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Apathy is associated with poorer abstinence self-efficacy in individuals with methamphetamine dependence

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ABSTRACT

Background: Confidence in one's ability to achieve and maintain drug abstinence (i.e., abstinence self-efficacy) is a strong predictor of substance use treatment outcomes. Neurobehavioral factors that may interfere with abstinence self-efficacy are less well established, particularly in methamphetamine (METH). This study investigated whether apathy, which is highly prevalent during active METH use and periods of abstinence, influences abstinence self-efficacy among METH dependent individuals.
Methods: Sixty-six participants with lifetime METH dependence and METH abuse/METH dependence diagnoses within the last 18 months (mean age [SD] = 39.5 years [10.7]), and no severe psychiatric or neurological diseases, completed the Methamphetamine Self-Efficacy Scale (MSES), alongside a comprehensive neurobehavioral evaluation. The MSES presents six situations that may lead to relapse and collects self-report ratings for two subscales: "Confidence" (i.e., confidence in one's ability to abstain from using METH, or METH abstinence self-efficacy) and "Temptation" (i.e., how tempted one is to use METH) with regard to each situation. Apathy was measured using a composite *T*-score comprised of items and scales from three well-validated, self-report assessments.
Results: Multivariable linear regression found that higher Apathy *T*-scores were significantly associated with lower Confidence ratings (i.e., poorer METH abstinence self-efficacy; $p < .05$), independent of potentially relevant factors (e.g., Temptation to use METH, comorbid HIV disease, and neurocognitive impairment).
Conclusions: Elevated apathy may adversely impact one's confidence to abstain from METH use. Findings highlight the importance of addressing apathy in order to improve METH abstinence self-efficacy, which may subsequently increase the likelihood of successful METH treatment outcomes.

1. Introduction

The 2018 National Survey on Drug Use and Health estimated >14.9 million people in the United States have used methamphetamine (METH) at least once, and almost 1.9 million people used METH in the year prior to survey publication (Substance Abuse and Mental Health Services Administration, 2019). METH use can lead to a range of adverse legal (e.g., METH-related arrest; Dobkin & Nicosia, 2009), psychosocial (e.g., poor social support and coping skills; Cretzmeyer, 2003; Halkitis & Shrem, 2006), and medical (e.g., cardiovascular) consequences (Chin, Channick, & Rubin, 2006), including death (Gibson, Leamon, & Flynn, 2002). METH can also damage the central nervous system, leading to a wide range of psychiatric (e.g., depression), neurobehavioral (e.g., apathy), and neurocognitive consequences (Looby & Earleywine, 2007; Marquine, 2014; McGregor, 2005; McKetin, 2006; Rippeth, 2004; Scott, 2007) that have been linked to numerous adverse health-related and everyday functioning problems (e.g., unemployment; problems independently completing daily activities; Cattie, 2012; Weber, 2012).

Importantly, adverse METH effects on the CNS may resolve, to some degree, following sustained abstinence periods (Iudicello, 2010; Schulte,

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2014; Volkow, 2001; Zhang, 2018). Cognitive and behavioral interventions (e.g., cognitive behavioral therapy, contingency management) can effectively reduce METH use and improve abstinence (Lee & Rawson, 2008). However, treatment programs modeled after these interventions struggle to enroll and retain participants. Even when patients engage in treatment, there are high rates of relapse (Brecht & Herbeck, 2014; Chen, Chen, & Wang, 2015). Many factors have been identified as barriers to treatment and sustained recovery, including negative social support, decreased motivation for treatment, and side effects from METH withdrawal (e.g., depression, anxiety, cravings; McGregor, 2005; Zorick, 2010).

Low self-efficacy has also been identified as a significant barrier to successful intervention and treatment of METH use disorders (Alexander, 2017; German, 2006). General perceived self-efficacy is considered a malleable construct, defined as when an individual visualizes themselves as executing activities skillfully, thereby enhancing subsequent performance on the task itself (Bandura, 1989, 1994). Higher self-efficacy can improve performance across many areas from academics (Talsma, 2018) to health outcomes (Sheeran, 2016). In the context of substance use, self-efficacy may be defined an individual's confidence in their ability to abstain from using substances in the future. Abstinence self-efficacy is often a targeted goal during treatment, and is a significant predictor of successful treatment outcomes across various substances of abuse (Ilgen, McKellar, & Tiet, 2005; Kadden & Litt, 2011) including tobacco (Gwaltney, 2009), alcohol (Adamson, Sellman, & Frampton, 2009; Kadam, 2017; Moos & Moos, 2006; Noyes, 2018), opioid (Kadam, 2017; Reilly, 1995), and cocaine dependence (Wong, 2004). There is preliminary evidence of its impact on METH treatment outcomes; in a sample of Filipino METH users, lower abstinence self-efficacy and poorer coping were the strongest predictors of relapse, after considering factors like negative behavior states, motivation to change, and drug craving (Tuliao & Liwag, 2011).

Despite the strong relationship between abstinence self-efficacy and successful treatment outcomes, research is limited regarding the predictors of abstinence self-efficacy among METH users. Studies conducted in other substance using populations (e.g., alcohol, cannabis, cocaine, opioid) have identified associations with demographics (e.g., older age, higher education), motivation (e.g., desire to quit), coping style, depressive symptoms, neurocognitive functioning, and other substance use-related factors (e.g., degree/recency of use, prior treatment outcomes; Demmel & Rist, 2005; Demmel, Nicolai, & Gregorzik, 2006; Demmel, 2004; Dolan, Martin, & Rohsenow, 2008; Greenfield, 2012; Ilgen, McKellar, & Moos, 2007; Majer, 2003). We sought to expand this literature by examining predictors of abstinence self-efficacy among METH dependent individuals with the goal of identifying potentially modifiable intervention targets. We were particularly interested in whether apathy (i.e., lack of motivation and relative absence of self-initiated, goal-directed behaviors), a common neurobehavioral disturbance among METH users (Looby & Earleywine, 2007), may contribute to abstinence self-efficacy. We hypothesized that more apathy would be significantly associated with poorer METH abstinence self-efficacy (i.e., confidence to abstain from using METH) in a sample of METH dependent individuals.

2. Materials and methods

2.1. Participants

Participants included 66 individuals enrolled in the National Institute on Drug Abuse-funded Translational Methamphetamine and AIDS Research Center (TMARC), which was designed to examine the CNS effects of HIV and METH dependence. Study protocols were approved by UCSD Human Research Protections Program. After providing written, informed consent, participants underwent a comprehensive substance use, neuromedical and neurocognitive evaluation. Participants were compensated for their participation.

Study participants included individuals who were enrolled and comprehensively assessed as part of the TMARC and met Diagnostic and Statistical Manual-Fourth Edition (DSM-IV; APA, 1994) criteria for lifetime METH dependence and for METH abuse or dependence within the last 18 months based on the Composite International Diagnostic Interview (CIDI) version 2.1 (Kessler & Ustun, 2004; Wittchen, 1994). General TMARC exclusion criteria included history of psychotic disorders (e.g., schizophrenia), HCV co-infection, or other neurological conditions known to impact neurobehavioral functioning (e.g., stroke, seizure disorders, head injury with loss of consciousness >30-min). TMARC's substance-related exclusion criteria included meeting DSM-IV criteria for 1) alcohol dependence within the last year; 2) other substance (e.g., cocaine, opioid) abuse within the past 12 months, or dependence within the past 5 years. Participants were not excluded on the basis of current or lifetime cannabis use or lifetime alcohol abuse diagnoses given the high proportion of METH dependent individuals who use or abuse these substances. In this way, the TMARC eligibility criteria afford a more representative sample of METH users encountered in clinical settings, while at the same time minimizing the potential confounding effects of current/active use of other substances (e.g., cocaine, alcohol) known to affect important outcomes of interest.

2.2. Measures

Participants were administered a comprehensive neuromedical and neurobehavioral evaluation. Demographic characteristics and behavioral measures were obtained via self-report.

2.2.1. METH abstinence Self-Efficacy Scale (MSES)

The MSES was modified from the brief 12-item Alcohol Abstinence Self-Efficacy (AASE) Scale (McKiernan, 2011), an abbreviated version of the 20-item AASE Scale developed to assess self-efficacy (Bandura, 1977) as it applied to alcohol abstinence (DiClemente, 1994). Content-wise, the MSES is identical to the brief AASE (McKiernan, 2011), but was modified to assess METH, rather than alcohol, abstinence self-efficacy. It consists of six items/cues within four hypothesized high-risk categories related to METH abstinence: 1) negative affect, 2) social interactions and positive states, 3) physical and other concerns, and 4) withdrawal and urges (DiClemente, 1994). For each item/cue, participants rate themselves using a Likert Scale ranging from 1 (not at all) to 5 (extremely) regarding: 1) how tempted they would be to use METH in each situation ("Temptation" ratings); and 2) how confident they would be in their ability to avoid using METH ("Confidence" ratings). Temptation and Confidence ratings for each item are summed separately, each ranging from 6 to 30 with higher scores indicating greater Temptation or Confidence. The average "Confidence" (i.e., abstinence self-efficacy) rating was the primary outcome variable in analyses. Temptation was controlled for in analyses given its strong, negative correlation with Confidence (McKiernan, 2011).

2.2.2. Apathy composite

Apathy was measured using a validated composite (Marquine, 2014) derived from subscales and/or items from three self-report questionnaires: 1) Beck Depression Inventory – II (BDI-II; Beck, 1996); 2) Profile of Mood States (POMS; McNair, Lorr, & Droppleman, 1981); and 3) Frontal Systems Behavior Scale (FrSBe; Grace & Malloy, 2001). The BDI-II is a 21-item inventory assessing the severity of current depression symptomatology; higher scores indicate greater severity. The four apathy-related items from the BDI-II (loss of pleasure, loss of interest, difficulties making decisions, and feelings of tiredness and fatigue) were included in the apathy composite (Castellon, 2006). The POMS is a 65-item measure of current affective distress with six subscales. The POMS "Vigor-Activity" subscale was included in the apathy composite. The FrSBe is a 46-item behavior rating scale designed to assess current and before illness/injury-behaviors related to frontal dysfunction; higher scores reflect greater behavioral disturbance. Current ratings from the

FrSBe Apathy subscale were included in the apathy composite. Details of the Apathy *T*-score composite are in Marquine et al. (Marquine, 2014). Higher *T*-scores indicate greater Apathy.

2.2.3. Neurocognitive and psychiatric/substance use assessment

Neurocognitive functioning was assessed using a comprehensive, standardized seven-domain test battery (Heaton, 2010), which included an estimate of premorbid cognitive ability (WRAT-4 reading subtest; Wilkinson & Robertson, 2006). A global deficit score ranging from 0 (normal) to 5 (severe) was created (Carey, 2004), with GDS $\geq$ 0.5 indicative of neurocognitive impairment (NCI). Current and lifetime Major Depressive Disorder (MDD) and substance use diagnoses (abuse/dependence) were assessed using the CIDI v2.1. Current and lifetime Attention Deficit Hyperactivity Disorder (ADHD) and lifetime Antisocial Personality Disorder (ASPD) were evaluated using the Diagnostic Interview Schedule (Robins, 1981). Detailed METH use characteristics (see Table 1) were collected using a semi-structured timeline follow-back substance use interview (Rippeth, 2004). The POMS "Depression-Dejection" subscale was also examined as a measure of current, self-reported depression symptoms.

2.2.4. Neuromedical assessment

The neuromedical assessment included a medical history interview, physical and neurological exam, blood draw, urine drug screen, and alcohol breathalyzer. HIV serostatus was determined via self-report and confirmed by the Miriad HBc/HIV/HCV finger stick point-of-care test (MedMira Inc., Nova Scotia, Canada). Approximately 58% of our sample were HIV+ (n = 37). The following HIV disease and treatment-related variables were also collected: estimated duration of HIV disease, nadir and current $CD4^{+}$ T-cell counts, antiretroviral therapy (ART) status, AIDS diagnoses, and plasma HIV RNA viral load.

Table 1
Participant demographic and descriptive statistics.

	METH+ (n = 66)
Demographic characteristics	
Age (years)	39.5 (10.7)
Education (years)	13.2 (2.5)
Gender (% male)	80.3%
Race/Ethnicity	
non-Hispanic White (%)	40.9%
Hispanic (%)	34.9%
Other[a] (%)	24.2%
HIV Status (% PWH)	56.1%
Psychiatric and substance use Characteristics	
POMS Depression-Dejection Subscale Total, median [interquartile range]	14.0 (5.5, 25.5)
Current Major Depressive Disorder (%)	9.1%
Lifetime Major Depressive Disorder (%)	37.9%
Attention-Deficit/Hyperactivity Disorder (%)	9.1%
Antisocial Personality Disorder (%)	28.8%
Lifetime other non-METH Substance Use Disorder (%)	83.3%
Neurocognitive characteristics	
Estimated premorbid verbal IQ[b]	100.5 (13.2)
Neurocognitive impairment[c] (% impaired)	27.3%
METH use characteristics	
Current[d] METH use diagnosis (%)	18.2%
Self-reported days since last use (days), median [interquartile range]	121.7 [6.5, 182.6]
Positive METH urine toxicology (%)	21.2%
Age of first use (years), median [interquartile range]	25.6 (9.6)
Total lifetime duration of use (years), median [interquartile range]	4.6 [2.1, 9.0]
Total lifetime quantity of use (grams), median [interquartile range]	1334.9 [371.4, 3435.5]
History of METH use treatment (% ever in lifetime)	70.8%
Apathy Composite *T*-Score	66.7 (18.0)
METH Abstinence Self-Efficacy Scale (MSES)	
Confidence Rating	18.3 (7.5)
Temptation Rating	20.3 (7.3)

Note. Values represent means (standard deviations), or proportions, unless otherwise noted.
[a] African-American (n = 9), Asian (n = 2), and Native American and/or mixed (n = 5) ethnicities.
[b] Wide Range Achievement Test.
[c] Calculated using Global Deficit Score (GDS $\geq$ 0.5).
[d] Within 30 days of assessment. METH = methamphetamine; POMS = Profile of Mood States.

2.3. Statistical analyses

Univariable analyses (e.g., Pearson's r correlations or Spearman's ρ for non-parametric data, and/or independent samples t-tests or Wilcoxon Rank Sums χ^2 test for non-parametric data), were conducted to examine the relationship between Apathy *T*-score and Confidence ratings, and to identify candidate covariates for inclusion in multivariable analyses (screened covariates listed in Table 1). Given previous literature demonstrating strong, significant associations between Temptation and Confidence ratings (McKiernan, 2011), and between current MDD and abstinence self-efficacy among other substance-using populations (Greenfield, 2012), these variables were selected, *a* priori, for inclusion in multivariable analyses.

Multivariable analyses were conducted to examine Apathy as a predictor of Confidence ratings, while controlling for variables that met our *a* priori selection criterion of $\alpha = 0.10$ (see Table 2). Variables were entered into a stepwise linear regression model using a backward selection method and Akaike Information Criterion (AIC; Akaike, 1974) to select the best model, balancing explanatory value and efficiency. The final model was selected by minimizing AIC, taking into account both the goodness of fit and the model complexity.

3. Results

3.1. Participant characteristics

Demographic, psychiatric, neurocognitive, and METH use characteristics of our sample are presented in Table 1. On average, participants were 39.5 years old (*SD* = 10.7), with 13.2 years of education (*SD* = 2.5), predominantly male (80.3%), and the majority self-identified as either non-Hispanic White (40.9%) or Hispanic (34.9%). Lifetime MDD (37.9%) and ASPD (28.8%) were the most prevalent psychiatric conditions. Approximately 27.3% of our sample was classified as having NCI. Per TMARC inclusion criteria, all participants met criteria for lifetime METH dependence and for METH abuse or dependence within 18 months of assessment. Approximately 18% of our sample (n = 12) met criteria for current ($\leq$30-days) METH abuse (n = 1) or dependence (n =

Table 2
Confidence ratings (i.e., poorer METH abstinence self-efficacy) for 6 specific cues/situations within 4 four hypothesized high-risk categories related to METH abstinence.

	Confidence *Mean* (*SD*)
Negative affect	
When you are emotionally upset.	3.02 (1.4)
Social interactions and positive states	
When you are around others who are using or when you see others using - such as during celebrations or on vacation.	2.71 (1.4)
Physical and other concerns	
When you experience physical injury, such as headache, injury, or are physically tired.	3.26 (1.5)
When you feel a physical need or craving for METH.	2.92 (1.4)
Withdrawal and urges	
When you have thoughts of using – while either awake or dreaming.	3.32 (1.4)
When you have an urge to use METH just once to see what happens.	3.09 (1.4)
TOTAL	18.32 (7.5)

11), and 21.2% ($n = 14$) had positive urine toxicology results indicating recent METH use. Age at first METH use, days since last METH use, total lifetime duration and quantity of METH use, and the proportion of individuals with a history of treatment for METH use at least once in their lifetime are provided in Table 1. Five participants met DSM-IV criteria for cannabis abuse or dependence ($n = 3$) or alcohol abuse ($n = 2$) in the year prior to assessment (none within the past 30 days). In addition to their lifetime METH use diagnoses, approximately 83% of our sample ($n = 55$) met DSM-IV criteria for lifetime abuse or dependence for at least one other substance (within the above mentioned limits of TMARC's eligibility criteria), with the most common being alcohol (74.2%), cannabis (34.8%), cocaine (28.8%), and opioids (16.7%). The majority of our participants reported use of at least one (94%; $n = 62$) or two (67%; $n = 44$) other non-METH substances within the past year (if excluding cannabis and alcohol, then 59% [$n = 39$] and 30% [$n = 20$], respectively).

Fifty-six percent ($n = 37$) of our sample were HIV+. On average, the estimated duration of infection for the HIV+ subset was 8.2 years ($SD = 6.9$; median = 7.1, interquartile range [IQR] = 2.4, 12.8). Approximately 39% had AIDS ($n = 14/36$, one missing AIDS status). Average nadir and current $CD4^+$ T-cell counts were 334.6 ($SD = 242.6$; median [IQR] = 278.0 [178.0, 450.0]) and 654.3 ($SD = 282.5$; median [IQR] = 615.0 [441.5, 862.5]), respectively. All were on ART regimens at the time of their assessment and, on average, had been on their current ART regimen for 2.4 years ($SD = 45.5$; median = 1.0 [0.3, 2.2]). Approximately 78% reported adherence (≥90% of doses taken as prescribed), and 77% were virally suppressed ($n = 27/35$, missing data for two participants).

Descriptive statistics for the primary study variables (i.e., Apathy *T*-score, Confidence ratings) are also presented in Table 1. The Apathy *T*-score corresponded to almost 2 SD above the mean of a non-METH dependent, HIV- control group. Average Confidence ratings for each of the six cues/situations are presented in Table 2. The lowest Confidence ratings were observed for the social situation item (i.e., confidence in abstaining from METH use when around others who are using [i.e.., during gatherings or vacation]).

3.2. Univariable analyses examining associations with confidence ratings

Given the non-normal distributions of the Confidence ratings (Shapiro-Wilk *W* Test: $W = 0.94$, $p < .01$), non-parametric tests (Spearman's ρ and Wilcoxon Rank Sums χ^2 Test) were used for analyses. Higher Apathy *T*-Scores were significantly associated with lower Confidence ratings ($\rho = -0.41$; $p = .0006$). Consistent with the aforementioned literature (McKiernan, 2011), higher Temptation ratings were significantly associated with lower Confidence ratings ($\rho = -0.56$; $p < .0001$).

More recent self-reported METH use ($\rho = 0.45$; $p = .0002$), higher POMS Depression/Dejection scores ($\rho = -0.42$; $p = .0006$), and NCI ($\chi^2 = 6.42$, $p = .01$) were associated with significantly lower Confidence ratings. PWH rated themselves as *more* confident to abstain from METH relative to their HIV- counterparts ($\chi^2 = 3.88$, $p = .049$). None of the above mentioned non-METH substance use variables (e.g., cannabis use or alcohol abuse diagnoses in the past year, lifetime non-METH substance abuse or dependence disorder, or use of other non-METH substances within the past year that did not meet diagnostic criteria for abuse or dependence) were significantly associated with Confidence Ratings at the univariable level, nor were any of the other variables listed in Table 1 (*ps* > 0.10).

3.3. Multivariable analysis: apathy as an independent predictor of confidence ratings

Based on univariable analyses, and prior literature, variables considered for multivariable regression included Apathy *T*-score, Temptation ratings, POMS Depression/Dejection, NCI, HIV status, and days since last METH use. Positive METH urine toxicology was not included since it was highly correlated with days since last use, although results remained the same regardless of which recent METH use variable was considered. The best AIC selection model ($R^2 = 0.52$, $p < .0001$) included higher Apathy *T*-score ($\beta = -0.28$, $p = .004$), higher Temptation ratings ($\beta = -0.50$, $p < .001$), presence of NCI ($\beta = -0.23$, $p = .014$), and being HIV- ($\beta = -0.23$, $p = .012$) as significant contributors of lower Confidence ratings (see Table 3). Fig. 1**(a–d)** displays univariable associations with Confidence ratings for the four significant predictors in the final multivariable regression model (Fig. 1a and b are correlation plots showing bivariate associations; Fig. 1c and d are box plots showing medians and quartiles).

While current depression symptoms (POMS Depression/Dejection) was not a significant predictor of Confidence ratings at the univariable level ($p > .10$), the above model was re-run with current MDD added given research suggesting that current MDD may play an important role in abstinence self-efficacy (Greenfield, 2012).

Apathy remained a significant, independent predictor of Confidence ratings ($\beta = -0.37$, $p < .001$; $R^2 = 0.56$, $p < .0001$). Current MDD was a significant predictor in this model (although contrary to what was observed in literature; current MDD in our model was associated with *increased* Confidence ratings), as were the original covariates (i.e., Temptation, NCI, and HIV status; *ps* < 0.05). We used the same approach to further characterize any influence of previous METH treatment and/or other non-METH substance use variables described above. As with current MDD, these characteristics were not significantly associated with Confidence ratings in univariable analyses (*ps* > 0.10), though they have been linked to abstinence self-efficacy in the literature (Ilgen et al., 2005; Kadden & Litt, 2011). Our multivariable regression results remained unchanged regardless of the substance use variable considered, none of which explained a significant proportion of the variance in Confidence ratings in multivariable analyses (*ps* > 0.10).

4. Discussion

Results from this study found that among METH dependent individuals, apathy plays a significant role in reducing confidence in one's ability to maintain abstinence from using METH. Difficulties with motivation, self-direction, and goal-orientation appear to have a unique impact on METH abstinence self-efficacy, regardless of the degree of temptation, cognitive impairment, recency of METH use, co-morbid HIV disease, or depression. Despite the fact that apathy is highly prevalent, and a neurobehavioral consequence among METH users (Looby & Earleywine, 2007), these results suggest that it may also provide an important assessment and intervention target for METH substance use

Table 3
Univariable and multivariable regression analyses examining predictors of Confidence (i.e., METH abstinence self-efficacy).

Predictors	Risk Direction (lower Confidence)	Univariable Analyses[a]	Multivariable Regression Analyses[b]	
		rho (ρ) or χ^2	β	p
Apathy *T*-Score	More apathy	$\rho = -0.41$**	−0.28	0.004
Temptation ratings	More temptation	$\rho = -0.56$**	−0.50	<0.001
HIV Status	HIV-	$\chi^2 = 3.88$*	−0.23	0.012
Neurocognitive Impairment (NCI)	NCI	$\chi^2 = 6.42$*	−0.23	0.014
Model Statistics				
R^2			0.52	
p-value			<0.0001	

Note.
[a] Univariable analyses were conducted using Spearman's *rho* (ρ) or Wilcoxon Rank Sums tests (χ^2).
[b] AIC and backward selection methods.
* $p < .05$.
** $p < .01$.

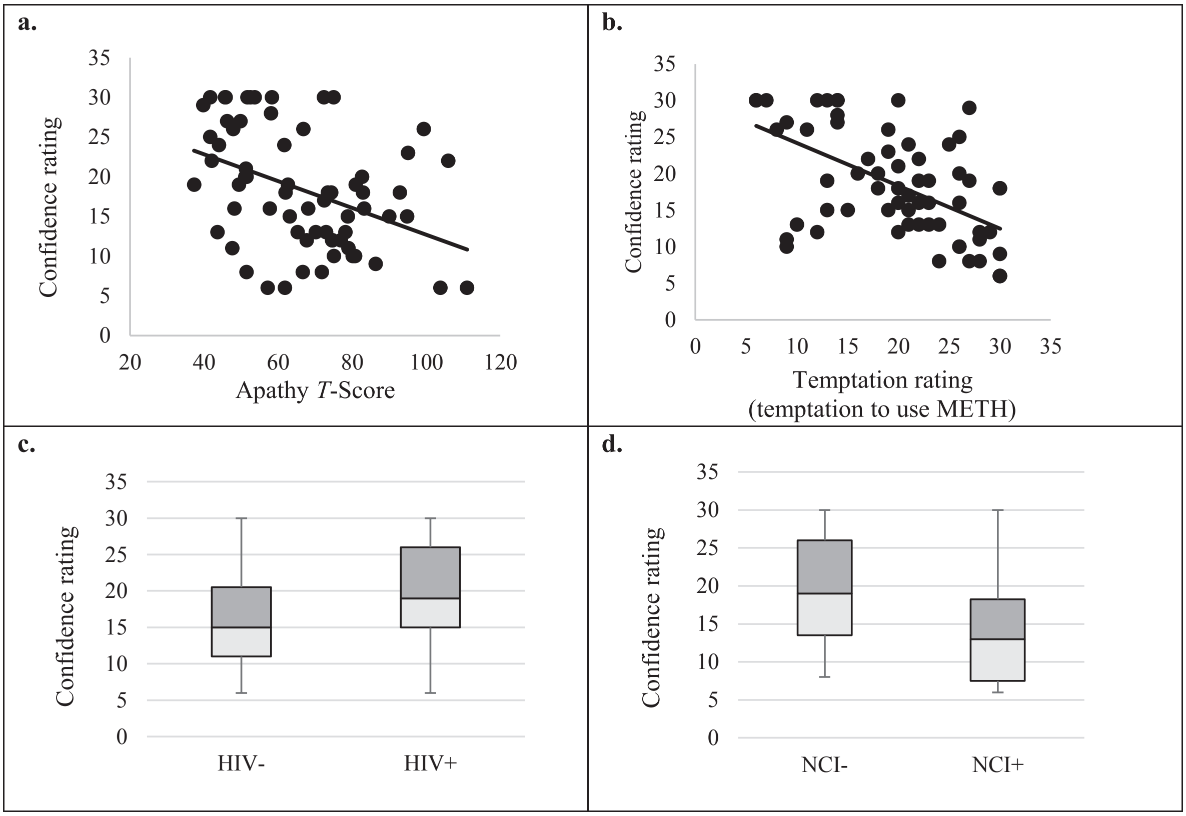

Fig. 1. Univariable associations with Confidence ratings for: (**a**) Apathy *T*-Score (Spearman's $\rho = -0.41$; $p < .001$); (**b**) Temptation ratings (Spearman's $\rho = -0.56$; $p < .001$); (**c**) HIV status ($\chi^2 = 3.88$, $p = .049$); and (**d**) NCI (Wilcoxon Rank Sums $\chi^2 = 6.42$, $p = .01$).

treatment. For example, in addition to other mood and behavioral treatments (i.e., contingency management), improving motivation and self-direction and may serve as an additional buffer to enhance the likelihood of successful METH substance use treatment and relapse prevention through improving abstinence self-efficacy. Indeed, abstinence self-efficacy is an important predictor of these outcomes (Tuliao & Liwag, 2011), and there is promising work emerging regarding the treatment of apathy by pharmacological and non-pharmacological means (Manera, 2019; Roth, Flashman, & McAllister, 2007).

Consistent with prior work (McKiernan, 2011; Soravia, 2015), more temptation to use METH was a significant risk factor for poorer METH abstinence self-efficacy. The type and amount of temptation would be important to consider prior to engaging individuals in treatment, especially when they are working through different stages recovery and/or sobriety. Our results also highlight cognitive impairment as a contributing factor to poorer METH abstinence self-efficacy. This may reflect an individual's difficulties to learn and apply new treatment strategies, and related difficulties with prior abstinence attempts (Jovanovski, Erb, & Zakzanis, 2005; Verdejo-Garcia & Perez-Garcia, 2007). This relationship may be further compounded by increased apathy, which is also independently associated with executive function deficits and learning difficulties (Castellon, Hinkin, & Myers, 2000; Cole, 2007). Combined with evidence linking NCI with a variety of other adverse health and functional outcomes in METH users, which may further interfere with treatment outcomes (Aharonovich, Nunes, & Hasin, 2003; Henry, Minassian, & Perry, 2010; Minassian, 2017; Sadek, 2007; Weber, 2012), individuals should be screened for NCI prior to treatment to appropriately tailor intervention strategies to their cognitive strengths and/or weaknesses.

Recency of METH use was the only METH use characteristic significantly associated with abstinence self-efficacy at the univariable level. However, it was not a significant predictor in the final multivariable model. This may be, in part, because current, active METH use was not a recruitment criterion for our sample. Though use within the past 18-months was an inclusion criterion, only 18% of our sample ($n = 12$) met criteria for current (≤30-days) abuse or dependence diagnoses, and 21% ($n = 14$) screened METH+ on their day-of-testing urine toxicology. Inclusion of current METH diagnoses or urine toxicology did not alter our primary findings, though future research in larger samples is needed to confirm these associations in active, heavy METH users. While significant recent use of most other substances was not permitted due to the eligibility criteria of the parent study, we did examine the potential influence of non-METH substance use characteristics, including allowable substance use diagnoses in the past year (i.e., cannabis abuse or dependence, alcohol abuse) and use (i.e., yes/no) of other non-METH substances in the past year (which was allowed as long as criteria for abuse or dependence were not met, and urine drug screens were negative). None of these variables altered the relationship between apathy and abstinence self-efficacy, nor were they significant predictors in univariable or multivariable analyses. These findings suggest that apathy may play a role in abstinence self-efficacy more broadly across other substance using populations, which is an important avenue for future research.

Among METH users, risky drug use (e.g., needle sharing) and risky sexual behavior (e.g., condom-less sex) are common (Hoenigl, 2016; Ropelewski, 2011), increasing transmission risk for infectious diseases (Passaro, 2015). In our cohort, HIV seronegative individuals reported poorer abstinence self-efficacy compared to PWH. This may illustrate particular vulnerability of METH dependent individuals without HIV to acquire it in the future, resulting in negative downstream public health outcomes. Poor METH abstinence self-efficacy in HIV seronegative individuals compared to PWH appear unrelated to METH use characteristics (e.g., recency/quantity of use) since there were no significant METH use differences between the groups. Education was not associated with Confidence ratings in our analyses, though prior research suggests education may impact drug abstinence self-efficacy (Ilgen et al., 2007), and PWH in our sample were more educated than HIV seronegative individuals ($p < .001$). Among PWH, METH use is also a significant risk factor for medication non-adherence and poorer HIV disease outcomes (Carrico, 2011; Moore, 2012). However, PWH in our sample were on their current treatment regimen for about six years. It is possible that previous exposure to care and long-term, successful ART adherence improves self-efficacy in various areas of life, including METH abstinence self-efficacy, though we do not have sufficient data to examine this fully.

Analyses examining item responses on the four categories of high-risk situations for abstinence (McKiernan, 2011) identified social pressure and physical pain/illness as potential risk factors for relapse. Social pressure had the largest impact on temptation to use METH and confidence to abstain from METH. Findings emphasize the importance of considering an individual's social context when tailoring treatment and prevention efforts, perhaps integrating components of assertiveness or social skills training to aid in practicing refusal.

Prior work illustrates significant associations between depression and poor abstinence self-efficacy in substance users, though findings are mixed (Greenfield, 2012; Haukkala, 2000; Hodgins, Peden, & Cassidy, 2005). Interestingly, depression, whether measured via self-report or diagnostic evaluation, was not univariably associated with Confidence ratings in our study, and inclusion of current MDD in multivariable analyses did not alter the relationship between apathy and abstinence self-efficacy. Current MDD emerged as a significant predictor in multivariable analyses, though in an unexpected direction (presence of current MDD was associated with *more* Confidence). However, very few participants had current MDD ($n = 6$) and we did not observe a significant univariable association, therefore it is likely that other factors may have influenced this finding. To clarify these findings, we evaluated whether different assessment methods of depression available (e.g., current self-reported depression symptoms and lifetime diagnoses of MDD) may alter the findings though again, our main findings held regardless of the depression measure included (which themselves were not significant predictors in the model; $ps > 0.10$). Collectively, these results highlight the importance of apathy, perhaps beyond depression, in abstinence self-efficacy among METH users, which is consistent with a previous study that found apathy, but not depression, was associated with drug abstinence self-efficacy (Kalechstein, Newton, & Leavengood, 2002). While apathy shares features with depression (e.g., reduced insight, energy, and interest in activities; Ishizaki & Mimura, 2011), the two constructs may be dissociable (Paul, 2005; Paul, 2005; Tate, 2003) and may differ in their clinical impact. Indeed, apathy has important clinical consequences (e.g., NCI, poor treatment compliance, reduced quality of life; Kamat, 2012, 2016), and these findings extend this literature to lower abstinence self-efficacy and possible poor substance abuse treatment outcomes. Therefore, although depression is important to consider in substance treatment programs (Glasner-Edwards, 2009; Kay-Lambkin, 2011; Swendsen & Merikangas, 2000), our results suggest that assessing and addressing apathy may additionally improve treatment initiation, adherence, and efficacy.

Although not directly examined, the strong link between apathy and poorer abstinence self-efficacy in METH dependence may shed light on the neural mechanisms of initiating and maintaining abstinence. The neural basis of apathy involves disruption of the dorsal anterior cingulate cortex and ventral striatum networks (Husain & Roiser, 2018). This circuitry potentially underlies a willingness to work, to keep working, and to learn what is worth working towards (Le Heron, Apps, & Husain, 2018). For abstinent, METH dependent individuals, greater activation of the dorsal anterior cingulate cortex and other dorsal cognitive control systems are needed when choosing larger, delayed rewards than smaller, immediate rewards (Hoffman, 2008). Thus, the motivational impairment that stems from apathy may play an important role in perpetuating harmful behaviors, even when temptation to use drugs is low. To address this challenge, METH treatment should identify motivators of abstinence through values-based care or motivational interviewing prior to program engagement. Additional work is needed to elucidate the directionality between apathy and METH abstinence self-efficacy via prospective or longitudinal designs, and their impact on treatment outcomes.

This study is not without limitations. Our sample size was relatively small, limiting our ability to perform more sophisticated analyses. Another limitation is that the modified MSES was originally designed for alcohol users. Though our findings provide support for the use of this measure in METH, tailored METH-specific cues and situations may be useful. Importantly, since the TMARC study was cross-sectional and observational, we were unable to examine the effects of apathy in the context of treatment, or longitudinally to address implications for treatment engagement or outcomes. Moreover, due to the primary aims of the parent study (e.g., cross-sectional examination of the CNS effects of METH dependence), only limited data were collected regarding the history of METH addiction (i.e., general information regarding whether or not the participant had a history of treatment in their lifetime), which was not associated with study outcomes. Detailed treatment history and characteristics (e.g., number and types of treatments and/or relapses) collected by future studies would provide valuable insight into the role of apathy in the context of other addiction characteristics as they relate to METH abstinence self-efficacy.

Lastly, while our findings generalize to some METH users encountered in clinical settings, we are limited in our ability to extend these findings to METH users with concurrent active and/or significant recent use of other commonly used substances of abuse (e.g., cocaine), since these participants were excluded, by design, of the parent study. This would be an important future direction, particularly since polysubstance use is common among METH users and associated with elevated risk of neurobehavioral problems that may affect treatment outcomes (Reback, 2012). For example, polysubstance users such as METH dependent individuals who co-abused alcohol, cocaine, and/or marijuana have been shown to experience apathy (Verdejo-García, 2006), and has been a barrier to successful substance use treatment (Balsamo, 2016; Mathew, 2017). Moreover, among individuals addicted to alcohol, nicotine, opiates, amphetamines, heroin, and cannabis (Garfield, Lubman, & Yucel, 2014), anhedonia, which can be a symptom of apathy, has been shown to increase cravings and the likelihood of relapse. Thus, the role of apathy in abstinence self-efficacy is an important direction for further exploration, not only in METH, but across other substance using populations, and may be an important target for intervention to improve abstinence self-efficacy and subsequently improving treatment efficacy.

5. Conclusions

Despite study limitations, our findings offer significant clinical implications. Apathy, beyond other factors, may have a direct impact in one's perceived ability to effectively abstain from METH use in the future (i.e., abstinence self-efficacy), which is an important factor associated with successful treatment outcomes. Thus, current treatment programs addressing comorbid substance use disorder and depression with techniques such as behavioral activation (Daughters, 2016) may be more efficacious if apathy was also an integrated treatment focus, particularly in METH. Though there is not yet a gold standard for apathy treatment, potential pharmacological and psychological treatments (e.g., acetylcholinesterase inhibitors, dopamine-reuptake inhibitors, and cognitive-communication therapies) are being investigated (Manera, 2019; Roth et al., 2007).

Many non-pharmacological interventions for apathy have risen from research on apathy in dementia. This research may provide suggestions for interventions in addiction, as well. A unifying theme for many of these interventions is the incorporation of socially-based activities that are tailored to the individual (e.g., music therapy, multi-sensory behavioral therapy, art therapy, and therapeutic conversations; Massimo, Kales, & Kolanowski, 2018). Thus, these interventions may offer intrinsic reward, thereby increasing motivation. Although research in non-pharmacological treatment for apathy among substance use disorder populations is limited, a similar socially-based model for addiction treatment may help to reduce apathy. Potential interventions may include those that rebuild social networks to support abstinence through community programs (Worley, 2014; Zywiak, Longabaugh, & Wirtz, 2002), incorporate relationship-enhanced approaches with standard cognitive behavioral therapies (Bouma, Halford, & Young, 2004), emphasize communication skills training to help successsfully navigate social environments that may result in temptation to use in the future (Monti, 1990), and increase positive affect through adaptive coping interventions (Carrico, 2013). These socially-focused approaches may help reduce apathy and increase drug abstinence self-efficacy, particulary among METH dependent indivduals.

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7. Contributors

M.A.H. developed the current manuscript's study concept, performed formal data analysis and interpretation for the current study, wrote the original draft, and took part in review and editing during the writing process. J.E.I. provided supervision to M.A.H during the development of the current manuscript's study concept, formal data analysis and interpretation, and took part in review and editing during the writing process. E.E.M and R.K. provided help with the development of the current manuscript's study concept, and took part in review and editing during the writing process. R.K.H. provided supervision to M.A.H. during the development of the current manuscript's study concept, and took part in review and editing during the writing process. I.G., the Principal Investigator of the current research study, developed the larger study concept and acquired funding for the Translational Methamphetamine Research Center (TMARC), as well as provided review and editing during the writing process.

CRediT authorship contribution statement

Mariam A. Hussain: Conceptualization, Formal analysis, Writing - original draft, Writing - review & editing. **Jennifer E. Iudicello:** Conceptualization, Formal analysis, Writing - review & editing, Supervision. **Erin E. Morgan:** Conceptualization, Writing - review & editing. **Rujvi Kamat:** Conceptualization, Writing - review & editing. **Robert K. Heaton:** Conceptualization, Writing - review & editing, Supervision. **Igor Grant:** Conceptualization, Writing - review & editing, Funding acquisition. **:** .

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