Commentary

Cumulative Stress Burden on Motivated Action Revealed

Henry W. Kietzman and Shannon L. Gourley

Anhedonia is a primary feature of depression and other psychiatric illnesses and refers to a loss of pleasure in activities that were previously enjoyable—e.g., social interaction, sex, hobbies. "Motivational anhedonia" refers to difficulties in volitionally acting for outcomes known to be reinforcing based on previous experiences. Motivational anhedonia can be debilitating, interfering with day-to-day activities. The neurobiology of motivational anhedonia is not well understood, in part because traditional behavioral assays for model organisms require little "motivation" or goal seeking. Historically, mice or rats have been presented with a palatable food, such as sugar water. The organism need only approach and ingest, providing little insight into whether a rodent is translating previous experience into reward-seeking action. A second limitation is that mice or rats are typically tested after some period of stressor exposure or other insult, leaving opaque the processes by which anhedonic-like behavior forms.

Investigations using elaborate operant conditioning procedures in which rodents must work for reward indicate that stress and stress hormones cause amotivation and failures in goal-directed action ([1],[2])—resembling motivational anhedonia in depression—but the emergence of these behaviors remains understudied. In the current issue of *Biological Psychiatry*, Barthas *et al.* ([3]) presented a procedure for rapidly measuring aspects of anhedonic-like behavior in mice. The authors dissociated motivational from consummatory anhedonic-like behaviors (Figure 1), longitudinally characterized their development upon repeated threat, and, interestingly, revealed that they emerged and recovered on different time scales, allowing for the identification of potential causal factors.
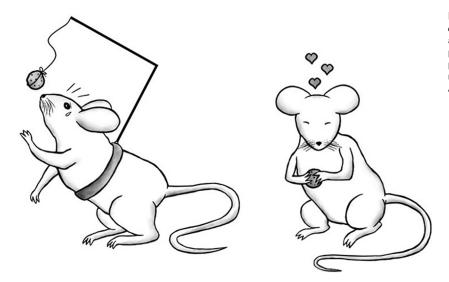
Fluid-restricted mice were trained to lick a spout for sucrose. Effectively, 10 licks triggered sucrose delivery, followed by a 5-second timeout while mice ingested the sucrose. Then, the response requirement was reinstated, and the mouse had to lick 10 more times to access the sucrose, and so on. Reinforcer delivery cycled between 0%, 3%, and 10% sucrose concentrations in predictable testing blocks, allowing the authors to measure response sensitivity to absolute outcome value—the 10% solution being most highly "valued"—as well as relative positive and negative contrast. A stress-related decrement in the number of reinforcers earned or sensitivity to the value of future reinforcement (inferred by energized responding ahead of higher sucrose concentrations) would be interpreted as evidence of motivational anhedonia. Meanwhile, a stress-related decrement in consummatory licks would be interpreted as "appetitive anhedonia" because it directly reflects the ingestion of a palatable food.

To trigger a recurring stress response, mice were subjected to repeated attack and threat in a "social defeat" procedure.

The experimental mouse is placed in the home cage of an aggressive male mouse, experiencing periods of both direct physical aggression and indirect sensory interaction. Conspecific-directed attack occurs in most animal species and is thus an ethologically relevant threat ([4]). In recent years, defeated mice have routinely been classified as "susceptible" versus "resilient," generally referring to those that avoid novel conspecifics versus those that resemble nonstressed control animals after defeat, revealing specific brain circuits and molecular factors involved in stressor vulnerability and resilience [e.g., ([5])].

Here, Barthas *et al.* ([3]) repeatedly tested mice as they underwent the social defeat procedure. Control mice obtained more reinforcers as the sucrose concentration increased, as expected, while mice ultimately categorized as susceptible developed insensitivity to sucrose concentration—responding equivalently for "low" and "high" concentrations. This insensitivity persisted even after the stressor exposure period. Mice that were ultimately categorized as resilient exhibited similar impairments, but this apparent reward insensitivity was transient, recovering once the defeat procedure ended. Interestingly, consummatory licks also dropped with repeated defeat in susceptible mice, but the deviation from baseline was transient, recovering upon cessation of the defeat procedure. Thus, the authors dissociated persistent motivational anhedonic-like behavior from briefer appetitive anhedonic-like behavior in susceptible mice and revealed that resilient mice were not identical to control mice but rather appeared to "bounce back" from repeated threat.

The authors next developed a computational model of "response vigor," taking into account the "cost" of licking (the energetic requirement of physical actions performed in quick succession), the "opportunity cost" (incurred when rewards are delayed due to inaction), and an estimation of satiety. Their efforts revealed a loss of motivational vigor in the "opportunity cost" parameter, indicating that susceptible mice were less able to discriminate between the opportunity cost of "losing out" on a high versus low sucrose concentration, and this loss emerged relatively late in the testing procedure, presumably representing cumulative effects of repeated duress.

To begin to understand cellular predictors of behavior, Barthas *et al.* ([3]) turned to Cg1 and M2, subregions of the anterior cingulate and motor cortices, respectively, involved in reward-related behavior. Equipped with a bicistronic expression vector permitting the visualization of somatic calcium transients in pyramidal neurons, the authors found that a single acute stressor elevated spontaneous activity in layer II/III neurons in mice ultimately categorized as susceptible, but not those categorized as resilient. Meanwhile, resilient mice

Figure 1. Separating seeking and taking. Barthas *et al.* (3) develop a procedure that rapidly captures—and dissociates—the mouse's propensity to work for palatable foods and consume those foods. The task provides a platform for quantifying stress burden on motivated behavior over time. (Illustration courtesy of Aylet Allen.)

exhibited a more dispersed distribution of Cg1/M2 activity change after a single social defeat—potentially a signature of resilience-related activity representing acute adaptation to stress.

A more nuanced picture arose in response to repeated defeat, with longitudinal Cg1/M2 activity tracking revealing marked cellular heterogeneity. Using hierarchical clustering to categorize this heterogeneity, 4 predominant profiles of cellular activity emerged, which the authors term cell types 1–4. Of these profiles, type 2 cells exhibited a monotonic decline in spontaneous activity and represented a greater percentage of cells in response to chronic social defeat in resilient mice. The other 3 cell clusters appeared in roughly equivalent percentages between groups, suggesting that type 2 cell activity confers stressor resilience. Thus, Barthas *et al.* (3) differentiate between cellular responses to repeated stress in susceptible versus resilient mice, and they reveal a cellular activity profile that may underlie behavioral adaptation over time.

Interestingly, some stress-related changes in neural activity were detectable before the emergence of behavioral modifications. If they are causally related to behavior, some process presumably bridges Cg1/M2 neuronal activity and stress-related behavioral (mal)adaptations. Determining the distinguishing features of type 2 cells in the future will be informative. Are they positioned within specific neural circuits? Do they communicate with the hypothalamic-pituitary-adrenal axis, or so-called reward circuitry—regions like the ventral striatum or ventral tegmental area?

A longitudinal analysis of the molecular/genomic profile of type 2 neurons may also shed light on divergent factors in stressor vulnerability and resilience. Presumably, the activity of certain intracellular signaling pathways in type 2 neurons changes and evolves with repeated stressor exposure. Understanding these modifications could reveal molecular "building blocks" of susceptibility and resilience. Famously, chronic stress disrupts neurotrophin systems in many regions of the brain, including the prefrontal cortex (6), and stimulating

BDNF-TrkB (brain-derived neurotrophic factor–tropomyosin receptor kinase B) systems can correct amotivation and failures in goal-oriented action in mice that are exposed to excess stress hormones (2,7). Thus, neurotrophin systems could provide an entryway into investigating individual differences in stress vulnerabilities; these investigations could be complemented by discovery-based strategies to reveal previously unappreciated factors.

Of note, stressors modify the structure of excitatory neurons throughout the cortex (8), and neuron structure (dendritic spine densities) in some regions correlates with stress-related insensitivity to goals (9). A future challenge will be to determine whether stress-related structural modifications are causally associated with stressor vulnerability or resilience.

One final point is that the stressor-exposed mice in Barthas *et al.* (3) did not consume less sucrose than control mice—rather, response patterns changed as stressor-exposed mice failed to differentiate between low and high sucrose concentrations. Thus, what is referred to as anhedonic-like behavior can be described in simple terms as insensitivity to the value of future reward. This definition differs significantly from what we might typically conceptualize as anhedonic-like behavior in rodents—in which a mouse or rat neglects a sucrose solution or generates less effort for reinforcers relative to nonstressed control animals [e.g., (2)]. Hopefully, pairing new, diverse behavioral assays with traditional procedures will ultimately lead to meaningful insights into different aspects of multifaceted disease symptoms like anhedonia.

Repeated stress has long-term physical and emotional consequences at both individual and societal levels. The clinical understanding that stressful life events can precipitate neuropsychiatric disorders such as depression (10) has invigorated decades of translational research aimed at better understanding the stressed brain. Although an acute stressor activates neural efforts presumed to maintain homeostasis, continued exposure to stress over time may instead bias the

brain toward maladaptation. This series of adaptations is perhaps best characterized by the concept of allostatic load, or a cascading series of adaptations resulting in heightened reactivity and an accumulation of putatively deleterious changes in the brain. How and when successive stress episodes result in such maladaptive responses is not well understood. Barthas *et al.* (3) make important inroads in resolving this issue by revealing the progressive emergence of behavioral impairments (or resiliencies) and heterogeneous adaptations in cortical activity through successive episodes of social stress.

Article Information

From the Medical Scientist Training Program (HWK) and the Departments of Pediatrics and Psychiatry (HWK, SLG), Emory University School of Medicine, and the Graduate Training Program in Neuroscience (HWK, SLG), Center for Translational Social Neuroscience (HWK, SLG), and the Yerkes National Primate Research Center (HWK, SLG), Emory University, Atlanta, Georgia.

Address correspondence to Shannon L. Gourley, Ph.D., Yerkes National Primate Research Center, 954 Gatewood Road NE, Atlanta, GA 30329; E-mail: shannon.l.gourley@emory.edu.

References

1. Dias-Ferreira E, Sousa JC, Melo I, Morgado P, Mesquita AR, Cerqueira JJ, *et al.* (2009): Chronic stress causes frontostriatal reorganization and affects decision-making. Science 325:621–625.
2. Gourley SL, Swanson AM, Jacobs AM, Howell JL, Mo M, Dileone RJ, *et al.* (2012): Action control is mediated by prefrontal BDNF and glucocorticoid receptor binding. Proc Natl Acad Sci U S A 109:20714–20719.
3. Barthas F, Hu MY, Siniscalchi MJ, Ali F, Mineur YS, Picciotto MR, Kwan AC (2020): Cumulative effects of social stress on reward-guided actions and prefrontal cortical activity. Biol Psychiatry 88:541–553.
4. Covington HE III, Newman EL, Leonard MZ, Miczek KA (2019): Translational models of adaptive and excessive fighting: An emerging role for neural circuits in pathological aggression [version 1; peer review: 3 approved]. F1000Research 2019, 8(F1000 Faculty Rev):963.
5. Krishnan V, Han MH, Graham DL, Berton O, Renthal W, Russo SJ, *et al.* (2007): Molecular adaptations underlying susceptibility and resistance to social defeat in brain reward regions. Cell 131:391–404.
6. Gerhard DM, Duman RS (2018): Rapid-acting antidepressants: Mechanistic insights and future directions. Curr Behav Neurosci Rep 5:36–47.
7. Barfield ET, Gerber KJ, Zimmermann KS, Ressler KJ, Parsons RG, Gourley SL (2017): Regulation of actions and habits by ventral hippocampal trkB and adolescent corticosterone exposure. PLoS Biol 15: e2003000.
8. McEwen BS, Morrison JH (2013): The brain on stress: Vulnerability and plasticity of the prefrontal cortex over the life course. Neuron 79:16–29.
9. Barfield ET, Gourley SL (2019): Glucocorticoid-sensitive ventral hippocampal–orbitofrontal cortical connections support goal-directed action – Curt Richter Award Paper 2019. Psychoneuroendocrinology 110:104436.
10. Kessler RC (1997): The effects of stressful life events on depression. Annu Rev Psychol 48:191–214.