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Weaker Memory Performance Exacerbates Stress-Induced Cannabis Craving in Youths' Daily Lives

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Abstract

Theories of addiction posit that stimuli associated with drug use, including both exteroceptive (e.g., paraphernalia) and interoceptive (e.g., feeling tense or stressed), evoke craving and contribute to the pathogenesis of substance misuse. Control over drug cue response and stress is essential for moderating use. Building from laboratory data supporting associations between cue exposure, stress, and craving, this study tested whether these associations generalize to real-world settings and examined whether a well-vetted neurocognitive control capacity (i.e., working memory, or WM) moderated associations. Youths ($N = 85$; 15–24 years old) completed baseline and ecological momentary assessments. Cue exposure and participants' average stress predicted higher craving. Youths with weaker WM experienced stronger craving at higher-stress moments but not when faced with cues. Interactions were present for both previous-moment and same-moment stress. Craving among adolescents with stronger WM was not swayed by momentary stress. Findings suggest that stronger WM protects against craving at more stressful moments.

Keywords

cannabis, adolescence, executive function, working memory, ecological momentary assessment, open data

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Expansion of cannabis legalization is outpacing the capacity of clinical science to inform policy decisions. This trend appears to reflect society's rising acceptance of cannabis, and studies show that cannabis is perceived as less harmful than alcohol and other drugs (Nutt, King, Saulsbury, & Blakemore, 2007). However, nearly 1 in 10 individuals who experiment with cannabis will become addicted (Lopez-Quintero et al., 2011), and these odds increase to about 1 in 2 among daily users (Hall & Degenhardt, 2009). This addiction potential, coupled with strong evidence that regular cannabis use is associated with a host of other adverse consequences (Volkow, Baler, Compton, & Weiss, 2014), calls for increased efforts to elucidate factors associated with the development and maintenance of maladaptive use.

Adolescence and emerging adulthood are key periods for the onset and escalation of cannabis use (Brook, Zhang, Leukefeld, & Brook, 2016; Ellickson, Martino, & Collins, 2004; Ellickson, Tucker, Klein, & Saner, 2004). In the United States, the first use of cannabis typically begins at age 13 years and peaks before age 20 years; an estimated 3.2 million youths ages 18 to 25 years use cannabis each day (Substance Abuse and Mental Health Services Administration, 2012, 2014). Moreover, early cannabis use is associated with myriad acute and lasting adverse effects, such as unintentional injury, suicide, heightened risk for addiction, and neurocognitive decline (Lubman, Cheetham, & Yucel, 2015; Meier et al.,

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2012; Volkow, Compton, & Weiss, 2014; Volkow, Swanson, et al., 2016; Wagner & Anthony, 2002). Understanding the factors that shape cannabis misuse among youths is critical for prevention, early intervention, and treatment strategies aimed toward reducing harmful outcomes and curbing lasting struggles with addiction.

Leading theories of addiction postulate that conditioned responses to stimuli associated with repeated drug use, including both exteroceptive cues (e.g., paraphernalia) and interoceptive cues (e.g., emotional states), drive desire for drug taking (i.e., craving) and are important contributors to the pathogenesis of addiction (Volkow, Koob, & McLellan, 2016). Human laboratory studies have demonstrated that exposure to exteroceptive cannabis-related stimuli increases subjective craving and physiological arousal in adults and youths with cannabis use disorder (CUD; Gray, LaRowe, & Upadhyaya, 2008; Gray, LaRowe, Watson, & Carpenter, 2011; McRae-Clark et al., 2011). Neuroimaging research shows that cannabis cue exposure activates brain regions that govern reward and craving and are associated with relapse (Charboneau et al., 2013; Filbey & DeWitt, 2012), and these activation patterns are distinct from persons with no history of cannabis use (Cousijn et al., 2013). In addition, adults with cannabis dependence show patterns of functional brain connectivity during cannabis cue exposure that differ from nondependent cannabis users (Filbey & Dunlop, 2014).

Negative emotions can also become conditioned cues that elicit craving, promote addiction, and precipitate relapse (Volkow, Koob, & McLellan, 2016). Within this framework, stress has received the most empirical attention. Affect regulation theories of addiction posit that stress evokes craving, which in turn precipitates cannabis use. From this perspective, craving functions as an important middle step between stress and cannabis misuse (Baker, Piper, McCarthy, Majeskie, & Fiore, 2004; Wise, 1988). Laboratory paradigms that elicit stress evoke cannabis craving among adult cannabis users with and without cannabis dependence (Buckner, Zvolensky, Ecker, & Jeffries, 2016), a finding that is similar across most abused substances (Childs & de Wit, 2010; Fox, Bergquist, Hong, & Sinha, 2007; Sinha et al., 2009). These controlled observations are consistent with survey research that shows that stress relief is a commonly reported motivational factor for cannabis use (Copeland, Swift, & Rees, 2001), and coping-related motives are associated with greater levels of cannabis use and cannabis-related problems among both adolescents and adults (Bonn-Miller, Zvolensky, & Bernstein, 2007; Lee, Neighbors, & Woods, 2007; Simons, Gaher, Correia, Hansen, & Christopher, 2005).

Despite evidence that exposure to cannabis cues and stress drives a strong desire for drug use, mounting research suggests that individual differences in executive function may influence these associations. Behavioral self-regulation draws on a critical balance between the strength of the impulse, urge, or desire to engage in maladaptive behavior, such as cannabis use, and an individual's ability to inhibit this desire (Kelley, Wagner, & Heatherton, 2015). Failures to self-regulate often occur when an individual is faced with drug cues or emotional distress but his or her capacity to moderate impulses or desires is limited or impaired (Heatherton & Wagner, 2011).

Nearly all contemporary models of addiction purport a functional association between neurocognitive executive abilities and substance misuse, and this connection appears especially salient for youths (Gustavson et al., 2017). Key facets of executive function govern emotional regulation and continue to develop into the mid-20s (Luna, Garver, Urban, Lazar, & Sweeney, 2004). Immature or compromised executive function is associated with difficulty regulating emotional reactions to affectively laden stimuli and stressful events (Heatherton & Wagner, 2011; Kelley et al., 2015), which may predispose youths to maladaptive emotion-driven behavior and substance use (Gustavson et al., 2017). There is also strong evidence that drug use compromises or delays maturation of executive abilities (Squeglia & Gray, 2016), which further confers liability for substance use and may play a central role in the pathogenesis of addiction.

Working memory (WM), a core facet of executive functioning, is impaired by acute, heavy cannabis use (Owens et al., 2019; Scott et al., 2018). WM governs the capacity to briefly store, update, and monitor goal-directed behavior as well as shield these goals from distractions (Engle, Tuholski, Laughlin, & Conway, 1999; Hofmann, Schmeichel, & Baddeley, 2012; Kane, Bleckley, Conway, & Engle, 2001). This capacity for cognitive control facilitates adaptive regulation of one's own thoughts (Brewin & Beaton, 2002; Brewin & Smart, 2005; Kane et al., 2007) and emotions (Schmeichel & Demaree, 2010; Schmeichel, Volokhov, & Demaree, 2008). When exposed to highly salient information, WM load is increased, thereby decreasing one's ability to attend to other less salient information and inhibit responses (Hester & Garavan, 2005). The combined effect of weak WM with increased salience of drug cues and emotionally charged contexts (e.g., stress) makes it challenging for substance users to regulate impulsive drives, such as craving (Goldstein & Volkow, 2011). For example, a well-powered investigation found that recent cannabis use is associated with reduced activation in brain regions in the executive-control network during a WM task (Owens et al., 2019). Neurostimulation that targets the dorsolateral prefrontal cortex, a key

brain area in WM (Petrides, 2000), decreases craving across different substances (Jansen et al., 2013). Preliminary findings from targeted cognitive-training interventions support the role of WM in reducing or stabilizing drug use in community and clinical samples (Houben, Wiers, & Jansen, 2011; Rass et al., 2015; Verdejo-Garcia, 2016), although recent findings on these interventions are mixed (Khemiri, Brynte, Stunkel, Klingberg, & Jayaram-Lindstrom, 2019; Wanmaker et al., 2018). Yet despite a strong theoretical basis, there are no data evaluating whether WM indeed modulates substance craving in association with drug cues or stressful contexts.

The present study leveraged ecological momentary assessment (EMA) methods to examine within-day associations between exposure to cannabis cues (i.e., cannabis-related stimuli and locations and people associated with prior use) and stress and cannabis craving among adolescents and young adults. EMA methods capture phenomena at the moment they occur and provide a rigorous and ecologically valid test of associations among variables that fluctuate in tandem with contextual influences. We sought to elucidate whether exposure to cannabis cues or stress potentiates craving and test whether variation in WM moderates these associations. We focused on craving for conceptual and methodological reasons. Craving is a chief motivational determinant of substance use in nearly all conceptual models of addiction (Skinner & Aubin, 2010; Tiffany & Wray, 2012), and research shows that it is a strong predictor of subsequent substance use (Ramirez & Miranda, 2014). Methodologically, by focusing on craving with EMA, we captured a construct that is unconstrained by situational factors (e.g., drug availability, opportunity to use) and fluctuates within persons, affording greater variability.

Our EMA approach addressed gaps in existing literature by focusing on real-time momentary craving among young cannabis users and evaluating whether exposure to cannabis cues and stress, assessed concurrently and earlier in the day, help explain within-day fluctuations in craving. No study has leveraged EMA methods to evaluate associations between stress and cannabis craving, although researchers have used EMA to show how stress is associated with craving in methadone-maintained cocaine- and opioid-dependent outpatients (Preston et al., 2017). Additionally, several EMA studies examined the association between cannabis craving and general negative affect. Findings show that high-arousal negative affect (e.g., anxiety) is associated with cannabis craving (Buckner, Crosby, Silgado, Wonderlich, & Schmidt, 2012; Shrier, Ross, & Blood, 2014; Shrier, Walls, Kendall, & Blood, 2012). Although suggestive, these studies did not directly assess stress in cannabis users or test the modulating effects of WM.

EMA also affords the advantage of temporal specificity. We were specifically interested in examining within-day associations of both same-moment (i.e., concurrent) and previous-moment (i.e., lagged) cue exposure and stress with craving to address temporal ordering of effects. Therefore, we tested a concurrent model in which associations between cue exposure, stress, and craving reported during the same measurement time were evaluated. We hypothesized that exposure to cannabis cues and stress would be positively associated with cannabis craving reported during the same measurement time, after accounting for other contextual influences (e.g., time of day, day of week), and this association would be more pronounced among youths with lower WM performance.

For better temporal resolution, we also examined a lagged model to test whether cue exposure or stress experienced earlier in the day predicted craving later that day after accounting for other contextual influences and concurrent effects. Temporal ordering was particularly relevant for stress because a same-moment association of stress and craving could plausibly indicate either that stress increases craving or that craving increases stress. For cue exposure, however, it seemed less likely that craving would lead to same-moment cue exposure. Additionally, we expected cues to have a stronger immediate (i.e., same moment), rather than delayed (i.e., previous moment), association with craving. We hypothesized that interactions between WM and previous-moment cue exposure as well as stress would be associated with craving.

Method

Participants

Participants were 85 youths, ages 15 to 24 years (M = 19.75, SD = 2.08; 41 female, 48.2%). Fifty-five percent were White, 3.5% American Indian/Alaska Native, 2.4% Asian, 29.4% Black, 1.2% Native Hawaiian/Pacific Islander, and 1.2% another race, and 17.6% reported their ethnicity to be Hispanic. Participants were recruited for a larger randomized clinical trial that tested the effects of a medication on cannabis use (Miranda et al., 2017). The current secondary analysis, which includes momentary data culled from a 1- to 2-week EMA monitoring period, focused solely on data collected at baseline prior to randomization and medication administration. To be eligible, participants had to use cannabis at least twice weekly in the past 30 days and endorse at least one symptom of cannabis abuse or dependence (i.e., show some clinically significant problems associated with use). Exclusion criteria were cannabis treatment in the past 30 days;

mandated treatment; current Axis I psychopathology other than cannabis, alcohol, nicotine, or disruptive behavior disorders; current suicidal thoughts or psychotic symptoms; and medical conditions or medications that contraindicated the pharmacotherapy. Female participants were excluded if they were pregnant, nursing, or unwilling to use birth control.

At baseline, participants reported using an average of 43.7 g (*SD* = 46.7) of cannabis over 62.5 days (*SD* = 24.5) of the previous 90 days. Forty percent of the total sample reported using cannabis on at least 78 of the previous 90 days, and approximately 10% reported using every day. Sixteen participants (18.2%) met the criteria for cannabis abuse according to the fourth edition, text revision, of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM–IV–TR*; American Psychiatric Association, 2000), and 51 participants (60%) met the *DSM–IV–TR* criteria for dependence, substantially higher than the estimates of past-year CUD among adolescents ages 12 to 17 years (2.7%) and young adults ages 18 to 25 years (4.9%; Center for Behavioral Health Statistics and Quality, 2015), with a mean age of onset of 16.5 (*SD* = 1.97) years for abuse and 17.32 (*SD* = 2.04) years for dependence.

Procedures

Participants were recruited from the community through advertising (e.g., flyers, stationed informational booths) for the larger clinical trial registered at http://clinicaltrials.gov (NCT01110434) and described in the work by Miranda et al. (2017). All measures, conditions, and data exclusions relevant to the current study are described herein, along with how the sample size was determined. Interested volunteers completed a phone screening to ascertain preliminary eligibility status, and those found tentatively eligible completed an in-person screening at our research facility. Before participants were enrolled in the study, written informed consent was obtained from youths 18 years and older and the parents of minors; assent was obtained from minors. Participants completed a baseline assessment of demographic and clinical characteristics.

Data for the present study were from a prerandomization, premedication EMA period that lasted 4 to 14 days (*M* = 7.35, *SD* = 1.58). Participants were not instructed to reduce or otherwise alter substance use patterns. They received thorough instructions on how to use the handheld wireless electronic device (Omnia; Samsung Electronics, Ridgefield Park, NJ) to complete the EMA protocol with software developed for this study. Participants were compensated $10 per day for any interaction with the EMA device, regardless of report type. The Brown University Institutional Review Board approved the study protocol (No. 0903992676), which adhered to the World Medical Association Declaration of Helsinki.

Measures

Demographic and clinical characteristics. Psychiatric diagnoses, including CUD, were derived using the Kiddie Schedule for Affective Disorders for School-Age Children, a semistructured interview based on *DSM–IV–TR* criteria (Kaufman et al., 1997). Interviewers received systematic training and achieved a high level of interrater reliability ($\kappa > .90$). Cannabis abuse and dependence diagnoses were determined through case consensus, and a symptom count was used to match more closely with the *DSM–5* diagnostic system, which assesses CUD on a continuum with mild (2–3 symptoms), moderate (4–5 symptoms), and severe (6+ symptoms) specifiers.

Cannabis use. Cannabis use at baseline was assessed using the 90-day Timeline Follow-Back (TLFB) interview (Sobell & Sobell, 1992). Daily cannabis use during the EMA period was captured using EMA, with any missing data culled from a TLFB interview. Specifically, for days when EMA data for cannabis use were missing, we pulled data regarding the total quantity of cannabis used on that day from TLFB interview data. To facilitate accurate reporting of the quantity of cannabis use on a specific day, we had participants estimate how much cannabis they used by weighing a surrogate substance (i.e., oregano). When participants shared cannabis with others, the total weight reported was divided by the number of users. This method of estimating daily quantities of cannabis use has shown evidence of reliability and validity (Mariani, Brooks, Haney, & Levin, 2011; Norberg, Mackenzie, & Copeland, 2012), and the TLFB is shown to correlate strongly with plasma THC levels (Hjorthoj, Fohlmann, Larsen, Arendt, & Nordentoft, 2012).

Memory performance. The memory-for-words subtest of the Woodcock-Johnson III Tests of Cognitive Abilities (Schrank, 2005), which is based on the Cattell-Horn-Carroll theory of cognitive abilities, captured WM performance. This subtest captures the short-term/working memory construct, defined as the ability to apprehend and hold information in immediate awareness and then use it within a few seconds. This conceptualization is consistent with the Baddeley model, a dominant theoretical model of WM in which the slave systems of WM (i.e., phonological loop and visuospatial sketchpad) are responsible for storing and rehearsing information (Baddeley, 2003; Leffard et al., 2006). According to this model, memory for words measures the storage and rehearsal components of the phonological loop, a WM slave system that processes verbal and auditory information (Leffard et al., 2006). Trained staff administered the test in accordance with standard administration

instructions. Testing occurred in the afternoon whenever possible to control for any possible effects of diurnal variation on neuropsychological test performance, and all participants reported abstinence from cannabis on the day of testing and tested 0.00 for alcohol using a breathalyzer.

Momentary assessments. EMA instructions were provided in simple English, and participants recorded data by tapping directly on the screen. Participants completed EMA recordings each day after waking (morning reports), immediately before and after each time they used cannabis (cannabis reports), and in response to audible prompts (random assessments) delivered randomly within every 3-hr block (e.g., 12 p.m.–3 p.m.) throughout the day except when sleeping or otherwise unable to respond (e.g., driving). This investigation focused on data collected during morning reports (total grams of cannabis used the previous day) and random assessments (stress and craving in the moment). Data from cannabis reports and random assessments occurring after cannabis use each day were excluded to avoid the confounding effects of cannabis intoxication.

Cannabis craving. Momentary craving was assessed with a single-item measure of urge to use cannabis on an 11-point visual analog scale from 0 (*no urge*) to 10 (*strongest ever*).

Contextual variables. The following contextual variables were recorded to include as time-varying covariates: weekend and time of day. The EMA software recorded the date and time of each entry. Weekend status was defined as 6 p.m. on Friday through 6 p.m. on Sunday and dichotomized into the weekend (1) or weekday (0). Time of day was represented by four categories (i.e., 6-hr blocks starting from midnight) with 6 a.m. to noon serving as the reference category.

Environmental cues. Participants identified the presence of cannabis at random assessments by selecting one of three options (not visible, visible directly, or visible indirectly, e.g., *High Times*, photo). The latter two options were collapsed so that there was a dichotomization of cues not present (0) or directly or indirectly present (1). Participants also indicated whether they were in a setting in which they typically use cannabis or in the company of people with whom they typically use cannabis. These three environmental cue variables were moderately correlated, ranging from .243 to .330.

Stress. At all random assessments, participants reported on their current levels of stress and tension, using 11-point visual analog scales (0 = *not at all*, 10 = *extremely*). These were combined into a single composite variable of momentary stress (α = .80).[1] A within-person average of momentary stress assessments reflected general stress levels.

Analytic plan and statistical power

Analyses used multilevel modeling in SAS (Version 9.4; SAS Institute Inc., Cary, NC) with an unstructured variance–covariance matrix and between-within degrees of freedom. Momentary random assessments (Level 1, or L1) were nested within the person (Level 2, or L2). Multilevel modeling accounts for nonindependence of observations because of the nesting of time-varying observations assessed via momentary random assessments (L1) within person. L1 variables consisted of momentary stress, momentary presence of environmental cannabis cues (i.e., presence of visible cannabis cues, in places usually smoke, with people usually smoke with), time of day, and weekend status. Momentary stress and cues were centered at the person mean. L1 stress therefore reflected momentary deviations from a person's typical stress level. L2 variables consisted of age, gender (dichotomous, male as reference), between-person stress (i.e., the person average of momentary stress reports), between-person cannabis cues, WM, and CUD symptom count. All continuous L2 variables were grand-mean centered and reflect person deviations from the overall sample average.

We considered the inclusion of a random slope for stress to account for random variation across participants in the association of stress and craving. This random slope was not significant. We additionally considered the inclusion of random slopes for the three cue predictors. Although these random slopes were significant, they did not affect the pattern of estimates or significant results for fixed effects; therefore, random-slope effects were excluded for model parsimony.

We expected that environmental cues with strong theoretical and empirical links to craving (i.e., presence of visible cannabis cues, in places usually smoke, with people usually smoke with) would elicit greater craving but that WM would moderate these associations. Distinguishing between-person from within-person stress and cues capitalized on the richness of the EMA data. Stress and the presence of cannabis cues were expected to vary both within each person over time and from person to person. The inclusion of between- and within-person stress and cues allowed for isolation of the within-person associations with craving. Multilevel models included cross-level interactive effects with WM to test the primary hypotheses. To aid in interpreting interactive effects, we calculated simple slopes using a method appropriate for multilevel models (Preacher, Curran, & Bauer, 2006).

To examine whether exposure to cannabis cues or stress was positively associated with cannabis craving at the same moment (i.e., concurrent) and whether WM moderated these associations, we first conducted a multilevel model that included only concurrent indicators for cues and stress. Second, to examine whether cue exposure or stress experienced at the previous moment (i.e., lagged) was associated with subsequent craving and whether WM moderated these associations, we conducted an additional multilevel model that also included lagged indicators for stress and cues. These indicators were lagged within day to focus on within-day associations and to prevent the inclusion of lengthy between-day lags in analyses (e.g., cue exposure or stress experienced the night before paired with morning reports of craving). In this lagged model, concurrent indicators were interpreted as change in that indicator relative to the previous moment.

Power analysis for the final model was conducted via computer simulation, using the Monte Carlo feature of Mplus (Muthén & Muthén, 2017). Consistent with previous research, 50% of the variance in craving was specified at the within-person level with the remaining variance specified at the between-person level (Treloar & Miranda, 2017). The focal effects of interest in this study are the cross-level interactions between within-person stress/cannabis cues and between-person WM. Unfortunately, previous research has not examined these associations using multilevel analyses. Thus, we conducted multiple Monte Carlo simulations with small effect sizes (β) ranging from 0.05 to 0.20 for the cross-level interaction effects on cannabis craving. Results of the power analysis using 10,000 replications indicated that a sample of 85 individuals with 765 observations would be sufficiently powered to detect the hypothesized WM × Momentary Stress or Cues cross-level interactions on craving for effects above 0.10. Power estimates for effects of 0.10 or below ranged from 0.26 to 0.73, whereas power estimates for effects of 0.11 or higher ranged from 0.81 to 1.00. It is important to note that the final models will have more observations, especially tests of concurrent associations, and a substantial number of covariates, which will account for additional residual variance not estimated in this model, effectively increasing power above what was seen here.

Results

Participants completed 1,730 nonsmoking random assessments over the course of the EMA monitoring period. Overall random-assessment compliance was defined by total random assessments completed by all participants divided by total random assessments completed plus missed random assessments. There were 1,730 completed random assessments and 2,065 combined completed + missed random assessments; thus, overall random-assessment compliance was 83.8%. Of the completed random assessments, 462 assessments were excluded from the analyses because they occurred during or after cannabis use on a given day, leaving 1,268 eligible random-assessment observations.

Over the EMA monitoring period, participants reported using cannabis on 51% of days and reported an average of 0.49 g (*SD* = 0.42) per smoking day. Participants reported greater than zero level of craving on 81.1% of the study days with an overall average cannabis craving rating of 3.75 (*SD* = 3.67). Day-average, pre-use craving was not associated with the likelihood of smoking cannabis on a given day (b = 0.05, 95% confidence interval, or CI = [–0.02, 0.12], p = .132).[2] On days on which participants used cannabis, however, greater day-average pre-use craving was associated with smoking more total grams of cannabis (b = 0.02, 95% CI = [0.001, 0.03], p = .033),[3] supporting the clinical significance of craving. Additionally, the association between craving and likelihood of use became significant (b = 0.09, 95% CI = [0.01, 0.17], p = .031) only on days on which participants reported that cannabis was available at one or more prompts.

Interrelationships of WM with L2 covariates were explored with bivariate correlations. WM was not related to person-average stress (p = .831) or CUD symptoms (p = .685). A higher level of WM was marginally associated with being male (r = −.210, p = .054). Youths with a higher level of WM were younger (r = −.303, p = .005) and also reported lower average levels of our focal outcome, craving (r = −.256, p = .018). Average WM performance for the full sample was 18.68 (*SD* = 2.15). Average WM performance across CUD severity was 18.40 (*SD* = 2.30) for no CUD (n = 5), 19.04 (*SD* = 2.72) for mild CUD (n = 25), 18.43 (*SD* = 1.83) for moderate CUD (n = 28), and 18.67 (*SD* = 1.88) for severe CUD (n = 27).

Effects of exteroceptive and interoceptive cue exposure on craving

Before considering the moderating effect of WM, we used an initial model to examine associations between momentary exteroceptive cues (i.e., cannabis cues, persons with whom participants typically use cannabis, and places in which participants typically use cannabis) and craving as well as between interoceptive cues (i.e., stress) and craving (see Table 1). Craving was stronger among individuals with more severe CUD (i.e., greater symptom count) as well as in the evening and late night, relative to the morning. In terms of exteroceptive cues, at the momentary level, participants experienced

Table 1. Multilevel Model of Craving From Cues, Stress, and Covariates

Variable	*b*	95% CI LL	95% CI UL	*p*
Intercept	3.17	2.17	4.18	< .001
Time varying (within person)				
Weekend	0.25	–0.14	0.65	.201
Time of day				
6 p.m. to midnight	1.17	0.48	1.87	.001
Midnight to 6 a.m.	0.65	–0.35	1.66	.198
Noon to 6 p.m.	1.05	0.39	1.71	.002
6 a.m. to noon [reference]				
Place usually smoke[a]	0.49	–0.01	0.99	.056
With people usually smoke[a]	0.80	0.33	1.27	.001
Visible cannabis cues[a]	0.81	0.28	1.34	.003
Stress[a]	0.08	–0.02	0.18	.114
Lagged place usually smoke[a]	0.09	–0.41	0.59	.722
Lagged with people usually smoke[a]	–0.19	–0.67	0.28	.428
Lagged visible cannabis cues[a]	–0.17	–0.73	0.40	.568
Lagged stress[a]	0.06	–0.05	0.16	.279
Time invariant (between person)				
Person-average stress[b]	0.65	0.30	0.99	< .001
Person-average place usually smoke[b]	0.13	–2.08	2.35	.905
Person-average people usually smoke[b]	0.49	–2.24	3.22	.721
Person-average visible cannabis cues[b]	2.09	–0.31	4.49	.086
Age[b]	–0.03	–0.31	0.26	.861
Cannabis-use-disorder severity[b]	0.34	0.07	0.62	.016
Female gender	–0.11	–1.28	1.07	.857

Note: CI = confidence interval; *b* = unstandardized estimate; LL = lower limit; UL = upper limit.
[a]Person centered. [b]Grand-mean centered.

higher craving when in the company of people with whom they typically use cannabis and while in the presence of cannabis cues. Results also showed a statistical trend for higher craving when youths were in locations in which they typically use cannabis. There were no significant associations for any of the lagged cue indicators. Neither within-person lagged nor concurrent stress was associated with craving. At the person level, between-person stress was significantly associated with craving; participants who reported more stress across the EMA period reported stronger craving at any given moment.

WM function as a moderator

To test our primary hypotheses, we modeled the main effect of WM and its interactions with our three focal exteroceptive cues (i.e., cannabis cues, persons with whom participants typically use cannabis, and places in which participants typically use cannabis) and with our interoceptive cue (i.e., stress). We first examined concurrent associations (see Table 2). Contrary to our hypothesis, there were no significant cross-level interactions for WM and any of the exteroceptive cues. As we hypothesized, however, the cross-level interaction between concurrent stress (L1) and WM (L2) predicting cannabis craving was significant. Of note, the interactive effect of stress and WM existed beyond the influences of other L1 (context) and L2 predictors, including person-average stress levels and CUD severity.

We next added lagged indicators of cues and stress to the model (see Table 3). There were no changes to concurrent and between-person associations. There were no main effect associations for lagged cues or stress. There was additionally an interaction between lagged presence in a place in which participants typically used and WM. Finally, there was an interaction between lagged stress and WM (see Fig. 1). We calculated simple slopes to better quantify these interactions (Preacher et al., 2006). For participants with low levels of WM (i.e., 1 *SD* below the mean; $n = 14$), prior moments with elevated stress were positively associated with greater cannabis craving at the subsequent moment ($b = 0.17$, $SE = 0.07$, $p = .018$). This effect was attenuated in participants at the mean of WM ($n = 59$; $b = 0.03$,

Table 2. Multilevel Model of Craving From Same-Moment Cues, Stress, Executive Functioning, and Covariates

Variable	*b*	95% CI LL	95% CI UL	*p*
Intercept	3.26	2.47	4.05	< .001
Time varying (within person)				
Weekend	0.06	–0.24	0.37	.674
Time of day				
6 p.m. to midnight	1.35	0.93	1.76	< .001
Midnight to 6 a.m.	0.42	–0.27	1.11	.230
Noon to 6 p.m.	1.16	0.79	1.52	< .001
6 a.m. to noon [reference]				
Place usually smoke[a]	0.36	–0.02	0.75	.062
With people usually smoke[a]	0.76	0.39	1.12	< .001
Visible cannabis cues[a]	0.68	0.27	1.09	.001
Stress[a]	0.04	–0.03	0.12	.267
Time invariant (between person)				
Person-average stress[b]	0.56	0.24	0.87	.001
Person-average place usually smoke[b]	0.80	–1.27	2.86	.445
Person-average people usually smoke[b]	1.32	–1.17	3.82	.295
Person-average visible cannabis cues[b]	1.04	–1.24	3.32	.367
WM[b]	–0.36	–0.64	–0.09	.011
Age[b]	–0.12	–0.40	0.16	.385
Cannabis-use-disorder severity[b]	0.29	0.03	0.55	.031
Female gender	–0.20	–1.28	0.89	.715
Cross-level (within × between)				
Place usually smoke × WM	–0.03	–0.21	0.16	.778
With people usually smoke × WM	–0.04	–0.21	0.13	.653
Visible cannabis cues × WM	–0.09	–0.29	0.11	.385
Stress × WM	–0.06	–0.10	–0.02	.001

Note: CI = confidence interval; *b* = unstandardized estimate; LL = lower limit; UL = upper limit; WM = working memory.
[a]Person centered. [b]Grand-mean centered.

SE = 0.05, *p* = .514). For participants with higher levels of WM (i.e., 1 *SD* above the mean; *n* = 12), there was a nonsignificant negative association of craving and stress (*b* = –0.10, *SE* = 0.08, *p* = .247). Similarly, being in a place in which use typically occurred in a prior moment was positively associated with greater cannabis craving at the subsequent moment for participants with low WM (*b* = 0.81, *SE* = 0.39, *p* = .037). This effect was attenuated and nonsignificant at the mean of WM (*b* = 0.18, *SE* = 0.26, *p* = .476) and nonsignificant and negative at high levels of WM (*b* = –0.44, *SE* = 0.34, *p* = .201).

Discussion

Contemporary models of addiction offer strong theoretical support for the role of conditioned stimuli, including both exteroceptive and interoceptive cues, in the pathogenesis of drug craving and maladaptive substance use. Few studies, however, have investigated how these phenomena unfold in daily life or the individual difference factors that moderate these effects. This study leveraged EMA methods to examine momentary associations among both exteroceptive and interoceptive cues and cannabis craving in the natural environment among adolescents and emerging adults. Furthermore, this investigation was the first to examine whether executive abilities central to self-regulation—namely, WM—are associated with the urge to use cannabis in the face of conditioned cues. Our results showed that exteroceptive cues—namely, the presence of cannabis cues and presence of peers with whom one typically uses cannabis—were associated with higher craving. This finding is consistent with laboratory-based cue reactivity studies and provides additional evidence that external cues elicit craving in daily life. In addition, youths who experienced more stress in general were more likely to report craving at any given moment.

As we hypothesized, in-the-moment associations between stress and craving were moderated by individual differences in WM performance. This was true

Table 3. Multilevel Model of Craving From Same- and Previous-Moment Cues, Stress, Working Memory, and Covariates

Variable	*b*	95% CI LL	95% CI UL	*p*
Intercept	3.45	2.45	4.45	< .001
Time varying (within person)				
Weekend	0.08	–0.32	0.48	.685
Time of day				
6 p.m. to midnight	1.06	0.37	1.75	.003
Midnight to 6 a.m.	0.58	–0.41	1.58	.249
Noon to 6 p.m.	0.92	0.26	1.58	.007
6 a.m. to noon [reference]				
Place usually smoke[a]	0.42	–0.09	0.93	.108
With people usually smoke[a]	0.80	0.32	1.28	.001
Visible cannabis cues[a]	0.72	0.19	1.25	.008
Stress[a]	0.06	–0.04	0.16	.251
Lagged place usually smoke[a]	0.21	–0.30	0.72	.414
Lagged with people usually smoke[a]	–0.27	–0.76	0.22	.277
Lagged visible cannabis cues[a]	–0.12	–0.69	0.45	.677
Lagged stress[a]	0.04	–0.06	0.14	.441
Time invariant (between person)				
Person-average stress[b]	0.63	0.29	0.97	.001
Person-average place usually smoke[b]	0.43	–1.81	2.67	.703
Person-average people usually smoke[b]	0.72	–1.97	3.41	.597
Person-average visible cannabis cues[b]	1.53	–0.93	3.99	.220
WM[b]	–0.26	–0.56	0.04	.087
Age[b]	–0.12	–0.42	0.18	.428
Cannabis-use-disorder severity[b]	0.30	0.02	0.58	.036
Female gender	–0.31	–1.48	0.86	.601
Cross-level (within × between)				
Place usually smoke × WM	0.01	–0.24	0.27	.913
With people usually smoke × WM	–0.06	–0.29	0.17	.603
Visible cannabis cues × WM	–0.07	–0.32	0.18	.588
Stress × WM	–0.06	–0.11	–0.01	.017
Lagged place usually smoke × WM	–0.30	–0.54	–0.05	.017
Lagged with people usually smoke × WM	–0.04	–0.26	0.18	.722
Lagged visible cannabis cues × WM	–0.11	–0.40	0.18	.456
Lagged stress × WM	–0.06	–0.11	–0.01	.019

Note: CI = confidence interval; *b* = unstandardized estimate; LL = lower limit; UL = upper limit; WM = working memory.
[a]Person centered. [b]Grand-mean centered.

for both previous-moment and same-moment stress. Although the present study precludes any statement on causality, the interaction with previous-moment stress provides some information on the temporal ordering of the association. Youths with weaker WM experienced stronger craving when their stress was heightened. These findings held even after adjusting for exteroceptive cannabis-related cues, which were also associated with craving. WM did not moderate the associations of exteroceptive cues and craving, except for the previous-moment presence in a place in which participants typically used. It is not entirely clear why this interaction was significant; the other interactions involving cues were not. This is especially true given that we primarily expected associations for cue exposure to be immediate (i.e., same moment). This expectation was accurate for the main effects of cues as same-moment associations for two of the three indicators (whereas place in which participants smoked was a nonsignificant trend), but there were no associations for the main effects of previous-moment cues.

The finding of a between-person relationship for overall stress and craving, such that participants who experienced greater stress during the EMA monitoring

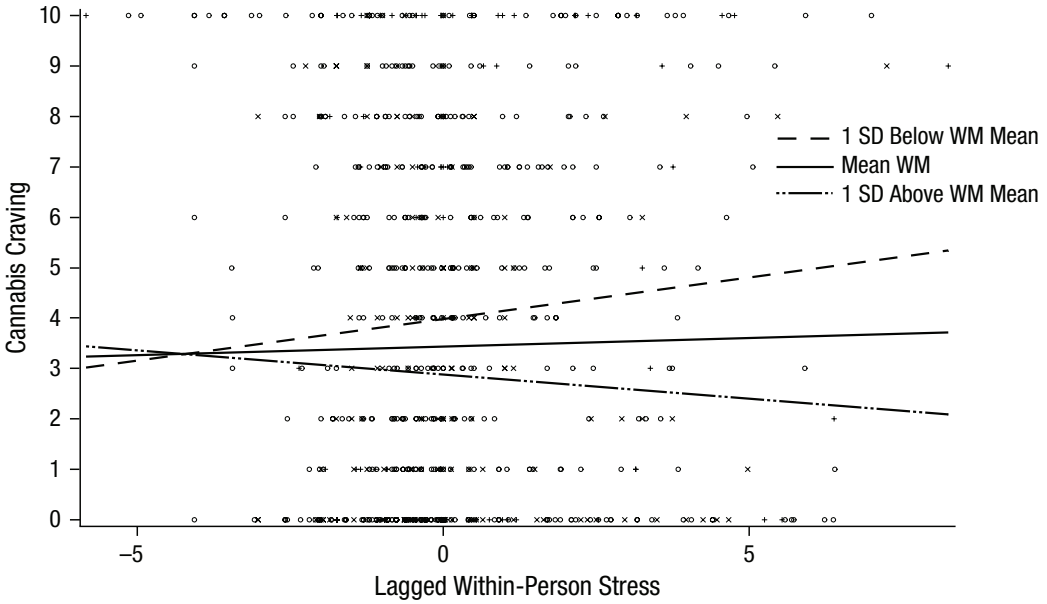

Fig. 1. Association of within-person previous-moment (lagged) stress and cannabis craving, moderated by between-person working memory (WM). The solid lines represent mean level WM and dotted lines 1 *SD* below and above the mean for WM. + = observations more than 1 *SD* below the mean; o = observations at the mean; × = observations more than 1 *SD* above the mean.

period had stronger craving at any given moment, is consistent with previous work on craving for other substances in daily life (Preston & Epstein, 2011). This finding also fits with laboratory studies that show that individuals randomly assigned to a stress-induction paradigm reported higher levels of cannabis craving compared with individuals randomly assigned to a nonstress control condition (McRae-Clark et al., 2011). We did not find within-person concurrent or lagged associations between stress and craving, however, which contrasts with laboratory studies that show that stress-induction tasks increase cannabis craving relative to pretask levels (Buckner, Ecker, & Vinci, 2013). Other laboratory studies, however, found this within-person effect only among women (Buckner, Silgado, & Schmidt, 2011).

Our findings regarding WM add context to the association of stress and craving, indicating that the association may not be invariant across youths. Executive functions, including WM, are still developing during youth; thus, cognitive ability may be a particularly important influence on the association of stress and craving in this population. The finding of moderation suggests that youths who possess weaker WM ability may have a response to stress that is different from that of youths with stronger WM. Potentially, youths higher in WM have developed other, more adaptive, means of responding to stress and can "short circuit" the association of stress and craving, a topic that should be addressed in future research. In contrast, given the role of craving in addiction, youths lower in WM are potentially at risk for engaging in problematic cannabis use both in the present and later in life (Gustavson et al., 2017). Additionally, although contrary to our hypotheses, the fact that WM moderated the association of stress and craving but not, for the most part, exteroceptive cues and craving lends specificity to the effect for WM. WM is an important cognitive construct involved in self-regulation of internal states (Hofmann et al., 2012; Williams, Suchy, & Rau, 2009) and, therefore, may be more closely involved in managing responses to stress than to external cues.

Potentially complicating the relationship of stress, WM, and craving are the possible effects of cannabis use on WM. Indeed, a recent meta-analysis concluded that there are small but consistent effects of acute cannabis use on WM performance (Scott et al., 2018). Ultimately, in the present study, we assessed WM only at one time in the laboratory; therefore, we were unable to test whether lower WM results in greater problematic use (e.g., as a result of greater stress-induced craving) or whether heavier and more problematic use leads to lower WM. It is possible that both are true and that cannabis use and WM may interact to create a mutually reinforcing cycle, with lower WM increasing the likelihood of problematic use, use then further decreasing WM, and, in turn, decreased WM leading to further increased use. Future studies utilizing longitudinal designs are needed to determine the causal relationship between cannabis use and WM and the effects of this relationship on craving.

Contrary to our hypotheses, unlike stress-induced craving, WM largely did not influence craving responses to exteroceptive cues, namely, cannabis use, peers, and locations. One possible reason for these findings is that cue-induced craving is more ubiquitous, affecting a broader range of regular cannabis users, and thus may be less sensitive to between-person differences. Preclinical and brain-imaging research shows that drug use produces a host of pleasurable effects by potentiating dopaminergic activity in reward regions of the brain (Volkow, Koob, & McLellan, 2016). As addiction unfolds, however, activation of reward neurocircuitry shifts from actual drug intake to exposure to exteroceptive conditioned stimuli. This neuroadaptation, which is presumed to occur in tandem with the progression of addiction pathology, allows previously neutral objects to become charged with incentive salience and drive motivation to seek substances and engage in drug use. Our findings indicate that there is considerable variability in stress-induced craving, compared with exteroceptive cues, across youths. The strength of WM capabilities appears to explain part of these differences and suggests that neurocognitive control capacity may be especially relevant for regulating reactivity to emotional responses, compared with environmental cues.

The current study had a number of strengths, including the use of EMA to examine the momentary association of stress and craving; the inclusion of WM, an important cognitive factor; and contrasting and adjusting for the effects of exteroceptive cannabis cues and environmental covariates. There were also limitations. First, participants ranged in age from 15 to 24 years and, therefore, collectively spanned a developmental period including adolescence and early adulthood. As a result, participants potentially differed significantly in developmental stage. Importantly, however, age was not related to craving in our models. Second, our sample consisted of individuals interested in receiving treatment for cannabis use and many met the criteria for CUD. Therefore, it is unclear whether results would generalize to individuals uninterested in treatment or not engaging in problematic use. Third, the current study focused specifically on cannabis craving. Future research should examine the relationships of stress, WM, and craving in other substances. Finally, we leveraged an instrument to measure WM that is not typically used in addiction research. This consideration is important for understanding our significant and null findings; we may have observed different patterns of results with other more commonly used indicators of WM function. In addition, our reliance on a less commonly used measure is important to consider when integrating this work within the broader empirical literature in this area.

In conclusion, the current study used EMA to examine the association of stress and craving, as well as the moderating role of WM, in cannabis-using youths in daily life. Our findings suggest that youths experience craving when under stress and that this association was particularly strong in youths lower in WM. Improving WM may enable individuals to disrupt the association between stress and craving and, thereby, both reduce and maintain reduced use. Researchers should test whether interventions targeting executive-functioning processes, such as WM, alter the association of stress with craving.

Action Editor

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Author Contributions

R. Miranda developed the study concept and supervised all testing and data collection. N. N. Emery performed the power analysis. R. W. Carpenter performed the data analyses. All the authors contributed to the study design and interpretation of findings. All the authors drafted the manuscript and approved the final manuscript for submission.

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The author(s) declared that there were no conflicts of interest with respect to the authorship or the publication of this article.

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Open Practices

All data and analysis scripts have been made publicly available via Open Science Framework and can be accessed at https://osf.io/usdq8/. The complete Open Practices Disclosure for this article can be found at http://journals.sagepub.com/doi/suppl/10.1177/2167702619841976. This article has received the badge for Open Data. More information about the Open Practices badges can be found at https://www.psychologicalscience.org/publications/badges.

Notes

1. All models produced the same pattern of results whether the single "stress" item was used or the aggregate of "stress" and "tension" were employed.
2. For this model, we used PROC GLIMMIX with a binary distribution.

3. For this model, for days on which use exceeded 2 g, total grams used was Winsorized to 2 g.

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