been labeled as stress-susceptible and exhibit depressive-like traits in other commonly used assays (24). We found that resilient mice displayed the fastest food intake renormalization rates ($F_{1,2} = 13.985$, $p < .001$; nondefeated vs. resilient: $t_{19} = 5.28$, $p < .0001$; nondefeated vs. susceptible: $t_{19} = 3.06$, $p < .01$; resilient vs. susceptible: $t_{20} = -2.27$, $p < .05$) (Figure 4J) (see Figures S7 and S8 for a full characterization of Restaurant Row metrics in these subgroups). Extending our decision-making trajectory analysis to these subgroups, we found a bifurcation in Euclidean distances in the OZ but not in the WZ (Figure 4K, L). While all subgroups followed similar decision trajectories in the WZ to decrease distance only to the theoretical maxima for food intake (food: $F_{1,39} = 53.866$, $p < .0001$; subjective value: $F_{1,39} = 0.889$, $p = .346$; no group interaction with distance type: $F_{1,1} = 0.928$, $p = .395$) (Figure 4L), resilient mice uniquely steered OZ trajectories more closely toward decision policies that decreased the Euclidean distance for subjective value while simultaneously driving the Euclidean distance down for food (group interaction with distance type: $F_{1,1} = 31.649$, $p < .0001$, food vs. value trajectory curve fit Akaike information criterion weights: nondefeated [linear: 0.721; cubic: 0.279]; resilient [linear: 0.004; cubic: 0.996]; susceptible [linear: 0.878; cubic: 0.122]) (Figure 4K). Subgroups did not differ in distances between theoretical maxima for food or value (Figure S6I). These data indicate that mice with a history of resilience to social stress are more capable of recovering from an economic challenge. Resilient mice accomplished this in a manner that not only ensures the food security necessary for survival but also better prioritizes subjective value. Lastly, differences in decision-making policy trajectories emerged only for certain types of choices (OZ but not WZ), suggesting that mice adapted unique circuit-specific

computational processes after experiencing subsequent economic challenges.

At the termination of the study, we retested mice on the SI screening test and found a change from baseline SI scores only in stress-susceptible mice ($F_{1,2} = 5.854$, $p < .01$) (Figure S9), which increased to levels approximating an SI ratio of 1 (see Supplemental Discussion). Finally, all mice were sacrificed, and trunk blood was collected. We performed an enzyme-linked immunosorbent assay on serum to measure corticosterone levels. We found that mice with a history of defeat stress had significantly higher levels of serum corticosterone than nondefeated mice ($F_{1,31} = 6.767$, $p < .05$) (Figure S2H). We also noted that both nondefeated and defeated mice had elevated levels of serum corticosterone compared to what has typically been reported in the literature even for nondefeated mice, food-restricted mice, or singly housed mice (Figure S2H), suggesting that longitudinal testing on the Restaurant Row task itself is stressful, interacts with prior history of social defeat stress, may influence or be a response to metabolic demand, and is reflected in an integrated response of hypothalamic-pituitary-adrenal axis activity (27–31).

DISCUSSION

We used a novel 2-hit stress model to examine how the behavioral processes involved in recovering from an economic challenge are altered in mice that have a history of social stress. We found that when tested longitudinally on a neuro-economic task, mice exposed to social defeat mounted a behavioral response that was more robust than that of nondefeated mice only after but not before abruptly transitioning into a reward-scarce environment. We found that the magnitude and learning trajectory of the decision-making response to this economic challenge differed between mice that were resilient versus susceptible to the initial social stress, with resilient individuals optimizing the recovery of both food intake and subjective value. We also found that decision-making strategy changes among groups emerged only for certain types of choices, suggesting that a complex interaction between stress history and environment can influence computationally distinct valuation algorithms.

Economic stress is widely considered one of the most pervasive and universal burdens to mental health in the human experience and has been made worse by the COVID-19 pandemic and current inflationary period (23). Economic crises, including job loss and recessions, are associated with increased use of mental health services as well as increased mortality and suicide rates (32–35). Financial strain can lead to impaired functioning, poor overall physical health including poorer nutrition, and a psychological toll that lead to mood disorders such as depression (36–38). Economic stress can also precipitate first-episode mental illness in at-risk or otherwise previously healthy individuals (11). Our knowledge of the neurobiological underpinnings of economic stress in psychiatric disorders is limited; however, several reports in the human literature have linked effects of recent financial but not other types of stressors to 1) polymorphisms in the serotonin transporter gene, 2) long-lasting connectivity changes in the default mode network associated with increased activity of the

hypothalamic-pituitary-adrenal axis during social stress, and 3) even lower remission rates during antidepressant treatment (39–42). Virtually no animal studies reported to date have characterized the effects of economic challenges on behavior in a psychiatric disease model. However, more generally, animal tasks that have been used to study similar topics that involve changing task rules, contingencies, or effort demand tax the individual in ways such that pressure shifts in behavior toward strategies that may be less costly, as has commonly been seen in traditional operant tasks with escalating work schedules or in reversal learning paradigms (43–48). However, rewards in such tasks are rarely critical for survival. Furthermore, few studies have examined how changes in task rules are necessary to extract group differences in animal models used for the study of stress-related disorders—differences that would otherwise go unobserved when task demand is low (49–51).

Whether the behavioral changes that we observed following the economic challenge are adaptive or maladaptive requires close examination. Defeated mice demonstrated a faster response profile when renormalizing food intake than non-defeated mice. This can be interpreted in several ways depending on whether this is considered an abnormal response. Ultimately, the direction of this change is arguably most favorable for survival. Stress responses classically follow an inverted U-shaped relationship wherein too little or too much stress exposure, as well as the degree of the individual's response to stress, can be deleterious (52). Where mice with or without a history of social defeat fall along this inverted U-shaped curve when experiencing economic stress is debatable. It is possible that nondefeated mice were, overall, under less pressure to perform following the economic challenge given no other prior history of stress, and consequently their renormalization rates sufficed for them, especially if these animals were subject to less hunger or metabolic pressures (see [Supplemental Discussion](#)). Alternatively, if a slowed response is abnormal, nondefeated mice may be achieving weaker renormalization rates because, in the absence of a prior adverse experience, they had no prior challenges to overcome compared to defeated mice. This interpretation seems less favorable because behavioral changes after experiencing social defeat are often thought to reflect impaired function overall whereas repeated bouts of stress generally sensitize responses to future stress rather than promote stress tolerance, although mixed findings have been reported (53–55). Nonetheless, we found fundamental differences in multiple valuation algorithms that emerged across testing. Mice with versus without a history of social defeat stress, including both resilient and susceptible subgroups, diverged in their complex decision-making responses to an economic challenge depending on the type of choice being made.

Choices made between the OZ and WZ are thought to reflect fundamentally distinct decision-making algorithms (15–17,20,25,56). Mice learn to discriminate tones and make economically advantageous decisions in the OZ late in testing, generally after food intake has renormalized. This suggests that mice may be using cost-related information in ways that are not entirely in the service of maximizing food intake (18,25). Previous reports with hippocampal recordings in rodents and functional magnetic resonance imaging of the default mode network in humans tested on translated versions of the

Restaurant Row task found signatures of prospective deliberative decision-making processes wherein individuals were more likely to represent future competing options before making a choice (56–59). The learning that takes place in the trajectory of the OZ decision policies of resilient mice were more likely to factor in subjective value while simultaneously maximizing food consumption. It is possible that part of the deliberative processes engaged in by resilient animals while making cost-informed choices involves contemplating flavor more earnestly with algorithms that utilize future thinking, ultimately contributing to more gains in subjective value over their susceptible and nondefeated counterparts. In contrast, change-of-mind decision policies in the WZ, which appear to entirely promote food intake with no differences between groups of mice, have been shown to be uniquely affected by manipulations of the medial prefrontal cortex without altering OZ choices (17,58,60). WZ choices are also thought to depend on other complex interactions with the ventral striatum and amygdala (18,19). These data suggest that physically separable circuits that are differentially recruited by dissociable decision-making processes—separated in our task across space and time—can promote distinct facets of reward-related information, may be uniquely altered between susceptible versus resilient individuals, and may be clinically relevant (61).

Building from this study, future work could explore different stress-related biomarkers, including circuit-specific physiological or neurohormone changes measured longitudinally across this paradigm in response to economic stress (41,62). In addition, other 2-hit stress models, including models of early-life stress (see [Supplemental Discussion](#)) followed by economic challenges in adulthood, could shed light on how different combinations of unique stressors and experiences of adversity across the life span may give rise to distinct stress-related vulnerabilities or pathophysiological states (63–67). A limitation here includes controlling for economic stress on the task itself. This could be mitigated by transitioning into a reward-scarce environment more gradually and less abruptly because this may lessen the impact on both one's metabolic demand and perceived scarcity. Another limitation entails the fact that there are no direct measures of metabolic physiology considerations that may change as a result of social defeat stress, food restriction, or the changing task rules and environmental demands. Other questions that remain include understanding how economic stress alone could directly promote depression-related phenotypes as is seen in humans and how sex differences may emerge in response to this novel stress model in both male and female animals that experience prior histories of stress then characterized on Restaurant Row (68,69).

Conclusions

In summary, we found that when we used a novel 2-hit stress model by combining social stress followed by an economic challenge, mice displayed unique changes in how they recovered from a severe change in economic scarcity in a longitudinal decision-making paradigm. We discovered that mice that were resilient to social stress were more capable overall in their ability to recover from an economic challenge and did so in a manner that not only ensured food security but also prioritized subjective value, with changes in only certain types of decisions. This neuroeconomic task has been

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translated and validated for use across species including humans, enabling the study of evolutionarily conserved circuits that not only serve basic survival needs but also promote subjective well-being. The distinct computational processes that we found are uniquely altered by socioeconomic stress and may be differentially dysfunctional in individuals who are struggling with stress-related disorders such as depression (16,56,70–72).

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RD-dC and BMS were responsible for conceptualization, data curation, and visualization. RD-dC, S.J.R., E.J.N., and BMS developed the methodology. RD-dC, F.J.M.-R., LL, AM-T, and BMS were responsible for investigation. RD-dC, ZD, and BMS were responsible for formal analysis. RD-dC, D.J.C., S.J.R., E.J.N., and BMS acquired the funding. RD-dC, D.J.C., S.J.R., E.J.N., and BMS supervised the study. RD-dC and BMS wrote the original draft of the manuscript. All authors participated in reviewing and editing the manuscript.

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ARTICLE INFORMATION

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