Commentary

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Capturing Individual Differences: Challenges in Animal Models of Posttraumatic Stress Disorder and Drug Abuse

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Many psychiatric disorders are comorbid with substance use disorder (SUD). Individuals with any mood or anxiety disorder are twice as likely to develop SUD compared with healthy individuals (1). Patients with posttraumatic stress disorder (PTSD) are no exception, with PTSD patients four times more likely to develop SUD than individuals without PTSD (2). However, despite numerous clinical reports of increased drug use in patients with PTSD and other mood disorders, preclinical studies have had difficulty replicating these effects in rodents.

In this issue of *Biological Psychiatry*, Enman *et al.* (3) investigated anhedonia-like symptoms and cocaine self-administration in an animal model of PTSD. Rats in the experimental group were exposed to single prolonged stress (SPS)—a putative animal model for PTSD—while rats serving as the control group were handled, and both groups were assessed 1 week later for sucrose preference, spontaneous locomotor activity, conditioned place preference for cocaine, cocaine self-administration, and dopamine receptor density within the striatum. In support of the face validity of SPS as an animal model of PTSD, the authors found that SPS resulted in reduced sucrose preference and reduced locomotor activity during the dark cycle, which seems to model clinical reports of anhedonia in patients with PTSD. Although evidence for dopaminergic disturbances in patients with PTSD has only limited support, Enman *et al.* also found decreased dopamine and D_2 receptor binding in the striatum, and increased dopamine transporter density in the caudal nucleus accumbens. Detracting from the face validity of SPS, however, they also found that their model resulted in reduced cocaine conditioned place preference and no difference from control animals in cocaine self-administration during acquisition or under extended access conditions, which appears to be at odds with clinical observations of increased comorbidity between PTSD and SUD.

Enman *et al.* are not alone in their inability to replicate comorbidity with SUD and anxiety and mood disorders in rodents, particularly disorders for which symptoms include anhedonia. One argument is that, unlike humans, rodents do not alleviate anhedonia by self-medicating with increased levels of drug use. However, a more likely explanation for these discrepant findings is the tendency to ignore the time course and individual differences when attempting to model comorbid psychiatric diseases.

In humans, PTSD is a serious, debilitating, often lifelong disorder that cannot be clinically diagnosed until >1 month after trauma exposure. Epidemiologic reports have shown that most individuals adapt to a severe stressor or trauma within 1–4 weeks (4), and rodent studies have paralleled this observation (5). However, despite this evidence and diagnostic requirement for substantial temporal separation from trauma to PTSD manifestation, many preclinical researchers do not wait an adequate amount of time from stress exposure to behavioral tests assessing for PTSD-like symptoms. Although the 1-week isolation period in the study by Enman *et al.* (3) was informative, face and translational validity would be improved, and perhaps the results would be different, with a more disease-relevant spacing from stress exposure to behavioral and neurochemical evaluation.

In order to model clinical PTSD, it is imperative to consider the importance of individual differences in response to trauma exposure. In the National Comorbidity Survey, Kessler *et al.* (2) reported epidemiologic findings in a national, noninstitutional cross-sectional sample. As shown in Figure 1 (2), an estimated 45.56% of individuals are exposed to one or more traumatic events in their lifetime. However, of individuals exposed to trauma, only an estimated 13.99% later develop PTSD. The fact that only a proportion of stress-exposed individuals subsequently develop a maladaptive phenotype is far too often disregarded in preclinical studies, which more often than not probe the stressed group as a homogeneous group for PTSD-like symptoms. Although there is a general focus on whether an animal model results in disease-relevant symptoms for face and translational validity, if an animal model does not capture similar proportions of disease-relevant symptoms it does not meet the burdens necessary for face, translational, and predictive validity.

Although Enman *et al.* (3) did not investigate individual differences in their SPS model of PTSD, a beautifully designed study by Toledano and Gisquet-Verrier (6) demonstrated that SPS can indeed engender phenotypes of susceptible and resilient rats long after stress exposure. In this study, rats were first tested for baseline anxiety-like and novelty reactivity behavior, after which the rats were exposed to SPS or control handling. To adequately model the time course of PTSD development, the authors waited 30 days before testing for anxiety- and PTSD-like symptoms in a battery of behavioral tests. Rats were classified as "susceptible" if their observed behavior was >1 SD from the mean of the control group in three indices—yielding a proportion of 37.5% "susceptible" and 62.5% "resilient" rats. Other researchers have found similar proportions of susceptible/resilient rodents 30 or more days following trauma exposure in different PTSD animal models (5), emphasizing the importance of both time course and individual differences.

The issue of individual differences in susceptibility/resiliency to PTSD following trauma becomes even more important when investigating comorbidity between disorders, as an

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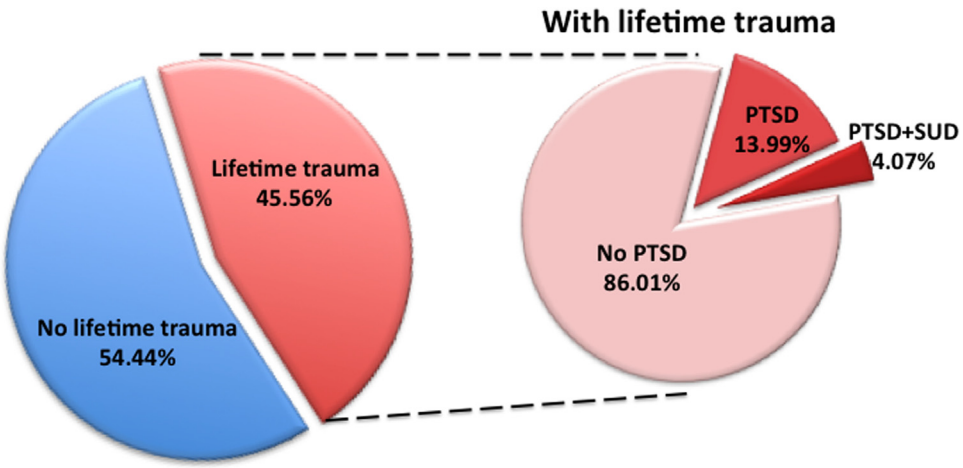

Figure 1. Lifetime trauma and incidence of posttraumatic stress disorder (PTSD) and substance use disorder (SUD). [Data from Kessler *et al.* (2)].

even smaller population is at risk for developing both disorders. As shown in Figure 1, of individuals who develop PTSD, only 29.10% will also exhibit comorbid SUD. Kessler *et al.* (2) reported that the incidence of SUD is four times higher in those with PTSD than those without PTSD. This comorbidity of PTSD and SUD is certainly a substantial concern, but the increased rate of SUD would occur in only approximately 4% of individuals exposed to severe stress or trauma.

Given these epidemiologic findings, it is not surprising that evidence for comorbid SUD and PTSD is limited in studies that do not account for individual differences. In the study by Enman *et al.* (3), no evidence for either increased cocaine conditioned place preference or self-administration was reported. With fewer than 10 rats per experiment exposed to SPS (only 5 for extended access cocaine self-administration), any effects of SPS-susceptible rats would be masked by the lack of effect in the SPS-resilient rats, composing at least 60% of the SPS group (6).

This issue is not unique to investigations of increased drug preference and self-administration in animal models of PTSD but in fact plagues research in the fields of other mood disorders as well. The incidence of SUD is also substantially increased in major depressive disorder (1), yet many researchers, including in our own laboratory, have struggled to replicate this effect in rodents. For example, we have previously demonstrated that chronic social defeat stress, an animal model that elicits some symptoms relevant to major depressive disorder results in attenuated as opposed to escalated cocaine self-administration in male rats (7), seemingly discrepant with clinical observations of increased rates of cocaine abuse within depressed patients.

However, an interesting study by Krishnan *et al.* (8) demonstrated that even an inbred strain of C57BL/6 mice showed distinct individual differences in susceptibility/resilience to chronic social defeat stress. After 10 days of subthreshold chronic social defeat stress, mice could be separated into two discrete groups, "susceptible" or "resilient," based on their responses in an array of behavioral and physiologic tests, most notably social interaction. When separated in this manner, only the susceptible mice showed increased cocaine conditioned place preference.

Similarly, we recently reported individual differences in anhedonia-like responses following chronic social defeat stress in female rats (9). Female rats were characterized as either "stress-vulnerable" or "stress-resistant" based on saccharin preference during chronic social defeat, and only one subgroup showed increased cocaine self-administration during a 24-hour "binge" as well as suppressed cocaine-induced extracellular dopamine efflux in the nucleus accumbens shell.

In conclusion, both time course and individual differences are essential considerations when studying stress-related disorders. Throughout life, we are all exposed to stress, from relatively minor stress to severe stress and trauma. However, only a subset of susceptible individuals goes on to develop a maladaptive psychiatric disorder such as PTSD or major depressive disorder, and among these susceptible individuals an even smaller subset develops comorbidity with SUD or other mood disorders. Furthermore, the effects of stress within these vulnerable individuals are observed long after stress exposure. Similar patterns of individual differences are observed in other psychiatric disorders, including SUD (10). It is imperative to consider individual differences when developing and implementing animal models to capture a human condition. We cannot study all animals that undergo stress in the same manner; even in inbred strains, individual animals may be more or less susceptible to experimental manipulations. Rather than individual differences being viewed as a limitation or impediment to preclinical research, such differences must be viewed as desirable and not disregarded as variability within a single stress-exposed group.

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Article Information

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