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Reward Mechanisms Across Aggressive and Addictive Forms of Externalizing Psychopathology

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The externalizing spectrum of psychopathology encompasses interrelated disinhibitory behaviors and distinctive aggressive and addictive conditions (1). Dysregulated reward mechanisms play a prominent feature in neurobiological models of addictive forms of externalizing (i.e., substance use disorders) (2). By contrast, theoretical perspectives on impulsive-aggressive behavior have emphasized the role of frontal-executive systems of the brain that regulate negative affectivity (anger and distress) and guide behavioral output (3). The article by Golden *et al.* (4) in this issue of *Biological Psychiatry* describes a series of studies that eloquently highlight the understudied role of reward mechanisms in aggressive-externalizing behaviors. Their findings suggest that appetitive processes seen in problematic substance use are also implicated in certain forms of aggressive behavior. The results reported by Golden *et al.* are in line with the externalizing spectrum framework in humans. Neurodevelopmental models of externalizing posit the role of dysfunctional mesolimbic (midbrain) dopamine function as a core liability conferring risk for a spectrum of disinhibitory problems that emerge in early childhood and result in aggressive and/or addictive problems by adulthood (5). In this commentary, I discuss the findings reported by these authors in relation to a neurobehavioral perspective on externalizing and consider their implications for the role of reward mechanisms in this debilitating, costly, and destructive spectrum of psychopathology.

The experiments reported by Golden *et al.* (4) underscore the important role of appetitive processes in certain aggressive phenotypes. Using well-validated rodent models of addiction involving operant conditioning procedures, the authors report compelling evidence for “addiction-like” reward mechanisms in aggressive behavior after forced abstinence, punished abstinence, and in preference for learned aggression over other rewards (palatable food). In the first experiment, they found that mice trained to act aggressively toward intruders were likely to “relapse” to aggressive behavior, as measured by seeking access to attack an intruder after a period of either 1 or 15 days of forced abstinence in their home cage (i.e., outside of the operant chamber). In the second experiment, aggression training was followed by an extinction procedure (punitive electric shocks) that initially eliminated aggressive behavior acquired through the training. Across two cohorts, relapse to aggression was observed by 35 days after punishment-induced abstinence from aggression.

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The third experiment in the series was conducted to examine individual differences in aggressive phenotypes and to determine whether a subset of animals exhibited “addictive” characteristics. Mice were first trained to self-administer food and act aggressively, and were then tested for relapse to aggression. In between tests for relapse to aggression, a voluntary suppression (discrete choice) procedure tested for aggression persistence where mice were given the mutually exclusive option for food or the opportunity to attack an intruder. Two cohorts of mice were tested at the beginning and end of the 14-day voluntary suppression period. Using within- and between-subjects designs, both cohorts exhibited increased relapse to aggression on the first day of the voluntary suppression period and the day after this test phase. Subsequent to the voluntary suppression period, procedures tested for the strength of reinforced aggression (progressive ratio schedule) and then sensitivity to punishment in extinguishing aggression. Cluster analyses were performed on dependent measures from experiment three in order to identify aggressive subtypes in the sample. One subset of mice (~19%) were classified as “compulsive aggression seeking,” showing addiction-like behavioral characteristics, including operant-induced attack behavior, relapse to aggression, decreased preference for food relative to opportunity to aggress, increased ratio of level pressing to obtain an opportunity to aggress, and resiliency to punishment-induced extinction. The remaining mice were classified as either typical aggression seeking (52%) or nonaggressive (29%).

A particularly important element of the approach taken by Golden *et al.* (4) was their focus on individual difference characteristics and identifying distinct aggressive phenotypes. While the majority of mice behaved in line with the hypothesis that aggression can be rewarding, a notable minority (~29%) were not trainable to self-administer access to an intruder and the opportunity to attack. The implication is that some animals are resistant to acting aggressively even when rewarded. Among those who did acquire aggression behavior through training, a key question is why some relapsed to aggression after forced or voluntary abstinence (~52%) whereas others exhibited a particularly pernicious form of aggression involving extensive reinforced attack behavior, strong likelihood to aggress in the face of alternative rewards, heightened susceptibility to relapse, willingness to increasingly work for opportunities to attack, and insensitivity to punishment. This latter subgroup of compulsive aggression seeking mice exhibited hallmark features of addiction, including heightened vulnerability to relapse and continued reinforced behavior in the face of negative consequences. As such, there is a clear parallel to draw between our currently limited abilities to effectively treat either form of externalizing. As discussed next, the research reported by Golden *et al.* (4) has important implications for neurobehavioral models of externalizing psychopathology in humans.

The externalizing spectrum model (1) provides an integrative framework for characterizing the well above chance co-occurrence between substance use and antisocial-aggressive behavior. Addictive and aggressive forms of externalizing are hypothesized to be interrelated in part because of a highly heritable common dispositional tendency toward weak impulse control (1,6). The externalizing spectrum model views callous-aggressive behavior (associated with psychopathy) (7) and substance-related addictions (2) as alternative (and often comorbid) expressions of a common disinhibitory liability. Aggressive and substance using outcomes are in turn shaped in one direction and/or the other by etiological influences

separate from the core disinhibitory liability. The findings of Golden *et al.* (4) suggest that an important etiological mechanism for the callous-aggressive expression of externalizing liability may involve an instinctual preference for aggressive action. Given that most animals in their research (~70%) acquired aggressive behavior through reward training, it can be theorized that the degree of linkage between reward circuitry and circuitry for agonistic action comprises a continuum, with some individuals possessing a higher degree of linkage between these systems. Given the separation between callous-aggression and substance addiction in the externalizing spectrum model, a critical question is whether this aggression-reward mechanism is separate from a reward-linkage mechanism for substance abuse. A neurodevelopmental perspective on externalizing proneness (5) highlights dysregulated mesolimbic dopamine functioning as a central etiological influence on a spectrum of disinhibitory problems from childhood into adulthood. In this model, bias for immediate rewards is a key mechanism shared across differing forms of externalizing. However, additional work will be needed to tease apart common versus distinctive reward-based mechanisms for aggressive compared to substance abusing facets of externalizing.

A further point is that neurobiological models are likely to provide a useful framework for differentiating aggressive phenotypes. Reward mechanisms are an integral feature of compulsive “addiction-like” aggression involving predatory, exploitative, and instrumentally motivated behavior. This is consistent with psychobiological perspectives on violence and psychopathic personality, a condition often involving proactive aggression and reckless disregard for others, indicating a role for rewarding processes in escalation of violent proclivities and repetitive aggressive action (8). From this perspective, it is hypothesized that the rewarding qualities of aggressive ideation and action may counteract chronic negative affectivity (e.g., feelings of alienation, dysphoria, and inefficacy) experienced by individuals who engage in mass violence (e.g., school or work shootings and certain acts of terrorism) (8). Fantasies of aggression/violence and the escalation to extreme behavioral enactment may involve a process in which aggressive behaviors are reinforced through their rewarding properties that also alleviate persistent negative affect. By contrast, impulsive (or reactive) forms of aggression likely involve distinct cognitive and affective features and underlying neural mechanisms (9). In particular, reactive aggression involves a lowered threshold for experiencing negative affect (anger and hostility forms of distress) coupled with reduced frontal-executive capacity for regulating affect and behavior (in the orbital medial prefrontal cortex in particular) (3,9). It will be important in future work to elucidate the neural mechanisms implicated in the observed results from the Golden *et al.* (4) study, including both premorbid factors and individual differences predictive of brain-based changes in the acquisition of operant-reinforced aggression. Related to this, a further important question concerns the role of frontal brain systems in modulating propensities toward both appetitive and reactive forms of aggression. Notwithstanding the potential limitations of rodent models of frontal-executive cognitive processes [however, see (10)], future work in both rodents and humans would benefit from examining the interactive and dynamic nature of frontal-executive, reward-based, and negative affectivity systems in predicting differing aggressive and substance abusing forms of externalizing problems.

In summary, in this issue of *Biological Psychiatry*, Golden *et al.* report on behavioral characteristics of aggressive behavior that appear consistent with findings from rodent

models of substance addiction. In addition to importantly emphasizing the role of appetitive (reward-based) processes in aggression, the reported research is notable for its focus on individual differences in aggressive subtypes. Their work is likely to further motivate future research directed at clarifying neurobiological mechanisms that are common and distinctive across aggression and substance abuse. Such efforts will be critically important for informing targeted assessment and intervention efforts for these costly and devastating conditions.

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