Commentary

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A New Paradigm to Investigate the Neuroscience of Irritability in Youth

Hugo Martin and Neir Eshel

Irritability—a heightened tendency to respond to events with anger or frustration—is among the most common reasons that children present for psychiatric care (1). A symptom of multiple psychiatric disorders, chronic irritability not only reduces a child's quality of life but also elevates a child's risk for developing anxiety and depression in adulthood (2). In fact, irritability in youth is the cardinal feature of a new diagnosis added to the DSM-5: disruptive mood dysregulation disorder. Despite its clinical importance, however, the neurobiology of irritability remains poorly understood.

One tractable route to study irritability in the laboratory is to teach a subject to expect a reward, then omit that reward and measure how this frustrating event affects behavior. For well over half a century, in species as varied as pigeons, fish, and chimpanzees, scientists have observed two consistent effects: increased locomotor activity and increased aggression [for review, see (3)]. Given their conservation across evolution, it is likely that these so-called frustrative nonreward behaviors are adaptive: for example, they may allow an individual to overcome barriers to reward. But taken to extremes, behavioral responses to frustration can be counterproductive, such as when the resulting aggression is excessive or directed at inappropriate targets (4). Understanding the brain basis for frustration would be a major advance, opening the door for treatments that prevent frustration responses from crossing this maladaptive threshold (5).

In a recent issue of *Biological Psychiatry: Global Open Science*, Naik *et al.* (6) provide the scientific community with an elegant new behavioral paradigm to model frustration in juvenile mice, thus paving the way for the in-depth neural studies the field has long needed. Termed the alternate poking reward omission (APRO) task, this paradigm is as simple as it is robust. Thirsty juvenile mice are trained, over 3 days, to alternate their movements between two sides of a custom running track to obtain water reward. During these training sessions, rewards are delivered on all correct trials. On the fourth and fifth day, rewards are probabilistically omitted, such that the experimental mice receive 50% of the rewards on the fourth day, and only 20% on the fifth day. When compared with control mice that continued to receive all of the rewards, frustrated mice increased both their running speed and the number of times they visited the reward port, similar to the hyperlocomotive effects observed in previous studies of adult rodents (7). Minutes after mice performed the APRO task, the authors then tested the effect of frustration on a full battery of behavioral tests. They found that frustration increased aggression against smaller intruder mice, as previously reported in adult mice (8), without affecting nonaggressive social interactions, anxiety-like behaviors, or depressive-like behaviors.

Taken together, the results validate APRO as a reliable way to model frustration in juvenile animals—a boon for translational work on irritability in children. Perhaps the most significant advance is the length of training. Most previous paradigms required extensive, weeks-long training regimens, such that by the end of training, juvenile animals might already be considered adult. Here, the entire procedure, including frustration, takes less than 1 week. Furthermore, the authors were able to elicit similar behavioral responses, including aggression, in both male and female animals, unlike most previous paradigms, where aggression was measured only in males. Since irritability is common in both sexes (9), such results increase the translational relevance of APRO.

Because of its speed and simplicity, APRO may be well suited to numerous future refinements. For example, one open question is whether the paradigm can be repeated in the same subject. How does a second or third frustration compare with the first? If the behavioral effect is contingent on novelty or surprise, then later frustrations might produce smaller effects. Alternatively, if the behavioral effect arises primarily from the reward omission, then repeated omissions might actually induce more substantial outcomes. Such a repeated approach would increase statistical power by allowing within-subject comparisons, thereby reducing the total number of animals needed for an experiment. The ability to repeat the task may also simplify any pharmacological screens or neural circuit manipulations. Another potential refinement would be to study different types of reward omission in addition to the probabilistic omission reported here. Would the animals respond similarly if the reward were fully omitted, or if it were replaced with a less palatable reward? Frustrations can come in many forms, and it would be important to explore which of these forms is most likely to elicit which behavioral outcome. Finally, future users of APRO can consider incorporating an element of effort. Perhaps juvenile mice that work harder for their rewards would react more strongly when the rewards are omitted or show phenotypes in the anxiety- or depression-like tasks that they did not show in the current version. Together, these and other tweaks to the basic APRO task may further define the parameter space for future mechanistic studies.

Recent neuroimaging studies have revealed several circuit dysfunctions that might underlie irritability in children, including broad changes in the circuits that mediate reward learning, threat processing, and top-down behavioral control [for review, see (10)]. These studies lay the foundation for our understanding of the neurobiology of irritability, but they are limited

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by the spatial and temporal resolution of human neuroimaging techniques and remain correlational. The APRO task, in juvenile mice, opens the door for more precise and causal neural experiments. For example, brain-wide screens for immediate early gene expression can replicate the human imaging data but at finer spatial resolution, providing an unbiased approach to discover the brain regions most affected by frustration. The top hits from these screens can then be subjected to optogenetic or chemogenetic manipulations to test if the activity of these regions indeed modifies an animal's behavioral responses to frustration. It would be important, for example, to discover if the same circuits underlie both hyperlocomotion and aggression, or if these two responses to frustration can be dissociated at the neural level. Recording the activity of the behaviorally relevant brain regions can then shed light on the underlying mechanisms, in particular how an event is considered frustrating enough that it induces a behavioral response. This frustration threshold can vary dramatically between individuals, so understanding the neural processes that set the threshold would be a major advance.

The existing literature on frustration in animals uses protocols that differ in many ways: different training regimens, different rewards, different types of reward omission, and different strains and ages of mice, among many other factors. Given this diversity, it is remarkable that the behavioral outcomes tend to be so consistent. To maximize impact, it may be helpful for research groups to standardize their efforts, using the same set of protocols to search for the neural circuits of frustration in juveniles. The relative ease and simplicity of APRO could be an important starting point for such collaborations, ultimately inspiring new treatments for children suffering from irritability.

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Article Information

From the Department of Psychiatry and Behavioral Sciences, Stanford University, Stanford, California.

Address correspondence to Neir Eshel, M.D., Ph.D., at neshel@stanford.edu.

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