AMERICAN PSYCHOLOGICAL ASSOCIATION

Psychology of Addictive Behaviors

ISSN: 0893-164X

2022, Vol. 36, No. 8, 1023–1035
https://doi.org/10.1037/adb0000821

Central Stress Response Among Deprived and Continuing Marijuana Users and Nonusers

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Objective: We examined central nervous system [CNS] stress responses among deprived and continuing heavy marijuana users and nonusers. ***Method:*** Participants (N = 210; 46.7% female; M_{age} = 21.99; 91.4% White, 94.3% Non-Hispanic) were heavy marijuana users (N = 134) and nonusers (N = 76). Heavy users were randomly assigned to a 3-day marijuana deprivation condition (N = 68) or to continue using regularly (N = 66). Participants completed two threat-of-shock stressor tasks that manipulated stressor predictability by varying shock probability or timing. We measured central stress responses via startle potentiation (stressor conditions minus matched no-stressor condition). We examined two group contrasts (heavy use: all heavy users vs. nonusers; deprivation: deprived vs. continuing heavy users) on startle potentiation overall and moderated by stressor predictability (unpredictable vs. predictable). ***Results:*** Deprivation did not affect startle potentiation overall (timing task: p = .184; probability task: p = .328) or differently by stressor predictability (timing task: p = .147; probability task: p = .678). Heavy use did not affect startle potentiation overall (timing task: p = .213; probability task: p = .843) or differently by stressor predictability (timing task: p = .655; probability task: p = .273). Posthoc analyses showed mixed evidence of general startle reactivity × deprivation interaction on startle potentiation overall (timing task: p = .019; probability task: p = .056) and differently by stressor predictability (probability task: p = .024; timing task: p = .364). ***Conclusions:*** A history of marijuana use or acute deprivation did not alter central stress responses despite prominent theoretical expectations. This study adds to growing research on central stress responses in individuals with a history of drug use and begins to parse moderating roles of individual differences and stressor characteristics.

Public Health Significance Statement
Individuals with a history of drug use have been theorized to display atypical stress responses. This study does not find evidence of altered CNS stress responses when comparing heavy marijuana users to nonusers or when comparing continuing marijuana users to acutely deprived marijuana users. Expanding research to include naturalistic stressors, more stressor characteristics, and multisystemic responses may improve understanding of stress mechanisms in substance use disorders and offer paths forward for theory refinement and treatment.

Keywords: marijuana, stress, allostasis, startle potentiation, deprivation

Supplemental materials: https://doi.org/10.1037/adb0000821.supp

Taylor has used marijuana heavily for many years. They also routinely experience stressful events related and unrelated to their marijuana use. For example, Taylor has just been told there will be layoffs at their job—though it is unclear if Taylor themselves will be laid off and, if so, when. Many people in this situation may experience some sense of setback but ultimately view this event as a challenge to be overcome (e.g., working harder to impress the company). Instead, Taylor may: (a) ruminate on the chance of losing their job to the detriment of job performance; (b) find themselves irritable and on physical "high alert" to other, minor stressors; or (c)

This article was published Online First February 24, 2022.
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All data, analysis scripts and annotated results, questionnaires, and other study materials publicly available at https://osf.io/k8td3/.

Gaylen E. Fronk played lead role in formal analysis, visualization, writing of original draft and writing of review and editing, and supporting role in data curation. Kathryn Hefner played lead role in writing of original draft and supporting role in investigation, methodology, and writing of review and editing. Rebecca Gloria played lead role in conceptualization, data curation, formal analysis, investigation, methodology, project administration, and writing of original draft. John J. Curtin played lead role in conceptualization, data curation, funding acquisition, methodology, resources and validation, and supporting role in formal analysis, project administration, software, supervision, visualization, writing of original draft, and writing of review and editing.

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turn to marijuana for short-term relief. Taylor's responses exemplify maladaptive stress allostasis.

Stress allostasis refers to a multisystemic set of responses recruited to cope in the face of stressors (McEwen & Wingfield, 2010). Basic stress research has established that stress allostasis includes biological, physiological, and hormonal responses from the body's multiple stress systems (Chattarji et al., 2015; Lane et al., 2009). Subsequent, behavioral components of stress allostasis include reactive, proactive, successful, and less successful behaviors like diet, physical activity, sleep, and drug use. Together, these coordinated responses make up stress allostasis.

The body's stress systems (e.g., central nervous system [CNS], hypothalamic–pituitary–adrenal [HPA] axis, autonomic nervous system [ANS]) work together to respond to stressors (Chattarji et al., 2015; Lane et al., 2009). However, the CNS is a crucial stress system because it identifies what is threatening (i.e., stressful) and coordinates behavioral and physiological responses (McEwen & Gianaros, 2011). It exerts top–down control over other components of the allostatic response process while also receiving positive and negative feedback from other organs and stress systems (Lane et al., 2009).

Stress allostasis, and particularly central (i.e., CNS) stress responses, have figured prominently in seminal and contemporary theories of drug use etiology. Indeed, numerous theories assert that drug use (acute or chronic) and/or deprivation are associated with atypical, maladaptive stress allostasis (Baker et al., 2004; Gorka & Shankman, 2017; Kaye et al., 2017; Koob & Le Moal, 2008; see Fronk et al., 2020 for review).

Individual theories differ with respect to when and how atypical stress allostasis emerges among individuals with a history of drug use. Several theories suggest that maladaptive allostasis should be apparent when comparing individuals who use drugs chronically with those who do not. These differences may reflect a premorbid, stable individual difference (Gorka & Shankman, 2017). Taylor may have been predisposed to maladaptive stress responses, possibly contributing to their developing a substance use disorder. Atypical stress responses may also reflect a drug use-induced adaptation (Kaye et al., 2017; Koob & Le Moal, 2008). Taylor's initially recreational marijuana use may have altered their stress responding such that it became maladaptive over time and ultimately made them more likely to escalate their drug use.

Other theories posit that discontinuing drug use leads to acute withdrawal and associated affective distress, suggesting that central stress responses may be sensitized during deprivation or abstinence (e.g., Baker et al., 2004). For example, Taylor may be more likely to display the "high alert" maladaptive response if they are in withdrawal from marijuana use. Taylor may identify more events as stressful or threatening (i.e., an exaggerated central stress response), which may lead to overuse and eventual, compensatory blunting of their peripheral stress responses (e.g., HPA axis response). Animal models support this theory of sensitization during deprivation: a behavioral phenotype of anxiety following chronic drug exposure was most apparent in rodents during periods of drug deprivation (Koob, 2015; Smith & Aston-Jones, 2008).

Theories also diverge regarding whether these atypical responses differ by stressor characteristics. Drug use may affect responses to all stressors equally. Many theories about the relationship between stress and drug use do not differentiate between distinct types of stressors (e.g., Koob & Le Moal, 2008). However, long-standing evidence from basic stress research shows that characteristics of the stressor affect allostatic response (Segerstrom & Miller, 2004). In particular, stressor predictability plays an important role in stress allostasis as it relates to drug use (Kaye et al., 2017; Koob, 2015; Mantsch et al., 2016). For example, Taylor may have found this event more stressful because there was unpredictability about whether they would be laid off (i.e., unpredictable probability) and when that decision might occur (i.e., unpredictable timing).

Beyond timing and stressor characteristics, expectations regarding stress allostasis become even more nuanced when individual difference characteristics are introduced. Individual differences manifested across genes, traits, environments, and experiences can promote resilience or vulnerability in stress allostasis (Sapolsky, 2015). For example, sex differences may affect stress allostasis via biological pathways or gendered roles (Cohen et al., 2019). However, there is not yet clear evidence as to whether sex moderates stress allostasis among individuals who use drugs (Fronk et al., 2020). Stable individual differences in stress reactivity may also predict or moderate stress allostasis in animals (Taylor et al., 2016) and in humans (Bradford, Kaye, et al., 2014; Bradford et al., 2013; Hogle et al., 2010).

Thus, theoretical and empirical evidence suggests (a) individuals with a history of heavy drug use may have atypical stress responses, (b) acute deprivation may additionally alter these responses, and (c) characteristics of the stressor (e.g., predictability) and the individual (e.g., sex, stress reactivity) may play moderating roles.

The present study aimed to address three questions at these theoretical intersections in heavy marijuana users. Marijuana users have not been well-represented in studies of stress allostasis (for recent review, see Fronk et al., 2020). Indeed, only one well-powered study has examined central stress responses among heavy marijuana users, including both continuing users and individuals undergoing acute deprivation (Hefner et al., 2018). Additionally, increasing discussion around marijuana-related policies (e.g., legalization) in the United States makes understanding marijuana-specific processes an important public health question.

First, we examined when (if ever) atypical central stress responses occur among individuals with a history of marijuana use. We recruited individuals with and without a history of heavy marijuana use, and we randomly assigned heavy users to continuing (i.e., use as usual) or deprived (i.e., 3-day acute deprivation) conditions. We compared central stress responses between heavy marijuana users and nonusers (heavy user contrast) as well as between deprived and continuing heavy marijuana users (deprivation contrast). Existing, well-powered research has found that history of heavy marijuana use, but not deprivation, increased central stress responding (Hefner et al., 2018). Stress-substance use theories would suggest that central stress responses should differ between individuals with and without a history of heavy marijuana use as well as between deprived and continuing heavy marijuana users.

Second, we examined whether central stress responses differ by stressor predictability. We examined if stressor predictability (i.e., unpredictable vs. predictable) moderates the effects of heavy marijuana use and acute deprivation on central stress responses. The existing study of central stress responses in heavy marijuana users included only unpredictable and no-threat conditions (Hefner et al., 2018), making the present study the first to examine stressor predictability explicitly. We used two laboratory stressor (threat-of-shock) tasks with manipulations of predictability that have

previously captured drug-related alterations in central stress responses: probability and timing (Bradford et al., 2015; Hefner et al., 2013; Hogle et al., 2010; Moberg et al., 2017). The probability manipulation examined stress responses when an individual did not know if a stressor would occur at all. The timing manipulation examined stress responses when an individual knew a stressor would occur but not when. Basic stress research and stress-substance use research suggest stressor predictability should moderate central stress responses, with responses heightened to unpredictable (vs. predictable) stressors.

Third, we explored whether individual difference characteristics moderated any group (i.e., heavy user, deprivation) and stressor predictability effects in posthoc analyses. We explored sex and baseline stress reactivity as individual difference moderators. These two individual difference moderators both have putative theoretical import and have been frequently (though inconsistently) considered in the stress-substance use literature. Given their somewhat haphazard inclusion in extant literature as well as the posthoc nature of these analyses, we did not have explicit predictions about how these potential moderators would affect stress allostasis.

Across our study questions, we indexed central stress responses using startle potentiation, which is calculated as eyeblink startle response magnitude during a stressor (i.e., threat of shock) minus startle response magnitude during periods of no stressors. Startle potentiation is a measure of central stress responding frequently used in stress-substance use research (Fronk et al., 2020). Startle potentiation has well-established mechanisms in the extended amygdala, a brain region that is critical for integrating stress-relevant information within the CNS stress system (Fox & Shackman, 2019; for review of neural mechanisms of startle potentiation, see Davis et al., 2010). Thus, startle potentiation allowed us to probe central stress responses, a key component of the multisystemic stress allostatic process.

Method

Transparency and Openness

Data collection for this project was completed prior to our laboratory's commitment to preregistration, and preliminary analyses were previously conducted for a dissertation project. These factors combined to make this project inappropriate for preregistration. However, we value the principles of research transparency that are essential to the robustness and reproducibility of science (Schönbrodt et al., 2015). Consequently, we maximized transparency through several complementary methods.

First, we report how we determined our sample size, all data exclusions, all manipulations, and all available measures in the study (Simmons et al., 2012). Second, we note when we made analytic decisions that involved researcher degrees of freedom and outlined why we selected that option. Third, we completed a transparency checklist (Aczel et al., 2019), which can be found in the supplement of this paper. Fourth, we made the data, analysis scripts and annotated results, questionnaires, and other study materials publicly available (https://osf.io/k8td3/). Finally, we present results from two separate but related laboratory stressor (threat-of-shock) tasks. Although these tasks differ in how they manipulate stressor predictability, they serve as inherent, internal replications. We note explicitly the extent to which results are coherent or discordant across tasks, and we discuss our confidence in any findings with this replication framework in mind.

Participants

We recruited heavy marijuana users and nonusers from the Madison, WI (USA) community via flyers and online advertisements. Eligible participants were required to: (a) be 18–35 years of age; (b) provide data for both laboratory stressor tasks; (c) (*heavy users only*) report marijuana use 5 or more days per week, two or more times per day on days when used for at least 1 year (Arnone et al., 2008; Hefner et al., 2018; Pope & Yurgelun-Todd, 1996); and (d) (*nonusers only*) report lifetime marijuana use <50 times, never meeting criteria for heavy use, and no use in the past month. Participants were additionally required to report no: (a) 1ifetime substance use disorder (except marijuana or tobacco use disorder); (b) lifetime posttraumatic stress disorder, panic disorder, or severe or persistent mental illness (e.g., bipolar disorder, psychosis); (c) current use of psychotropic medication(s); or (c) medical condition(s) contraindicating shock exposure.

Two hundred eleven participants met inclusion and exclusion criteria.[1] Participants who dropped out were replaced. One participant assigned to the deprivation group was excluded from analyses and sample characteristics because their urine drug test (see below) showed they did not successfully abstain from marijuana use. This resulted in a final sample size of 210, which included 134 heavy marijuana users (65 female) and 76 minimal use controls (33 female).

General Procedure

Study procedures were reviewed and approved by the University of Wisconsin-Madison's Institutional Review Board (#SE-2008-0164). Participants completed an initial phone screening during which they answered questions about their medical and drug use history and learned brief study details. Preliminarily eligible participants were scheduled for an in-person screening visit. Informed consent was obtained, and eligibility was determined via a medical screening questionnaire, self-report assessment of marijuana use, and Module E (substance use) of the Structured Clinical Interview for DIagnostic and Statistical Manual IV (DSM-IV) Disorders, Research Version (SCID-RV-IV; First et al., 2002). All participants provided a urine sample to verify recent drug use.

Eligible participants completed assessments of general startle reactivity (baseline startle response in the absence of a stressor) and shock sensitivity (see Laboratory Tasks). These tasks were completed at both screening and experimental visits to allow us to evaluate whether deprivation would affect either general startle reactivity or shock sensitivity thresholds and, if so, to use the most appropriate values for each.[2] Next, heavy marijuana users were randomly assigned to nondeprived ($N = 67$) or deprived ($N = 68$) groups. Deprived marijuana users were required to abstain from

[1] Our planned sample size was 144 (48 participants per group). However, recruitment and data collection proceeded more efficiently than expected, and additional funding allowed recruiting additional participants to further increase statistical power.

[2] Analyses of group effects on general startle reactivity appear in the Results section. Analyses of group and timing effects on shock sensitivity appear in the Supplemental Material.

all marijuana use for 3 days before their experimental visit to ensure sufficient time for the onset of marijuana withdrawal symptoms (Budney & Hughes, 2006; Budney et al., 2003). Nondeprived heavy users were instructed to use marijuana as usual but refrain from use for 2 hr immediately before their experimental visit to avoid acute intoxication. Nonusers continued to avoid marijuana use as per their typical patterns.

When participants returned for their experimental visit, all heavy marijuana users provided a second urine sample to assess recent drug use. We calculated Tetrahydrocannabinol (THC) to creatinine ratios from this experimental visit as well as specimen ratios, creatinine-normalized specimen 2 (experimental visit)/creatinine-normalized specimen 1 (screening visit), per existing guidelines (Hefner et al., 2018; Huestis & Cone, 1998; see Supplemental Material for full urinalysis details). Marijuana users also completed the Marijuana Craving Questionnaire-17 (MCQ-17; Heishman et al., 2001) and the Marijuana Withdrawal Checklist (MWC; Budney et al., 1999). All participants completed the general startle reactivity and shock sensitivity assessments again.

Next, participants completed two laboratory stressor tasks (see Laboratory Tasks) that included unpredictable and predictable stressors (threat of electric shock). Across these two tasks, unpredictable stressors were unpredictable with respect to the stressor's probability (stressor probability task; Bradford, Magruder, et al., 2014; Hefner & Curtin, 2012) or timing (stressor timing task; Hefner et al., 2013; Moberg et al., 2017). Predictable stressors were comparable in both tasks (i.e., 100% probable and temporally certain/immediate). Task order was counterbalanced across participants, and tasks were separated by a 10-min break. After the two laboratory stressor tasks, heavy marijuana users completed the marijuana self-report measures (MCQ-17, MWC) again. All participants completed a computerized battery of self-report measures (see Supplemental Material for full list of measures). At the end of the visit, participants were debriefed and paid at a rate of $30/hr for both visits. Deprived heavy marijuana users were mailed a $200 deprivation bonus once abstinence was confirmed via urinalysis.

Laboratory Tasks

General Startle Reactivity Measurement

This task measured participants' baseline startle response to an acoustic startle probe (see details below) in the absence of other stressors. Participants viewed a series of 20 colored square cues on a computer monitor. Each cue was presented for 5 s with a variable intertrial interval (ITI; range 5–12 s). We measured general startle reactivity to be used as a covariate to increase statistical power in all startle potentiation analyses following previous recommendations (Bradford, Kaye, et al., 2014).

Shock Sensitivity Assessment

We measured participants' subjective shock sensitivity using previously established procedures from our lab (Bradford, Magruder, et al., 2014; Kaye et al., 2016) using a custom, optically isolated electric shock generator (Curtin et al., 2001; see schematic in OSF materials). Participants rated a series of up to twenty-five 200 ms electric shocks of increasing intensity (7 mA maximum) administered across the distal phalanges of the 2nd and 4th fingers of the right hand. The procedure ended when participants reached their personal tolerance threshold indicated by giving a rating of 100, described as "maximum tolerable intensity." This value was used during the two stressor tasks to control for individual differences in subjective shock sensitivity.

Stressor Probability Task

This task manipulated stressor predictability by varying the probability of shock administration during cues. Participants viewed a series of 7–8 colored square cues per block. Each cue was presented for 5 s and separated by an ITI (range = 14.5–19.5 s). Shocks were administered 0.25 s before cue offset. There were three types of blocks: 20% shock (unpredictable stressor), 100% shock (predictable stressor), or no-shock (no stressor). Participants were informed of cue-shock contingencies to ensure robust differences in responding across block types. A message was presented on the monitor before each block to indicate block type, and text remained on-screen throughout the block. Participants completed two of each block (15 cues total per type) in one of four counterbalanced orders. The task lasted approximately 20 min.

Stressor Timing Task

This task manipulated stressor predictability by varying the duration of the cues, which produced varied timing of shock administration. Participants viewed a series of colored square cues separated by a variable ITI (range = 10–20 s). There were four types of blocks: unpredictable duration cues with shocks (unpredictable stressor), predictable duration cues with shocks (predictable stressor), unpredictable duration cues without shock (unpredictable no stressor), and predictable duration cues without shock (predictable no stressor). In unpredictable stressor blocks, there were 12 cues presented (6 per block). Cue duration varied among 5, 20, 50, and 80 s. In predictable stressor blocks, 10 cues (5 per block) were presented. Cue duration was 5 s for all cues in this block type. In both types of stressor blocks, shocks were administered during 100% of cues 0.25 s prior to cue offset. This made shock timing unpredictable during unpredictable stressor blocks (4.75–79.75 s after cue onset) and predictable during predictable stressor blocks (4.75 s after cue onset). Duration of cues and ITIs was identical in the corresponding no stressor blocks. Participants were informed of cue-shock contingencies to ensure robust differences in responding across block types. A message was presented on the monitor before each block to indicate block type, and text remained on-screen throughout the block. Participants completed two of each block in one of eight counterbalanced orders. The task lasted approximately 30 min, with a 5-min break after the 4th block.

Startle Response Measurement and Quantification

Electromyographic activity in the orbicularis oculi muscle was sampled with Neuroscan Synamps (see footnote 2) bioamplifiers (Compumedics Neuroscan, Charlotte, NC) at 2000 Hz with an onboard digital bandpass filter (.05–500 Hz) from electrodes placed under the right eye according to published guidelines (Blumenthal et al., 2005; van Boxtel, 1998). Eyeblink startle response was measured in response to startle-eliciting acoustic probes (50 ms of 102 dB white noise with near instantaneous rise time). Acoustic probe

intensity was verified weekly using a Bruel & Kjaer Type 2,203 Precision Sound Level Meter (Hottinger, Bruel, & Kjaer, Duluth, GA). Data reduction and processing followed published guidelines (Blumenthal et al., 2005). We performed offline processing in Matlab using EEGLab (Delorme & Makeig, 2004) and PhysBox (Curtin, 2011) plugins. This processing included high pass filtering (28 Hz, 4th-order Butterworth, zero phase shift), rectification, smoothing (30 Hz, 2nd-order Butterworth low-pass filter, zero phase shift), epoching (50–250 ms surrounding probe), and baseline correction. Startle magnitude was scored as the peak response between 20 and 100 ms postprobe onset. We rejected trials containing an artifact, consistent with standard practices from our laboratory (Kaye et al., 2016). This included trials with deflections greater than 20V in the 50 ms preprobe baseline (i.e., unstable baseline) and trials with mean activity 10V between 150 and 250 ms postprobe onset (i.e., baseline overcorrection due to preepoch artifact).

Across tasks, startle potentiation was calculated as the difference in startle magnitude during acoustic probes presented in stressor blocks relative to acoustic probes in corresponding no-stressor blocks. Startle potentiation served as our primary measure of central stress allostasis.

In the general startle reactivity task, three acoustic white noise startle probes were presented prior to the first cue to habituate participants to the acoustic probes. Following this, 16 probes were presented (4 during ITIs; 12 during cues). General startle reactivity was scored as the mean startle response across the 16 probes (Bradford, Magruder, et al., 2014). In the probability task, eight acoustic startle probes were presented during a subset of cues in each block (24 cue probes total). Probes occurred 4.5 s after cue onset. Unpredictable and predictable startle potentiation were calculated by subtracting mean startle response of no stressor blocks from mean startle response of unpredictable and predictable stressor blocks, respectively. In the timing task, 12 acoustic startle probes were presented during cues in unpredictable stressor and no stressor blocks (6 probes 4.5 s after cue onset; 2 probes each at 19.5, 49.5, and 79.5 s after cue onset). Six startle probes were presented during cues in predictable stressor and no stressor blocks (4.5 s after cue onset). Unpredictable and predictable startle potentiation were calculated by subtracting mean startle response of no stressor blocks from mean startle response of corresponding unpredictable or predictable stressor blocks (e.g., unpredictable stressor—unpredictable no stressor).

Analysis Plan

Data Exclusions

We excluded participants from analyses of a specific laboratory task if >20% of their trials were rejected for high artifact (see Startle Response Quantification & Measurement [above]), consistent with prior research in our laboratory, including preregistered studies (e.g., Kaye et al., 2019). These criteria excluded four participants from general startle reactivity analyses (final $N = 206$), five participants from the stressor probability task analyses (final $N = 205$), and three participants from the stressor timing task analyses (final $N = 207$).

Analytic Models

We evaluated study hypotheses using general linear models (multiple regression) using the tidyverse (Wickham et al., 2019) and lmSupport (Curtin, 2015) packages in R within the R Studio integrated development environment (R Core Team, 2020; RStudio Team, 2020). Models were estimated for startle potentiation with repeated measures for stressor predictability (unpredictable, predictable) in each laboratory stressor task. All models included Group as the focal predictor, which was coded with two planned orthogonal contrasts: a heavy user contrast (all heavy marijuana users vs. nonusers), and a deprivation contrast (deprived vs. nondeprived marijuana users). All models also included mean-centered general startle reactivity as an interactive covariate to increase power to detect focal effects following previous recommendations (Bradford, Kaye, et al., 2014). We report partial eta squared (η_p^2) to quantify effect size of significant effects in the linear models. Additional covariate selection and case analysis were conducted individually for each model (see Supplemental Material for details). Results are reported with outliers removed, but in all cases, results were identical with outliers included.

Results

Sample Characteristics and Manipulation Checks

Sample characteristics appear in Table 1 (Demographics) and Table 2 (Individual Differences).

Deprivation manipulation descriptive statistics and *p*-values appear in Table 3. Urinalysis confirmed lower THC to creatinine ratios at the experimental visit and overall specimen ratios in deprived versus continuing users, suggesting a successful deprivation manipulation. Self-reported withdrawal (MWC) and craving (MCQ) at the experimental visit (pretasks) were higher among deprived versus nondeprived heavy users, further supporting the manipulation.

We confirmed significant startle potentiation, (i.e., greater startle response during threat versus no-threat blocks) timing task: $b = 51.37$, $t(200) = 18.94$, $p < .001$; probability task: $b = 55.20$, $t(197) = 18.54$, $p < .001$. Simple effect analyses confirmed startle response was higher during unpredictable (vs. corresponding no-threat) blocks, timing task: $b = 52.33$, $t(200) = 17.17$, $p < .001$; probability task: $b = 62.33$, $t(197) = 18.12$, $p < .001$, and during predictable (vs. corresponding no-threat) blocks, timing task: $b = 48.86$, $t(199) = 15.83$, $p < .001$; probability task: $b = 48.69$, $t(198) = 15.66$, $p < .001$. There were no effects of task order (counterbalanced) on startle potentiation overall, (timing task: $p = .624$; probability task: $p = .222$) or differently by stressor predictability (timing task: $p = .923$; probability task: $p = .866$).

Startle potentiation outcomes had adequate internal consistency estimates that were comparable to values observed in a recent psychometric evaluation study (Kaye et al., 2016). See Supplement for full psychometric data for startle outcomes and all self-report measures.

General Startle Reactivity Analyses

The deprivation manipulation did not impact general startle reactivity (deprivation effect, $p = .608$). Consequently, we used each participant's mean general startle reactivity across sessions as a covariate in task analyses to improve reliability. If only one measurement was available (i.e., excessive artifact from one session), we used their single, nonartifactual measurement to avoid excluding

Table 1
Demographic Characteristics

Measure	Nonuser	Continuing	Deprived	Total
Gender				
Female	43.4% (33)	50.0% (33)	47.1% (32)	46.7% (98)
Male	56.6% (43)	50.0% (33)	52.9% (36)	53.3% (112)
Race				
American Indian	0.0% (0)	1.5% (1)	0.0% (0)	0.5% (1)
Asian	3.9% (3)	1.5% (1)	2.9% (2)	2.9% (6)
Black	1.3% (1)	9.1% (6)	4.4% (3)	4.8% (10)
White	93.4% (71)	87.9% (58)	92.6% (63)	91.4% (192)
Unreported	1.3% (1)	0.0% (0)	0.0% (0)	0.5% (1)
Ethnicity				
Non-Hispanic	96.1% (73)	92.4% (61)	94.1% (64)	94.8% (198)
Hispanic	2.6% (2)	7.6% (5)	5.9% (4)	5.2% (11)
Unreported	1.3% (1)	0.0% (0)	0.0% (0)	0.5% (1)
Education				
2-year degree	2.6% (2)	3.0% (2)	5.9% (4)	3.8% (8)
Advanced degree	2.6% (2)	1.5% (1)	0.0% (0)	1.4% (3)
College degree	27.6% (21)	9.1% (6)	13.2% (9)	17.1% (36)
High school/GED	6.6% (5)	25.8% (17)	13.2% (9)	14.8% (31)
Some college	59.2% (45)	60.6% (40)	67.6% (46)	62.4% (131)
Unreported	1.3% (1)	0.0% (0)	0.0% (0)	0.5% (1)
Age	22.00 (3.59)	22.64 (3.82)	21.35 (2.90)	21.99 (3.48)
Income	8982.31 (10361.78)	12153.03 (12960.38)	9914.71 (11886.26)	10280.74 (11739.84)

Note. Values for Age and Income represent mean (*SD*). All other values represent % (*N*). GED = General Equivalancy Diploma.

participants for artifactual or otherwise missing general startle reactivity.

Primary Analyses

Point estimates from primary analyses appear in Table 4.

Deprivation Effects

There were no significant main effects of deprivation on startle potentiation in the stressor probability task ($p = .328$) or in the stressor timing task ($p = .184$). There were also no significant deprivation × stressor predictability interactions in the stressor probability task ($p = .678$) or in the stressor timing task ($p = .147$).

Heavy Use Effects

There were no significant main effects of heavy use on startle potentiation in the stressor probability task ($p = .843$) or in the stressor timing task ($p = .213$). There were also no significant heavy use × stressor predictability interactions in the stressor probability task ($p = .273$) or in the stressor timing task ($p = .655$).

Power Analyses

Given the null effects reported above, we quantified power posthoc to detect key effect sizes given our final sample size using Cohen's rules of thumb for η_p^2 (large: 0.14, moderate: 0.06, small: 0.01; Cohen, 1992). We conservatively set $N = 205$ (the fewest participants in a task analysis, range of 205–207) and number of parameter estimates at seven (the most parameters among models, range of 4–7). We had 99.99% power to detect a large effect and 94.47% power to detect a moderate effect. The smallest effect we could detect with 80% power was $\eta_p^2 = 0.04$, which represents a small to moderate effect size. Previous research using startle potentiation in comparable stressor predictability tasks in substance use research has observed η_p^2 effect sizes ranging from .03 to .16 ($MD = .06$, $M = .09$; Bradford et al., 2013, 2017; Hefner & Curtin, 2012; Hefner et al., 2013, 2018; Moberg et al., 2017; Moberg & Curtin, 2009).

Posthoc Analyses: Moderation by General Startle Reactivity

Although general startle reactivity was included as an interactive covariate in our primary analyses for reasons of statistical power, the pattern of results we observed prompted us to explore these interactions explicitly.[3] Data displaying these interactions appear in Figure 1.

Deprivation × General Startle Reactivity

There was a significant general startle reactivity × deprivation interaction on startle potentiation in the timing task, $b = 0.21$, 95% CI [0.04, 0.39], $t(200) = 2.37$, $\eta_p^2 = 0.03$, $p = .019$. Follow-up region of significance analyses showed a significant deprivation contrast for participants with general startle reactivity in the 67th percentile ($p = .046$) and above. A descriptively similar general startle

[3] Exploring general startle reactivity as a moderator prompted us to conduct posthoc analyses examining whether biological sex (male vs. female) moderated deprivation or heavy use, given its frequent yet inconsistent inclusion in stress-drug use research (Fronk et al., 2020). We did not find sex × deprivation interactions (probability task: $p = .971$; timing task: $p = .381$) or sex × deprivation × stressor predictability interactions (probability task: $p = .362$; timing task: $p = .076$). We did not find sex × heavy use interactions (probability task: $p = .657$; timing task: $p = .740$) or sex × heavy use × stressor predictability interactions (probability task: $p = .911$; timing task: $p = .098$).

Table 2
Individual Differences Characteristics by Participant Group

Measure	Nonuser mean (*SD*)	Continuing user mean (*SD*)	Deprived user mean (*SD*)	Heavy user effect	Deprivation effect
BAI (BAS-drive)	0.67 (1.02)	1.44 (1.86)	1.57 (1.99)	$b = 0.84$, $t = 3.50$, $p = .001$	$b = 0.13$, $t = 0.45$, $p = .657$
BAI (BAS-fun seeking)	20.21 (3.26)	19.3 (3.60)	19.45 (3.49)	$b = -0.84$, $t = -1.69$, $p = .094$	$b = 0.14$, $t = 0.24$, $p = .809$
BAI (BAS-reward responsiveness)	16.43 (1.60)	17.2 (1.65)	16.82 (1.72)	$b = 0.58$, $t = 2.44$, $p = .016$	$b = -0.38$, $t = -1.31$, $p = .191$
BAI (BIS-punishment)	10.64 (1.74)	10.95 (1.91)	10.88 (2.14)	$b = 0.28$, $t = 1.00$, $p = .320$	$b = -0.07$, $t = -0.22$, $p = .825$
FSS (Total)	11.69 (1.86)	12.38 (1.90)	12.58 (2.38)	$b = 0.79$, $t = 2.66$, $p = .008$	$b = 0.20$, $t = 0.57$, $p = .568$
SMA (Total)	95.56 (19.61)	98.23 (21.56)	98.21 (21.27)	$b = 2.66$, $t = 0.89$, $p = .377$	$b = -0.02$, $t = -0.01$, $p = .996$
MPS (Constraint)	33.03 (6.12)	34.52 (6.88)	34.58 (5.19)	$b = 1.52$, $t = 1.73$, $p = .085$	$b = 0.07$, $t = 0.06$, $p = .950$
MPS (Positive emotionality)	16.88 (4.93)	17.89 (5.89)	17.61 (5.56)	$b = 0.87$, $t = 1.11$, $p = .269$	$b = -0.28$, $t = -0.30$, $p = .766$
MPS (Negative emotionality)	72.19 (16.42)	76.12 (15.16)	75.3 (12.92)	$b = 3.52$, $t = 1.63$, $p = .105$	$b = -0.82$, $t = -0.32$, $p = .752$
PANAS (Positive)	34.52 (13.43)	41.55 (15.08)	40.06 (17.32)	$b = 6.28$, $t = 2.85$, $p = .005$	$b = -1.49$, $t = -0.56$, $p = .576$
PANAS (Negative)	71.28 (14.52)	70.39 (13.12)	67.45 (12.99)	$b = -2.36$, $t = -1.20$, $p = .231$	$b = -2.95$, $t = -1.25$, $p = .213$

Note. BAI = Behavioral Activation and Inhibition Scales; BAS = Behavioral Activation Scale; BIS = Behavioral Inhibition Scale; FSS = fear survey schedule; SMA = Short Michigan Alcohol Test; MPS = Multidimensional Personality Scale-Brief; PANAS = positive and negative affect schedule.

reactivity × deprivation interaction emerged in the probability task, $b = 0.19$, 95% CI [0.00, 0.38], $t(197) = 1.92$, $\eta_p^2 = 0.02$, $p = .056$. Region of significance analyses showed a significant deprivation contrast for participants with general startle reactivity in the 85th percentile ($p = .048$) and above.

There was a significant general startle reactivity × deprivation × stressor predictability interaction in the stressor probability task, $b = 0.19$, 95% CI [0.02, 0.35], $t(196) = 2.27$, $\eta_p^2 = 0.03$, $p = .024$. We conducted follow-up region of significance analyses of the deprivation contrast across general startle reactivity values for each stressor type (i.e., unpredictable and predictable startle potentiation, separately). The simple effect of deprivation was not significant during predictable stressors at any values of general startle reactivity. In contrast, the simple effect of deprivation was significant for participants with general startle reactivity in the 69th percentile ($p = .046$) and above. There was not a significant general startle reactivity × deprivation × stressor predictability interaction in the stressor timing task ($p = .364$).

Heavy Use × General Startle Reactivity

There were no general startle reactivity × heavy use interactions on startle potentiation (stressor probability task: $p = .306$; stressor timing task: $p = .621$) or general startle reactivity × heavy use × stressor predictability interactions (stressor probability task: $p = .557$; stressor timing task: $p = .619$).

Discussion

We did not find effects of acute deprivation (deprived vs. continuing heavy marijuana users) or history of heavy marijuana use (heavy users vs. nonusers) on startle potentiation either overall or as a function of stressor predictability. These findings were consistent across two laboratory tasks that manipulated stressor predictability with respect to stressor timing or probability. These findings suggest that neither acute deprivation nor a history of heavy marijuana use affects central stress responding, as indexed by startle potentiation.

These results are somewhat surprising given addiction etiology theories that would expect group differences in stress responses. Theoretical models differ with respect to when and how atypical stress allostasis emerges among individuals with a history of drug use, but they can agree that stress responses should differ between individuals with and without a history of drug use (Gorka & Shankman, 2017; Kaye et al., 2017; Koob & Le Moal, 2008). Additionally, there is theoretical and preclinical support for acute deprivation further affecting stress responses among individuals who use drugs (Baker et al., 2004; Koob, 2015; Smith & Aston-Jones, 2008).

Despite this theoretical impetus to expect group differences, evidence is accumulating to suggest otherwise. Among well-powered studies, individuals with a history of heavy drug use (vs. nonusing controls) generally do not display evidence of atypical central stress responses to stressors overall (Bradford et al., 2015; Gorka & Shankman, 2017; Hefner et al., 2018; Hogle & Curtin, 2006; Moberg et al., 2017; Piper & Curtin, 2006). Our study supports this conclusion, as we did not find an effect of history of heavy marijuana use on central stress responding.

Table 3
Deprivation Manipulation

Measure	Continuing user mean (*SD*)	Deprived user mean (*SD*)	Deprivation effect
Marijuana withdrawal checklist (total)	5.03 (4.66)	9.78 (7.61)	$b = 4.75$, $t = 4.34$, $p < .001$
Marijuana craving questionnaire (total)	74.18 (12.47)	80.26 (14.47)	$b = 6.08$, $t = 2.61$, $p = .010$
THC creatinine ratio (experimental visit)	2.96 (3.55)	0.94 (1.26)	$b = -2.02$, $t = -4.42$, $p < .001$
Specimen ratio	1.13 (0.9)	0.36 (0.26)	$b = -0.78$, $t = -6.84$, $p < .001$

Note. Self-reported withdrawal and craving are greater among deprived (vs. continuing) heavy marijuana users. Tetrahydrocannabinol (THC) creatinine ratio from the experimental visit (postdeprivation), and the specimen ratio across visits are lower among deprived (vs. continuing) heavy marijuana users. These findings support a successful deprivation manipulation.

There is some evidence that individuals with a history of drug use generally display increased (i.e., sensitized) central stress responses compared to nonusing controls when stressors are unpredictable (Gorka & Shankman, 2017; Hefner et al., 2018; Moberg et al., 2017; but see Bradford et al., 2015). In the present study, stressor predictability did not moderate the effect of heavy marijuana use in either laboratory stressor task. Our findings reduce confidence in the (tentative) conclusions from existing studies and suggest more research will be needed to clarify whether these effects are nuanced or are simply inconsistent due to no true population effect.

There is not convincing evidence that acute deprivation affects central stress responding either overall or differently by stressor predictability (Bradford et al., 2015; Cinciripini et al., 2006; Hefner et al., 2018; Lam et al., 2012; Piper & Curtin, 2006; Robinson et al., 2012; but see Hogle et al., 2010). The present study supports extant research, as we also did not find effects of deprivation on central stress responses overall or differently by stressor predictability.

Several strengths of the present study increase confidence in these null effects. First, our study was well-powered as demonstrated by our power analyses. Second, we had robust contrasts: heavy marijuana users were required to report substantial marijuana use (≥2 times per day, 5 days per week for ≥1 year), and our deprivation manipulation was successful, as evidenced by urinalysis and self-report results (see Table 2). Third, we used a dependent measure (startle potentiation) that has been shown previously to be sensitive to changes in central stress responses during alcohol challenge (Bradford et al., 2013; Hefner et al., 2013; Moberg et al., 2017). Fourth, all null effects from our primary analyses were consistent across two laboratory stressor tasks that had significant conceptual overlap (i.e., two different manipulations of stressor predictability). Finally, although it remains possible that the null effects observed here are unique to marijuana, they cohere with null effects from nicotine and alcohol studies, and they contrast with the only other well-powered marijuana study (Hefner et al., 2018), thus reducing the likelihood that these effects are specific to heavy marijuana (vs. other drug) use.

This pattern of null effects in these growing bodies of literature, supported by the present study, suggests that theories regarding the role of stress and stress allostasis in addiction etiology may no longer reflect the current state of the evidence. Although group and deprivation differences would be expected theoretically, effects are either consistently null or widely inconsistent across well-powered studies. Theoretical models may need to be updated to incorporate not only accruing evidence but also appropriate nuance given the complexity of the stress–substance use relationship. We must expand theories to move toward a more comprehensive understanding of atypical stress allostasis in individuals with a history of drug use. Specifically, we should include stressor characteristics, timing/phase of use/recovery, measurement, and stress systems. We unpack these elements in the following paragraphs.

One way that theories may become more nuanced is by considering individual differences. Individual differences manifested as genes, traits, environments, and experiences can promote resilience or vulnerability in stress allostasis (Sapolsky, 2015). We examined two individual difference moderators in this study in posthoc analyses: general startle reactivity and sex.

Preclinical evidence supports the moderating role of general startle reactivity: stressor exposure increased methamphetamine-seeking behavior and use in rats but only for animals identified as high-reactivity based on behavioral tests (Taylor et al., 2016). In humans, general startle reactivity predicts stressor response to predictable and unpredictable stressors (Bradford, Kaye, et al., 2014). It also moderates central stress responses to unpredictable stressors during alcohol challenge (Bradford et al., 2013) and among nicotine-deprived smokers, although this effect was not described in our earlier publication (Hogle et al., 2010).

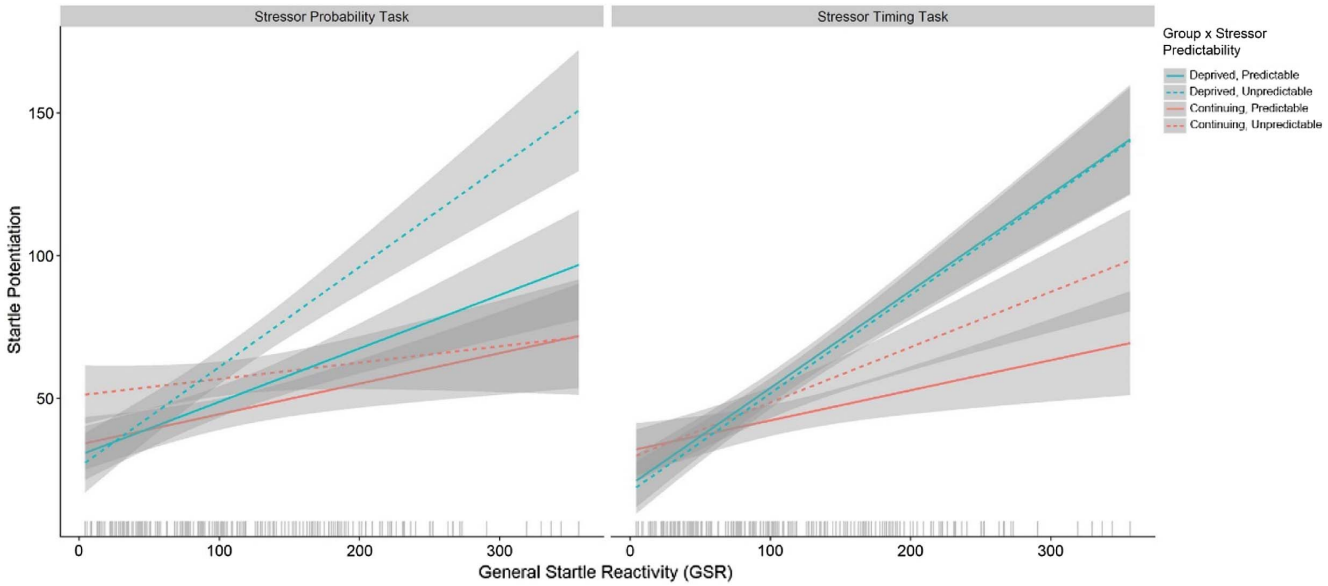
Table 4
Point Estimates From Primary Analyses

	Stressor probability task		Stressor timing task	
Group	Mean startle potentiation (*SE*)	Difference (U—P) in startle potentiation (*SE*)	Mean startle potentiation (*SE*)	Difference (U—P) in startle potentiation (*SE*)
Nonusers	54.34 (4.98)	18.19 (4.16)	46.67 (4.51)	1.40 (5.40)
Heavy marijuana users				
Continuing	51.94 (5.24)	11.15 (4.41)	49.20 (4.80)	7.99 (5.79)
Deprived	59.21 (5.25)	13.75 (4.44)	58.24 (4.78)	−1.71 (5.73)

Note. Values represent mean (*SE*). All values are displayed in microvolts (μV). U = Unpredictable; P = Predictable.

Figure 1

Group × General Startle Reactivity Effects on Predictable and Unpredictable Central Stress Responses



Note. General startle reactivity moderates the deprivation effect (deprived vs. continuing heavy marijuana users) on startle potentiation in the stressor timing (left) but not the stressor probability (right) task. There is also a stressor predictability × general startle reactivity × deprivation interaction on startle potentiation in the stressor probability task (left) but not in the stressor timing task (right). Raw general startle reactivity values are displayed in the strip chart along the *x*-axis. Models used to derive predicted values include additive covariates held at their mean and exclude outliers. Gray shaded areas represent ±1 standard error around point estimates. General startle reactivity and startle potentiation are displayed in microvolts (μV). See the online article for the color version of this figure.

We found some evidence that general startle reactivity (i.e., startle reactivity in the absence of a stressor) may moderate central stress responses among heavy marijuana users. Specifically, among heavy users with high general startle reactivity, deprivation increased central stress responses in both laboratory stressor tasks. Additionally, deprived heavy marijuana users (vs. continuing users) with high general startle reactivity displayed increased central stress responses selectively during unpredictable stressors; however, this latter moderating effect was not consistent across both laboratory tasks. In contrast, general startle reactivity did not moderate the effects of history of heavy marijuana use on CNS stress responses either overall or differently by stressor predictability in either task. Overall, these effects suggest that general startle reactivity may play a moderating role in central stress responses. However, the effects were not completely consistent, which may suggest that task-specific predictability manipulations (i.e., probability vs. timing) produced distinct effects. Regardless, any conclusions warrant caution given the exploratory nature of these analyses, and future research will be needed to explore this nuance.

We did not find evidence that sex moderates deprivation or heavy use effects for central stress responses either overall or differently by stressor predictability. Sex has been the most frequently studied moderator in stress-drug use research to date, perhaps motivated by research that suggests sex differences may affect stress responses via biological pathways or gendered social roles (Cohen et al., 2019). Despite frequent consideration, however, sex does not clearly moderate central stress responses across well-powered studies (Fronk et al., 2020).

Research examining the relationship between drug use and stress allostasis has thus far infrequently and haphazardly measured individual difference moderators, making it difficult to identify robust patterns of findings. Consequently, there is limited evidence to which we can compare the findings from the present study regarding moderator roles for general startle reactivity and sex in central stress responses, and it remains unclear whether inconsistent results in these areas are a product of inconsistent/infrequent measurement, selective reporting, or a lack of effect. However, if theories are to incorporate nuance surrounding individual differences, more research will need to be conducted to parse these and other moderating effects.

Theories also may need to incorporate nuance by employing more naturalistic stressors. Research examining how momentary perceived stress and explicit stressors affect drug use has begun to use in situ methods to monitor participants' responses to real-world stressors and any subsequent drug use (for recent, well-powered examples, see Cambron et al., 2019, 2020; Potter et al., 2021; Savoy et al., 2021; Schultz et al., 2022). These stressors have higher ecological validity than common laboratory stressors (e.g., electric shock, aversive pictures). Our understanding of how stress responses differ following a history of drug use or acute deprivation may change when we measure responses to naturalistic rather than contrived stressors.

The difficulty emerges when we consider how to measure central stress responses in situ. Technological advances may permit real-world monitoring of peripheral (i.e., ANS and HPA-axis) indices of stress allostasis such as heart rate or blood pressure (e.g., via clinical research-grade mobile physiology sensors and even common smartwatches) or subjective distress (e.g., via self-report ecological momentary assessment [EMA]). Some solutions are being developed for other purposes (e.g., a wireless electroencephalography [EEG] patch designed for continuous epilepsy monitoring) that may be adopted for use here. However, assessing central stress responses in situ remains a challenge.

Instead, researchers have begun to develop creative solutions to examine responses to naturalistic stressors in the laboratory. For example, in an unpublished manuscript, Villano and colleagues have conducted fMRI while undergraduates first receive their real midterm exam grades. This approach combines precise, powerful laboratory measurement of central stress responding with naturalistic stressors. Future research could use these methods to capture stress responses in the face of other anticipated naturalistic stressors such as court sentencing and appeal decisions, rent or bill due dates, or medical test results. Although measuring responses around a single stressor could limit the number of trials that could be collected, there may instead be opportunities to sample over a longer time (e.g., days, weeks) leading up to a known, upcoming naturalistic stressor. Additionally, dense sampling outside the laboratory (e.g., via EMA methods) can be time-locked immediately before and after a naturalistic stressor (Villano et al., 2020).

Stressor predictability has been routinely considered in the limited central stress response research, including the present study. However, basic stress research has established that stressor characteristics such as controllability, intensity/severity, duration and chronicity, stressor appraisal, and available coping resources all affect stress allostasis (Dimoff & Sayette, 2017; Lazarus, 1999; Maier & Seligman, 2016; Sapolsky, 2015; Sayette, 1993; Segerstrom & Miller, 2004; Weiss, 1972). It will be worthwhile to understand the impact of these characteristics on central stress responses and how those effects change or remain consistent across periods of drug use and recovery. If we hope to use naturalistic stressors, we must assess these stressor characteristics on an individual basis rather than manipulating them; however, we must be wary of how appraising these characteristics may itself affect stress allostasis.

Existing research examining central stress responses also typically (as in this study) compares groups at single timepoints or across a few widely spaced measurements. Moreover, the timepoints at which we conduct these measurements are limited by arbitrary definitions (e.g., "acute deprivation") that are simultaneously too broad (e.g., existing research includes periods of deprivation that range from 12 hr to 1 week) and too narrowly defined (e.g., a single measurement 12 hr postquit rather than continuous/dense measurement for 24 hr following quitting). Instead, we should prioritize denser sampling approaches. Gathering many dense observations across use and recovery phases in a single cohort may permit powerful within-subjects comparisons and a more nuanced understanding of the time course of when and how stress responding changes. Specifically, measuring stress responding prior to quitting, during quit attempts, and frequently across withdrawal and deprivation may help us to unpack when and how acute deprivation or withdrawal might potentiate responses. There is also very little research examining how stress responses change following continued abstinence; measuring densely across time would permit this understanding. Dense sampling of stress responses over time will allow us to identify critical windows for when response patterns shift across periods of use, deprivation, acute intoxication, recovery, and relapse. Understanding these patterns may inform treatment targets in any given phase; for example, perhaps stress management treatments may be key during deprivation but are not helpful later in recovery.

Finally, basic stress research has established that the CNS, HPA axis, and ANS stress systems do not operate in isolation but rather exhibit short- and long-term positive and negative feedback on one another (Chattarji et al., 2015; Lane et al., 2009). Consequently, stress responses can differ across systems (e.g., blunted ANS response and sensitized CNS response). Indeed, there is robust evidence that individuals with a history of drug use have decreased peripheral (i.e., ANS and HPA axis) stress allostasis (Al'Absi et al., 2013; Evans et al., 2012; Ginty et al., 2014; Nakajima & Al'Absi, 2014; Phillips et al., 2009; Sheffield et al., 1997; Ward et al., 1994). Research examining peripheral responses not only has many extremely well-powered studies but also has a plethora of small-*N* studies that generally support the same conclusions, thereby increasing confidence in those effects (see supplemental tables in Fronk et al., 2020). These conclusions suggest that a history of drug use is affecting stress responding but perhaps in more complex and dynamic ways than our current theories anticipate.

Understanding fully how a history of drug use affects stress allostasis will come only when it is examined as a multisystemic response; however, stress allostasis research in the substance use domain has typically only examined responses within a single system. The interplay among the various stress systems makes parsing individual mechanisms difficult, but appreciating these complexities offers a path forward toward targeting stress mechanisms in treatments for substance use disorders. Medications and psychosocial treatments (e.g., mindfulness meditation) that target responses across CNS, HPA-axis, or ANS stress systems will need to be tailored to incorporate these feedback loops among allostatic systems to maximize therapeutic benefit.

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Received July 9, 2021
Revision received November 16, 2021
Accepted January 11, 2022 ■