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Conditional Effects of Lifetime Alcohol Consumption on Methamphetamine-Associated Neurocognitive Performance

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Abstract

Objectives: Methamphetamine (MA) dependence contributes to neurotoxicity and neurocognitive deficits. Although combined alcohol and MA misuse is common, how alcohol consumption relates to neurocognitive performance among MA users remains unclear. We hypothesized that alcohol and MA use would synergistically diminish neurocognitive functioning, such that greater reported alcohol consumption would exert larger negative effects on neurocognition among MA-dependent individuals compared to MA-nonusing persons. **Methods**: Eighty-seven MA-dependent (MA+) and 114 MA-nonusing (MA−) adults underwent neuropsychological and substance use assessments. Linear and logistic regressions examined the interaction between MA status and lifetime average drinks per drinking day on demographically corrected global neurocognitive *T* scores and impairment rates, controlling for recent alcohol use, lifetime cannabis use, WRAT reading performance, and lifetime depression. **Results:** MA+ displayed moderately higher rates of impairment and lower *T* scores compared to MA−. Lifetime alcohol use significantly interacted with MA status to predict global impairment (ORR = 0.70, $p = .003$) such that greater lifetime alcohol use increased likelihood of impairment in MA−, but decreased likelihood of impairment in MA+. Greater lifetime alcohol use predicted poorer global *T* scores among MA− ($b = -0.44$, $p = .030$) but not MA+ ($b = 0.08$, $p = .586$). **Conclusions:** Contrary to expectations, greater lifetime alcohol use related to reduced risk of neurocognitive impairment among MA users. Findings are supported by prior research identifying neurobiological mechanisms by which alcohol may attenuate stimulant-driven vasoconstriction and brain thermotoxicity. Replication and examination of neurophysiologic mechanisms underlying alcohol use in the context of MA dependence are warranted to elucidate whether alcohol confers a degree of neuroprotection.

Keywords: Substance-related disorders, methamphetamine, ethanol, neuropsychology, neuroprotection, cognitive dysfunction

INTRODUCTION

Methamphetamine (MA) is a highly addictive and widely used psychostimulant that induces adverse effects on the central nervous system (CNS), predominantly through alteration of monoaminergic pathways. Chronic exposure to MA and other amphetamines is associated with a host of neurotoxic processes including gliosis, neuronal apoptosis, oxidative stress, brain thermotoxicity, and neuroinflammation (Cadet et al., 2003; Yu et al., 2015). Consequently, conditions of neurochemical and cerebrovascular abnormalities, including increased blood–brain barrier permeability and ischemic stroke, are more prevalent among stimulant users (Sajja et al., 2016; Turowski & Kenny, 2015; Yen et al., 1994) and can disrupt neural circuits, particularly fronto-striatal systems that support neurocognitive abilities. It has been widely documented that MA-dependent individuals are vulnerable to a constellation of neurocognitive deficits including impairments in episodic memory, executive functioning, working memory, information processing speed, verbal fluency, attention, and motor skills (Kalechstein et al., 2003; Scott et al., 2007; Wood et al., 2014).

Whereas it is evident that MA dependence is associated with neurocognitive dysfunction, the severity of such neurocognitive deficits remains unclear. Synthesis of clinical studies comparing neurocognitive profiles of MA-dependent

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individuals to non-using controls not only indicates a mild-to-moderate deleterious effect of MA on neurocognition, but also reveals considerable inter-individual variability in which many MA-dependent persons perform within normative standards whereas others may exhibit severe deficits (Dean et al., 2013; Hart et al., 2012). Variation in use patterns of MA alone does not appear to account for these individual differences in vulnerability to MA-related brain dysfunction as the existing human literature has generally failed to find a consistent dose-dependent relationship between MA exposure parameters and neurocognitive impairment (Chang et al., 2002; Cherner et al., 2010; Johanson et al., 2006; McCann et al., 2008). Given the unimpressive predictive utility of MA exposure parameters as moderators of neurocognitive impairment, susceptibility to MA-related neurocognitive dysfunction may be better explained by the influence of other modulating variables.

Considering that MA is seldom used on its own, patterns of polysubstance use among primary MA users may modulate vulnerability to neurocognitive impairment. Alcohol is of particular interest as it is the most commonly used secondary substance among primary MA users (Halkitis et al., 2005; Wang et al., 2017) and heavy drinkers are 4–5 times more likely to report using MA as compared to non-drinkers (Bujarski et al., 2014; Caetano & Weisner, 1995; Furr et al., 2000). The detrimental effects of chronic excessive alcohol consumption on CNS and neurocognitive functioning have been extensively studied. Briefly, heavy alcohol-related risks for brain damage include disruption to neurotransmitter systems, neuroinflammation, neurodegeneration, and cerebrovascular disease (Gorelick, 1987; Oscar-Berman & Marinkovic, 2003; Syapin et al., 2005). Long-term alcohol misuse has been linked to alterations in frontal and limbic neural circuitry, most commonly resulting in neuropsychological deficits of episodic memory, problem solving, and cognitive control (Bernardin et al., 2014; Oscar-Berman et al., 2014; Sullivan et al., 2010).

Given that MA and alcohol independently disrupt overlapping neurobiological mechanisms, neuroanatomical structures, and neurobehavioral functions, one may expect a synergistic neurotoxic effect of combined MA and alcohol misuse. Previous animal studies have reported that alcohol enhances the absorption and delivery of MA in the brain (Liang et al., 2012). Additional animal model research has shown that concurrent exposures to MA and alcohol synergistically increase oxidative stress in the rat hippocampus and contribute to behavioral impairments in learning, discrimination, and spatial working memory above and beyond the effects of either substance alone (Vahed, 2014; Yamamura et al., 1992). *In vitro* human brain tissue models provide converging evidence that both alcohol and MA impair glucose metabolism in astrocytes and neurons, a process that is a precursor to oxidative stress-mediated neurotoxicity (Abdul Muneer et al., 2011a, 2011b). Although less is known about combined MA and alcohol-induced biological damage *in vivo*, there is evidence that acute as well as repeated concurrent exposure induces adverse vascular effects, including increased heart rate and myocardial oxygen consumption (Kirkpatrick et al., 2012; Mendelson et al., 1995). Consistent with neurocognitive profiles of adult MA users, pediatric studies demonstrate that prenatal exposures to MA and alcohol synergistically damage fronto-striatal networks and compromises working memory abilities in children aged 5–15 (Roussotte et al., 2011; Sowell et al., 2010).

Chronic exposure to cocaine, another potent psychostimulant, is associated with moderate deficits in neurocognition across a range of domains, with the largest effects in executive function, working memory, and verbal learning/memory (Potvin et al., 2014). Whereas combined cocaine and alcohol use has been linked to altered neurophysiological activity (Althobaiti & Sari, 2016), including abnormal cerebral blood perfusion (Gottschalk & Kosten, 2002), elevated heart rate and cortisol levels (Farré et al., 1997), and dysregulated dopaminergic and serotonergic transmission (Horowitz & Torres, 1999), literature on the neurocognitive effects of comorbid cocaine and alcohol use disorders is mixed. Some studies report that increasing alcohol use provides an additive deleterious effect on neurocognition in primary cocaine users (Bolla et al., 2000; Woicik et al., 2009) and can also attenuate improvements in verbal memory following abstinence from cocaine (Rosselli & Simmers, 2016). Nevertheless, others have failed to detect a significant impact of alcohol consumption on neurocognition in the context of cocaine dependence (Abi-Saab et al., 2005; Bolla et al., 1999; Goldstein et al., 2004).

Although combined alcohol and MA misuse is common and may result in a convergence of mechanisms of neural injury, it remains unclear how historical patterns of alcohol use relate to neurocognitive functioning among primary MA users. Therefore, the current study aimed to address this gap in knowledge by examining the relationships between a continuous estimate of lifetime alcohol consumption and neurocognitive functioning in a sample of MA-dependent and MA-nonusing individuals. We hypothesized that greater reported lifetime alcohol consumption would contribute to poorer neurocognitive functioning regardless of MA dependence, but would exhibit significantly larger effects among MA-dependent individuals compared to MA-nonusing persons. Examination of these associations may assist in identifying specific risk factors for neurocognitive impairment among MA-dependent individuals, and may guide development of targeted polysubstance use prevention and treatment strategies for this population.

METHODS

Participants

Eighty-seven MA-dependent (MA+) and 114 MA-nonusing comparison (MA−) participants were evaluated at the HIV Neurobehavioral Research Program (HNRP) at the University of California, San Diego (UCSD), as part of federally funded, institutionally approved projects focusing on neuroAIDS effects of methamphetamine. All were recruited from substance dependence recovery programs or from the

Table 1. Methamphetamine use parameters by methamphetamine status

Methamphetamine use parameter Mean (SD) or median [IQR]	MA− ($n = 14/114$ only)	MA+ ($n = 87$)
Lifetime days of use	30 [7–30]	2640 [780–4706]
Lifetime grams consumed	1.9 [1.5–1.9]	1497.7 [342.4–4730.7]
Lifetime average daily use (grams/day)	0.1 [0.1–0.1]	0.7 [0.3–1.5]
Days since last use	2739 [1735–5022]	75 [30–152]
Age of first use	25.3 (10.34)	23 (10.57)

Note. MA – use represents occasional experimentation.

general San Diego community, and gave written informed consent as approved by the UCSD Institutional Review Board. Participants were confirmed to be HIV and HCV uninfected by standard antibody testing and were free of medical conditions that might confound interpretation of neurocognitive testing results, such as traumatic brain injury, stroke, or epilepsy. The MA+ individuals met criteria for a lifetime diagnosis of MA dependence according to the Structured Clinical Interview for DSM-IV (SCID-IV; Spitzer et al., 1995), with use within the previous 18 months. The MA− group consisted of participants who never met criteria for amphetamine use disorders and were not habitual users of any stimulant. Exclusion criteria for both groups included other substance dependence, except alcohol or cannabis, within 5 years, or abuse within the past 12 months. Participants were requested to be abstinent from MA for at least 10 days prior to testing and were required to show a negative urine toxicology for any non-prescribed substance except cannabis, as well as a negative Breathalyzer test for alcohol on the day of neurocognitive testing.

Procedures

Substance use and psychiatric information

The methods of drug use characterization have been described elsewhere (Cherner et al., 2010; Gonzalez et al., 2004). Briefly, participants were administered structured interviews from selected modules of the SCID-IV to assess history of substance dependence and mood disorder. A semi-structured timeline follow-back interview was administered to gather a detailed history of quantity, frequency, and duration of substance consumption over a participant's lifetime. Variables of alcohol, MA, and cannabis use derived from this interview were age of first use, days since last use, estimated lifetime grams (MA and cannabis) and drinks (alcohol) consumed, estimated lifetime days of use, and average grams per day of use (MA and cannabis) and average drinks per drinking day (referred to as "lifetime average daily alcohol use"). We conceptualized lifetime average daily alcohol use, an established metric utilized to quantify alcohol misuse (Dawson et al., 2005), as a proxy for typical level of alcohol use throughout the lifetime. Parameters of cannabis use were specifically examined because study criteria did not exclude recent cannabis use and prior research has suggested cannabis may be associated with better neurocognitive functioning among MA users (Gonzalez et al., 2004). Table 1 displays the MA use parameters of the MA+ group in addition to the 14 MA− participants who reported having tried MA occasionally (fewer than 10 lifetime uses). Current mood symptoms were assessed using the Beck Depression Inventory II (BDI-II; Beck et al., 1996).

Neurocognitive assessment

All participants completed a comprehensive neurocognitive evaluation that has been described in detail elsewhere (Rippeth et al., 2004). In short, this neurocognitive test battery covers seven ability domains: verbal fluency, abstraction/executive functioning, processing speed, learning, delayed recall, attention/working memory, and complex motor skills (see Supplementary Table 1 for individual tests in each domain). Raw test scores were converted to demographically corrected standard *T* scores (mean of 50 and standard deviation of 10) that adjusted for the effects of age, education, sex, and race/ethnicity, as appropriate (Heaton et al., 2004; Heaton et al., 2003; Norman et al., 2011). The demographically corrected *T* scores for each measure were averaged to compute global and domain-specific *T* scores within each neurocognitive ability area. To determine the presence of neurocognitive impairment, individual test *T* scores were converted to deficit scores that give differential weight to impaired scores (>1 standard deviation below the mean), as opposed to normal scores. Deficit scores range from 0 to 5 according to the following *T* scores and impairment descriptors, based on half standard deviation decrements: $0 = T \geq 40$ (no impairment); $1 = T$ 35–39 (mild); $2 = T$ 30–34 (mild-to-moderate); $3 = T$ 25–29 (moderate); $4 = T$ 20–24 (moderate-to-severe); $5 = T$ <20 (severe). Deficit scores for each measure were averaged across the entire test battery to derive a global deficit score (GDS) and within each domain to derive domain-specific deficit scores (DDS). Consistent with prior studies (Blackstone et al., 2012; Carey et al., 2004), the presence of global impairment was defined by GDS ≥ 0.5 and domain-specific impairment by DDS > 0.5. The dichotomous GDS classification of impaired/unimpaired was used as an outcome measure in logistic regression analyses predicting global neurocognitive impairment.

Table 2. Demographic and clinical characteristics

Variable Mean (SD), Median [IQR], or *N* (%)	MA− (*n* = 114)	MA+ (*n* = 87)	*p*-value
Demographics			
Age (years)	37.2 (12.21)	38.6 (10.79)	.40
Education (years)	14.1 (2.08)	12.6 (2.20)	<.0001
WRAT reading	105.4 (10.14)	99.1 (9.27)	<.0001
Sex (male)	99 (86.8%)	81 (93.1%)	.14
Ethnicity (non-Hispanic White)	73 (64.0%)	59 (67.8%)	.58
Depressive symptoms			
Lifetime MDD	24 (21.1%)	34 (39.1%)	<.01
Current MDD	3 (2.6%)	8 (9.2%)	.06
BDI-II	2 (0–6)	11 (4–20)	<.001
Alcohol use			
Lifetime alcohol dependence	10 (8.8%)	32 (36.8%)	<.001
Lifetime drinking days	663 [127–1750]	1453 [470–3544]	<.001
Lifetime drinks consumed	2077 [271–5902]	8184 [2122–22,554]	<.001
Lifetime average daily use (drinks/day)	3.7 (2.53)	6.1 (4.00)	<.001
Days since last use	6.5 [2–99]	116 [14–411]	<.001
Age of first use	17.8 (4.29)	15.0 (4.63)	<.001
Cannabis use			
Lifetime cannabis dependence	4 (3.5%)	20 (23.0%)	<.001
Current cannabis dependence	1 (0.9%)	1 (1.2%)	1.000
Lifetime days of use	31 [0–395]	1261 [156–4176]	<.001
Lifetime grams consumed	5 [0–65.3]	496 [37.5–2465]	<.001
Lifetime average daily use (grams/day)	0.07 [0–0.25]	0.50 [0.19–2.07]	<.001
Days since last use	274 [12.5–2739]	365 [76–2739]	.48
Age of first use	16.0 (3.75)	14.1 (3.76)	<.001
Other lifetime substance dependence			
Cocaine	0 (0%)	14 (16.1%)	<.001
Hallucinogen	0 (0%)	2 (2.3%)	.19
Opioid	0 (0%)	6 (6.9%)	<.01
Inhalant	0 (0%)	1 (1.2%)	.46
Sedative	0 (0%)	0 (0%)	–
PCP	0 (0%)	0 (0%)	–

Note. Alcohol dependence greater than 12 months ago; other drug dependence greater than 5 years ago; cannabis may be recent. MA = methamphetamine status; WRAT Reading = Wide Range Achievement Test; MDD = major depressive disorder; BDI-II = Beck Depression Inventory-II.

Statistical Analysis

MA group comparisons of neuropsychological outcomes (i.e., *T* scores and impairment status), demographics, depressive symptoms, alcohol and cannabis use, and other lifetime substance dependence were conducted using Student's *t* tests, Wilcoxon Rank Sum tests, chi-square tests, and Fisher's exact tests as appropriate. MA group differences in neurocognitive performance were evident across domains. Given this non-specific pattern of MA group differences, and in order to limit multiple comparisons, we present the global *T* scores and global impairment classifications as outcome variables in linear and logistic regression analyses, respectively. Details of domain-specific results appear in Supplementary Table 2.

We first tested whether MA group differences in global functioning were attenuated by differences in estimated premorbid ability and neuropsychiatric factors by entering MA status along with performance on the Wide Range Achievement Test (version 3 or 4) Reading subtest (WRAT; Wilkinson & Robertson, 2006), lifetime major depressive disorder (MDD), and lifetime average daily cannabis as covariates into each model. Age, education, race/ethnicity, and sex were not considered as model covariates because they were already included in the neurocognitive test *T* score demographic adjustments. Next, we added lifetime average daily alcohol use and days since last alcohol use to test whether historical alcohol use, controlling for recency of alcohol use, incrementally predicted global functioning independent of MA status. Finally, an interaction term between MA status and lifetime average daily alcohol use was added to examine whether lifetime alcohol use modulated MA group differences in neurocognition. To probe interaction effects, simple slope analyses were conducted by examining the association of global functioning with lifetime average daily alcohol use within each MA group, adjusting for covariates. To avoid multicollinearity with lifetime MDD, BDI-II was not included as a covariate in initial models. Instead, BDI-II was added as a post-hoc covariate to

Table 3. Stepwise multivariable linear and logistic regression models predicting global *T* scores and impairment

Outcome	Step 1			Step 2			Step 3		
Global *T* scores	*b*	95% CI	*p*	*b*	95% CI	*p*	*b*	95% CI	*p*
WRAT	0.09	[0.01, 0.17]	.020	0.09	[0.01, 0.17]	.026	0.07	[−0.00, 0.15]	.061
LT MDD[a]	0.64	[−1.04, 2.31]	.453	0.68	[−1.04, 2.40]	.434	0.89	[−0.83, 2.61]	.307
Lifetime cannabis use[b]	−0.29	[−1.20, 0.61]	.521	−0.24	[−1.16, 0.68]	.605	−0.38	[−1.30, 0.54]	.421
MA[c]	−1.75	[−3.37, −0.13]	.034	−1.67	[−3.36, 0.03]	.054	−1.60	[−3.29, 0.09]	.063
Days since last alcohol use				−0.00	[−0.00, 0.00]	.983	−0.00	[−0.00, 0.00]	.938
Lifetime alcohol use[b,d]				−-0.08	[−0.31, 0.15]	.502	−0.41	[−0.80, −0.01]	.043
MA[c] × Lifetime alcohol use[b]							0.50	[0.01, 0.98]	.044
Outcome	Step 1			Step 2			Step 3		
Global impairment	OR	95% CI	*p*	OR	95% CI	*p*	OR	95% CI	*p*
WRAT	0.96	[0.92, 1.00]	.078	0.96	[0.92, 1.00]	.069	0.97	[0.93, 1.01]	.143
LT MDD[a]	0.82	[0.35, 1.80]	.635	0.77	[0.32, 1.72]	.530	0.64	[0.26, 1.48]	.308
Lifetime cannabis use[b]	0.71	[0.39, 1.13]	.206	0.73	[0.39, 1.15]	.232	0.76	[0.41, 1.22]	.310
MA[c]	2.05	[0.96, 4.39]	.064	2.34	[1.07, 5.26]	.035	2.23	[1.03, 4.85]	.043
Days since last alcohol use				1.00	[1.00, 1.00]	.610	1.00	[1.00, 1.00]	.530
Lifetime alcohol use[bd]				0.95	[0.84, 1.05]	.345	1.19	[0.99, 1.42]	.057
MA[c] × Lifetime alcohol use[b]							0.70	[0.54, 0.88]	.003

OR = odds ratio; CI = confidence interval; WRAT = Wide Range Achievement Test; MA = methamphetamine status; MDD = major depressive disorder.
[a] Lifetime diagnosis of MDD compared to no lifetime diagnosis of MDD.
[b] Represents lifetime average daily use.
[c] Effect of MA+ compared to MA−; Step 3 effect represents effect of MA group only at mean level of lifetime average daily alcohol use.
[d] Step 3 effect represents effect of lifetime average daily alcohol use in MA− individuals only (reference group).

final models in order to rule out the potential confounding influence of active depressive symptoms. To enhance interpretability of the logistic regression results predicting likelihood of global neurocognitive impairment, we present odds ratios (OR) estimated with 95% confidence intervals (CI). All analyses were performed using JMP Pro version 12.0.1 (JMP®, Version <12.0.1>. SAS Institute Inc., Cary, NC, 1989–2007).

RESULTS

Demographic and Clinical Characteristics

Demographic and clinical characteristics for each MA group are displayed in Table 2. Although groups were comparable with respect to age, sex, and race/ethnicity, the MA+ group had significantly fewer years of education and lower WRAT performance. The MA+ group displayed higher BDI-II scores as well as greater prevalence of lifetime non-MA substance use disorders and lifetime MDD.

With respect to parameters of alcohol consumption, the MA+ group generally reported a more extensive history of drinking behavior than the MA− group. Specifically, MA+ individuals on average drank on more days, consumed more total drinks, and subsequently had a greater lifetime average daily alcohol use than MA− individuals ($p < .001$). Furthermore, the MA+ group had a younger age of first alcohol use ($p < .001$). Conversely, the MA− group reported significantly fewer days since last alcohol use than the MA+ group ($p < .0001$). With the exception of days since last cannabis use ($p = .48$), MA+ individuals also reported a more extensive history of cannabis use. Spearman's correlations were conducted to examine the associations between lifetime average daily alcohol, cannabis, and MA use. Alcohol use positively correlated with both MA use ($r_s = .21$, $p = .038$) and cannabis use ($r_s = .36$, $p < .001$) indicating that MA+ individuals with elevated lifetime drinking patterns were also more likely to show elevated lifetime MA and cannabis use patterns. Although lifetime average daily MA use positively correlated with lifetime average daily cannabis use, this association failed to reach statistical significance ($r_s = .13$, $p = .194$)

Neurocognitive Performance Across MA Status

With respect to global performance, the MA+ group had significantly lower global *T* scores (47.5 *vs.* 49.9; $d = -0.45$; $p = .002$) and higher impairment rates (27.6% *vs.* 15.8%; OR = 2.03; $p = .042$) compared to the MA− group. Domain-specific neurocognitive *T* scores and impairment rates for MA groups are displayed in Supplementary Table 2. The MA+ group demonstrated worse neurocognitive performance compared to the MA− group across all ability areas for both *T* scores (Cohen's *d* range: −0.07–0.48) and impairment rates (OR range: 1.18–2.13).

Interaction of Lifetime Average Daily Alcohol Use and MA Status Predicts Neurocognitive Performance

Table 3 reports results for the stepwise multivariable linear regression analysis predicting global *T* scores. Step 1, which

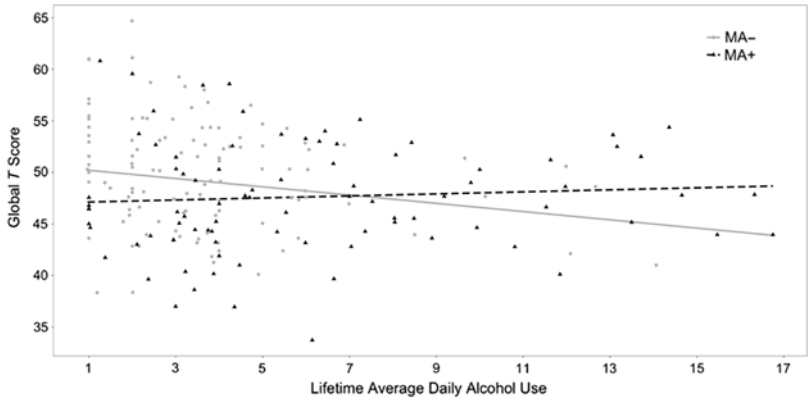

Fig. 1. Global *T* scores by lifetime average daily alcohol use, with predicted slopes for methamphetamine dependence (MA) status groups controlling for WRAT, BDI-II, lifetime MDD, days since last alcohol use, and lifetime average daily cannabis use. Higher lifetime average daily alcohol use significantly predicts lower global *T* scores among MA− individuals only.

examined the independent effect of MA status while controlling for WRAT scores, lifetime MDD, and lifetime average daily cannabis use, demonstrated significantly lower global *T* scores in the MA+ group compared to the MA− group ($b = -1.75$, $p = .034$). Of the covariates examined, only WRAT scores independently predicted global *T* scores, with higher WRAT performance predicting higher global *T* scores ($b = .09$, $p = .020$). Step 2, which added lifetime average daily alcohol use and days since last alcohol use as predictors of global *T* scores, did not demonstrate a significant effect of lifetime average daily alcohol use on global functioning independent of MA status and covariates ($b = -.08$, $p = .502$). Step 3, which examined whether lifetime average daily alcohol use modulated the effects of MA status on global *T* scores, showed a significant interaction of lifetime average daily alcohol use and MA status for global performance ($b = .50$, $p = .044$). Simple slope analyses indicated that lifetime average daily alcohol use negatively related to global functioning among MA− persons ($b = -0.44$, $p = .030$), but did not significantly predict global functioning among MA+ participants ($b = 0.08$, $p = .586$; Figure 1). Post-hoc adjustment for BDI-II scores did not attenuate the significant interaction effect of lifetime average daily alcohol use and MA status on global *T* scores.

Results for the binary logistic regression analysis predicting global impairment are also reported in Table 3. Similar to the step 1 global *T* score analyses, the MA+ group had a higher likelihood of global impairment (OR = 2.05, $p = .064$) and higher WRAT scores reduced the likelihood of impairment (OR = 0.96, $p = .078$), yet these effects only approached significance. The step 2 model did not demonstrate significant main effects for lifetime average daily alcohol use or days since last alcohol use on probability of global impairment. However, step 3 showed a significant interaction of lifetime average daily alcohol use and MA status for global impairment ($p = .003$). Simple slope analyses indicated that greater alcohol consumption increased the likelihood of global impairment (OR = 1.22, 95% CI [1.01; 1.48], $p = .033$) in MA− persons, but significantly decreased the likelihood of global impairment (OR = 0.82, 95% CI [0.68; 0.96], $p = .020$) in MA+ individuals. Similar to the *T* score analysis, post-hoc adjustment for BDI-II scores did not attenuate the significant interaction effect of lifetime average daily alcohol use and MA status on global impairment.

DISCUSSION

The present study explored how lifetime patterns of alcohol consumption, specifically a metric averaging drinks per drinking day over the lifetime, related to neuropsychological performance among MA-dependent and MA-nonusing individuals. Based on the current literature detailing the independent, adverse neurobehavioral contributions of chronic MA and alcohol consumption, it was hypothesized that the MA+ group would exhibit worse neurocognitive performance and that greater alcohol use would exacerbate the deleterious neurocognitive effects of MA use. Consistent with prior studies, we demonstrate that MA+ individuals perform worse on average across all neurocognitive domains while exhibiting modestly higher rates of neurocognitive impairment (Cherner et al., 2010; Scott et al., 2007) and consuming more alcohol and cannabis than their MA− counterparts. Whereas heavier drinking increased the likelihood of global neurocognitive impairment in the absence of MA dependence, no additive effects of alcohol were observed among MA+ participants. Contrary to expectations, lifetime average daily alcohol use did not predict global *T* scores and in fact was associated with reduced risk of global neurocognitive impairment in the MA+ group. To our knowledge, this is the first study to explore potentially modulating effects of historical patterns of alcohol consumption, as opposed to recent heavy drinking, on MA-associated neurocognitive performance.

Given the known neurotoxic and neurobehavioral consequences of heavy alcohol use (Brust, 2010; Grant, 1987), these results must be interpreted with caution. However, our finding that elevated historical levels of alcohol consumption attenuate MA-related global neurocognitive impairment

is consistent with prior studies demonstrating that singly addicted stimulant abusers consistently experience greater levels of neurocognitive dysfunction than those who simultaneously abuse stimulants and alcohol (Lawton-Craddock et al., 2003; Robinson et al., 1999). These prior findings are particularly applicable to the current investigation as both studies classified participants based on lifetime patterns of chronic stimulant and alcohol use (i.e., dependence) and administered comprehensive and validated neuropsychological batteries. Although studies of the neurocognitive effects of acute, combined stimulant and alcohol use may be less generalizable to our results, some studies have reported that administration of dextroamphetamine or amphetamine sulfate following ethanol-induced intoxication in humans may dampen ethanol-related neuropsychological decrements in psychomotor performance, executive function, and working memory (Perez-Reyes et al., 1992; Wilson et al., 1966). Nevertheless, further research is required to determine whether acute alcohol administration following MA-induced intoxication exhibits similar neurocognitive effects and to what extent such findings can be extrapolated to chronic substance abusers.

Our unanticipated results with respect to MA+ participants necessitate that we critically examine potential statistical and behavioral confounds. The significant relationship between lifetime average daily alcohol use and the dichotomous global impairment variable, as opposed to the null effect of lifetime alcohol use on continuous global *T* scores, reflects fundamental differences between these two measures of global neurocognition. Global *T* scores are computed by averaging individual *T* scores across the entire battery and can represent performance across the entire neurocognitive spectrum (e.g., severely impaired to very superior). As a result, above average performance on some measures can mask impaired performance elsewhere. Conversely, the GDS-based impairment classification accounts for the frequency and severity of deficits across the test battery with less consideration given to performance in the normal range (i.e., normal scores are set to zero; Blackstone et al., 2012). Figure 1 demonstrates that although *average* global *T* scores in MA+ individuals remain stable as lifetime average daily alcohol use increases, resulting in a null association, there is greater variability in performance at low levels of alcohol use, resulting in a higher percentage of MA+ individuals being classified as impaired on the GDS at low levels of use. Similarly, the MA+ group had an average global *T* score that only fell .35 standard deviations below the mean (i.e., $T = 47.5$), yet was twice as likely to have global impairment as compared to MA– individuals, suggesting that a global index of impairment may enhance detection of the subset of MA users that are disproportionally vulnerable to MA-related brain insults. Conversely, MA group comparisons on domain-specific performance illustrate the utility of *T* scores in detecting subtle yet significant differences that do not necessarily translate to differences in rates of impairment. The hypothesis that neurocognitive performance attributable to MA-induced neural injury may hinder the ability to detect the relatively subtle influence of alcohol is supported by evidence that MA abuse poses greater risk for neurocognitive deficits than alcohol abuse (Bechara & Martin, 2004; Gonzalez et al., 2007). Although our data demonstrate an adverse, multi-domain effect of MA dependence, this effect is modest and therefore unlikely to preclude us from detecting any additional influence of alcohol use patterns.

From a polysubstance use perspective, the strong positive correlation between self-reported lifetime MA and alcohol use indicates that the observed relationship between greater alcohol use and lower likelihood of global neurocognitive impairment is not an artifact of heavy drinkers having less exposure to MA. Although cannabis use correlated with alcohol use, and prior evidence suggests cannabis use may attenuate MA-related neurocognitive deficits (Gonzalez et al., 2004), lifetime cannabis exposure did not suppress our significant findings nor did it account for variance in neurocognitive performance. Furthermore, the negligible effects of days since last alcohol use and depressive symptoms rule out MA group differences in recent alcohol consumption and psychiatric comorbidities as a source of variance in neurocognitive performance. In a meta-analysis examining the neurocognitive effects of duration of alcohol abstinence, Stavro and colleagues found that neurocognitive dysfunction decreased following sustained abstinence for at least a year (Stavro et al., 2013). Importantly, this meta-analysis only included patients who met criteria for alcohol use disorder and excluded patients with non-alcohol substance use disorders. Given that the present study sample included MA-dependent individuals with varying levels of alcohol consumption, neurocognitive recovery facilitated by increased duration of abstinence from alcohol may be more prominent for heavier drinking populations without comorbid substance use disorders. Moreover, our study criteria excluded DSM-IV-based alcohol dependence within the past year as well as evidence of long-term lifetime alcoholism. Therefore, those meeting dependence criteria would have done so only in the past and on an episodic basis. With regard to MA group differences in time since last alcohol use, these are largely explained by many MA+ participants being in recovery and abstaining from all substances currently, whereas MA– participants may include current social drinkers. Nevertheless, days since last alcohol use did not predict our outcomes.

Drawing inferences about specific biological mechanisms underlying polysubstance use in humans is particularly challenging given that substance use disorders, such as MA dependence, cannot be experimentally modeled as independent factors in randomized controlled trials, and observational studies are often underpowered to examine potential confounds. Although the nature of our data prevents us from empirically investigating specific biological mechanisms that may explain the interactive effects of MA status and lifetime average daily alcohol use on neurocognitive functioning, we offer several plausible neurobiological interpretations. First, the cerebrovascular abnormalities evidenced in MA use are partially attributable to the vasoconstrictive properties of

MA that result in platelet aggregation (Ho et al., 2009; Kiyatkin & Sharma, 2009). Alcohol, in contrast, is recognized to have vasodilating properties that reduce platelet aggregation (Bau et al., 2005). Thus, alcohol-driven attenuation of MA-induced vasoconstriction may reduce the magnitude of neurovascular dysfunction and subsequent neurobehavioral deficits experienced by MA users. It is important to note, however, that certain studies have demonstrated a biphasic vasoregulatory effect in which alcohol's vasodilating properties may be limited to light-to-moderate drinkers, whereas heavier drinkers are at risk for a rebound effect in which an increase in platelet aggregation is observed following acute withdrawal from alcohol (Piano, 2017; Renaud & Ruf, 1996).

An additional source of MA-associated neurotoxicity is the induction of brain hyperthermia through increased neural activation (Brown et al., 2003; Kiyatkin & Sharma, 2009). Brain thermotoxicity is mediated through multi-level mechanisms in which adverse cellular (e.g., protein denaturation), local (e.g., infarction), and systemic (e.g., cerebral blood flow dysregulation) events can contribute to neurocognitive difficulties (Walter & Carraretto, 2016). Despite the sensations of warmth experienced during alcohol consumption, alcohol's vasodilatory properties result in brain and body heat dissipation (Lee et al., 1990) that may counteract the hyperthermic consequences of MA use. Animal experiments have demonstrated that rats exposed to alcohol before and after TBI recover from TBI-induced brain hyperthermia faster and exhibit fewer deficits in spatial learning than alcohol-naïve rats (Janis et al., 1998; Taylor et al., 2002). Whether such thermoregulatory benefits of alcohol, and subsequent attenuation of neurocognitive impairments, hold in the context of MA-induced hyperthermia requires further investigation.

Although the neurophysiological alterations associated with increased alcohol consumption may provide neuroprotective benefits in the context of MA addiction, our data demonstrate an adverse effect of lifetime average daily alcohol use on neurocognitive function in the absence of MA dependence. Unlike the MA+ group, who on average reported heavy lifetime alcohol consumption (i.e., >4 drinks/day), MA− individuals on average reported low-risk alcohol intake (National Institute on Alcohol Abuse and Alcoholism (U.S.), 2005). Neurocognitive performance in nondrinkers, low, and moderate drinkers has been widely studied yet has yielded mixed results. Whereas many researchers posit a "j-shaped" relationship, in which light-to-moderate consumption confers neurocognitive benefits over nondrinking but heavy consumption is more neurotoxic than abstinence (Britton et al., 2004; Elias et al., 1999; Neafsey & Collins, 2011; Rodgers et al., 2005), other studies have either found no relationship or a negative association between low-to-moderate consumption and neurobehavioral outcomes (Gross et al., 2011; Kalapatapu et al., 2017; Topiwala et al., 2017). Our findings are most consistent with the latter group of studies suggesting a deleterious dose-dependent effect of alcohol consumption, even at moderate levels, on cognition and brain structure (Gross et al., 2011; Topiwala et al., 2017). It is important to note that despite reaching statistical significance, our findings represent a small effect size in which one extra drink per day equates to about a one-half unit decrease in global *T* scores. As a result, the clinical significance of this relationship may be far more relevant for heavier drinkers with borderline neurocognitive performance than higher performing drinkers. Although the present study focuses on the conditional role of alcohol in MA-related neurocognitive performance, further studies that probe the neurocognitive effect of alcohol at varying levels of consumption and model non-linear relationships are warranted regardless of MA status.

Understanding limitations of the current study may guide future research to clarify the observed differential effects of alcohol use on neurocognitive functioning among MA+ and MA− individuals. Unsurprisingly, the MA+ group displayed significantly greater lifetime average daily alcohol use than the MA− group. Although the distribution of residuals from regression models were carefully examined to ensure no assumptions of normality were violated, the group difference in lifetime average daily alcohol use may impact the reliability of our MA effect estimates at high levels of consumption in which the MA− group is underrepresented. Additionally, these estimates of lifetime alcohol consumption are fully dependent on participant self-report. Given that the vast majority of participants began drinking during teenage years and must therefore recall multiple decades of alcohol use, estimates of alcohol consumption will naturally deviate from the true amount of alcohol exposure. Consequently, it is recommended that our estimates related to alcohol use and neurocognition be interpreted conservatively with a greater emphasis on directionality than exact magnitude.

The cross-sectional nature of our data prevents us from disentangling the effects of alcohol and MA use from long-standing individual differences in neurocognitive capacities (e.g., cognitive reserve). However, the inclusion of the WRAT Reading subtest as a covariate in all regression models increases our confidence that the observed effects of substance use on neurocognitive performance are not attributable to premorbid functioning. Furthermore, the application of demographic corrections to neuropsychological test scores improves the comparison of results between the MA groups despite differences in education. The positive association between WRAT scores and global neurocognition highlights the incremental predictive value of the WRAT above and beyond demographic effects, most notably education. These findings align with prior substance use studies that suggest that intellectual enrichment, as indicated by high IQ, can increase cognitive reserve and mitigate the deleterious effects of stimulant-induced neural injury on neurocognition (Cherner et al., 2010; Mahoney et al., 2017). Unsurprisingly, MA+ individuals more frequently met criteria for lifetime dependence for other substance use than MA− individuals. However, study exclusion criteria necessitated that such dependence be episodic in nature and remote (>5 years ago; alcohol >1 year ago; cannabis no restriction). Additional individual differences that we were not able to

capture in the present study include potential genetic differences in vulnerability to alcohol effects (e.g., metabolic differences); however, these would presumably be equally distributed among MA+ and MA– individuals.

The unexpected finding that alcohol reduces the likelihood of neurocognitive impairment in MA+ individuals raises intriguing biologically driven theories of neuroprotection that we unfortunately cannot answer with our data. Simultaneous administration of MA and alcohol *versus* non-overlapping periods of single substance use is an issue central to conceptualizing the interaction between MA and alcohol use. Many primary MA users report alternating use of MA and alcohol throughout a given binge in order to titrate their subjective experience of intoxication (Park & Nordahl, 2014). This coordinated pattern of MA and alcohol use may attenuate MA-related sleep disturbances, but may also increase risky behaviors (e.g., impaired driving) due to decreased perceptions of intoxication (Kirkpatrick et al., 2012). Although the lifetime average daily alcohol use metric captures lifetime alcohol patterns, it does not capture chronicity and persistence of alcohol use nor does it distinguish periods of concurrent MA and alcohol use from intervals of monosubstance use among the MA+ individuals. Such a distinction between lifetime periods of simultaneous intoxication *versus* non-overlapping intoxication would permit for a more nuanced understanding of the aforementioned neurophysiological hypotheses. Additionally, although our neurocognitive variables reflect the behavioral outputs of neural functioning, they do not directly measure the integrity of neural circuitry and neurobiological activity. Therefore, the inclusion of genetic, neuroimaging, and fluid-based biomarker data that more directly reflect neurobiological pathways is recommended for future studies of polysubstance use.

CONCLUSION

Taken together, our findings demonstrate a differential effect of lifetime alcohol consumption on neurocognitive performance such that hypothesized deleterious contributions of alcohol use were only detected in MA-nonusing individuals. Contrary to expectations, lifetime average daily alcohol use was associated with a reduced likelihood of global neurocognitive impairment in MA-dependent persons. Our findings are supported by prior animal and human studies identifying neurobiological mechanisms by which alcohol may attenuate the vasoconstriction and brain thermotoxicity associated with stimulant use (i.e., vasodilation and heat dissipation). Alcohol may diminish aspects of the neural dysregulation cascade that results in MA-associated neurocognitive dysfunction. Replication and examination of neurophysiologic mechanisms (e.g., neurovascular and metabolic effects) underlying alcohol use in the context of MA dependence, including concurrent use as well as acute and long-term effects, is warranted to elucidate whether alcohol confers a degree of neuroprotection in MA dependence.

SUPPLEMENTARY MATERIAL

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REFERENCES

Abdul Muneer, P.M., Alikunju, S., Szlachetka, A.M., & Haorah, J. (2011a). Methamphetamine inhibits the glucose uptake by human neurons and astrocytes: Stabilization by acetyl-L-carnitine. *PLoS One*, *6*(4), e19258. doi: 10.1371/journal.pone.0019258.

Abdul Muneer, P.M., Alikunju, S., Szlachetka, A.M., Mercer, A.J., & Haorah, J. (2011b). Ethanol impairs glucose uptake by human astrocytes and neurons: Protective effects of acetyl-L-carnitine. *International Journal of Physiology, Pathophysiology and Pharmacology*, *3*(1), 48–56.

Abi-Saab, D., Beauvais, J., Mehm, J., Brody, M., Gottschalk, C., & Kosten, T.R. (2005). The effect of alcohol on the neuropsychological functioning of recently abstinent cocaine-dependent subjects. *The American Journal on Addictions*, *14*(2), 166–178. doi: 10.1080/10550490590924854.

Althobaiti, Y.S. & Sari, Y. (2016). Alcohol interactions with psychostimulants: An overview of animal and human studies. *Journal of Addiction Research and Therapy*, *7*(3). doi: 10.4172/2155-6105.1000281.

Bau, P.F., Bau, C.H., Naujorks, A.A., & Rosito, G.A. (2005). Early and late effects of alcohol ingestion on blood pressure and endothelial function. *Alcohol*, *37*(1), 53–58. doi: 10.1016/j.alcohol.2005.10.034.

Bechara, A. & Martin, E.M. (2004). Impaired decision making related to working memory deficits in individuals with substance addictions. *Neuropsychology*, *18*(1), 152–162. doi: 10.1037/0894-4105.18.1.152.

Beck, A., Steer, R., & Brown, G. (1996). *Manual for Beck Depression Inventory II (BDI-II)*. San Antonio, TX: Psychology Corporation.

Bernardin, F., Maheut-Bosser, A., & Paille, F. (2014). Cognitive impairments in alcohol-dependent subjects. *Front Psychiatry*, *5*, 78. doi: 10.3389/fpsyt.2014.00078.

Blackstone, K., Moore, D.J., Franklin, D.R., Clifford, D.B., Collier, A.C., Marra, C.M., Gelman, B.B., McArthur, J.C., Morgello, S., Simpson, D.M., Ellis, R.J., Atkinson, J.H., Grant, I., &Heaton, R.K. (2012). Defining neurocognitive impairment in HIV: Deficit scores versus clinical ratings. *The Clinical Neuropsychologist*, *26*(6), 894–908. doi: 10.1080/13854046.2012.694479.

Bolla, K.I., Funderburk, F.R., & Cadet, J.L. (2000). Differential effects of cocaine and cocaine alcohol on neurocognitive performance. *Neurology*, *54*(12), 2285–2292.

Bolla, K.I., Rothman, R., & Cadet, J.L. (1999). Dose-related neurobehavioral effects of chronic cocaine use. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *11*(3), 361–369. doi: 10.1176/jnp.11.3.361.

Britton, A., Singh-Manoux, A., & Marmot, M. (2004). Alcohol consumption and cognitive function in the Whitehall II Study. *American Journal of Epidemiology*, *160*(3), 240–247. doi: 10.1093/aje/kwh206.

Brown, P.L., Wise, R.A., & Kiyatkin, E.A. (2003). Brain hyperthermia is induced by methamphetamine and exacerbated by social interaction. *The Journal of Neuroscience*, *23*(9), 3924–3929.

Brust, J.C.M. (2010). Ethanol and cognition: Indirect effects, neurotoxicity and neuroprotection: A review. *International Journal of Environmental Research and Public Health*, *7*(4), 1540–1557. doi: 10.3390/ijerph7041540.

Bujarski, S., Roche, D.J., Lunny, K., Moallem, N.R., Courtney, K.E., Allen, V., Hartwell, E., Leventhal, A., Rohrbaugh, T., & Ray, L.A. (2014). The relationship between methamphetamine and alcohol use in a community sample of methamphetamine users. *Drug and Alcohol Dependence*, *142*, 127–132. doi: 10.1016/j.drugalcdep.2014.06.004.

Cadet, J.L., Jayanthi, S., & Deng, X. (2003). Speed kills: Cellular and molecular bases of methamphetamine-induced nerve terminal degeneration and neuronal apoptosis. *The FASEB Journal*, *17*(13), 1775–1788. doi: 10.1096/fj.03-0073rev.

Caetano, R. & Weisner, C. (1995). The association between DSM-III-R alcohol dependence, psychological distress and drug use. *Addiction*, *90*(3), 351–359.

Carey, C.L., Woods, S.P., Gonzalez, R., Conover, E., Marcotte, T.D., Grant, I., & Heaton, R.K. (2004). Predictive validity of global deficit scores in detecting neuropsychological impairment in HIV infection. *Journal of Clinical and Experimental Neuropsychology*, *26*(3), 307–319. doi: 10.1080/13803390490510031.

Chang, L., Ernst, T., Speck, O., Patel, H., DeSilva, M., Leonido-Yee, M., & Miller, E.N. (2002). Perfusion MRI and computerized cognitive test abnormalities in abstinent methamphetamine users. *Psychiatry Research*, *114*(2), 65–79.

Cherner, M., Suarez, P., Casey, C., Deiss, R., Letendre, S., Marcotte, T., Vaida, F., Atkinson, J.H., Grant, I., Heaton, R.K., & HNRC Group (2010). Methamphetamine use parameters do not predict neuropsychological impairment in currently abstinent dependent adults. *Drug and Alcohol Dependence*, *106*(2–3), 154–163. doi: 10.1016/j.drugalcdep.2009.08.010.

Dawson, D.A., Grant, B.F., & Li, T.K. (2005). Quantifying the risks associated with exceeding recommended drinking limits. *Alcoholism: Clinical and Experimental Research*, *29*(5), 902–908.

Dean, A.C., Groman, S.M., Morales, A.M., & London, E.D. (2013). An evaluation of the evidence that methamphetamine abuse causes cognitive decline in humans. *Neuropsychopharmacology*, *38*(2), 259–274. doi: 10.1038/npp.2012.179.

Elias, P.K., Elias, M.F., D'Agostino, R.B., Silbershatz, H., & Wolf, P.A. (1999). Alcohol consumption and cognitive performance in the Framingham Heart study. *American Journal of Epidemiology*, *150*(6), 580–589.

Farré, M., De La Torre, R., González, M.L., Terán, M.T., Roset, P.N., Menoyo, E., & Camí, J. (1997). Cocaine and alcohol interactions in humans: Neuroendocrine effects and cocaethylene metabolism. *Journal of Pharmacology and Experimental Therapeutics*, *283*(1), 164–176.

Furr, C.D., Delva, J., & Anthony, J.C. (2000). The suspected association between methamphetamine ('ice') smoking and frequent episodes of alcohol intoxication: Data from the 1993 National Household Survey on Drug Abuse. *Drug and Alcohol Dependence*, *59*(1), 89–93.

Goldstein, R.Z., Leskovjan, A.C., Hoff, A.L., Hitzemann, R., Bashan, F., Khalsa, S.S., Wang, G.J., Fowler, J.S., & Volkow, N.D. (2004). Severity of neuropsychological impairment in

cocaine and alcohol addiction: Association with metabolism in the prefrontal cortex. *Neuropsychologia*, *42*(11), 1447–1458. doi: 10.1016/j.neuropsychologia.2004.04.002

Gonzalez, R., Bechara, A., & Martin, E.M. (2007). Executive functions among individuals with methamphetamine or alcohol as drugs of choice: Preliminary observations. *Journal of Clinical and Experimental Neuropsychology*, *29*(2), 155–159. doi: 10.1080/13803390600582446

Gonzalez, R., Rippeth, J.D., Carey, C.L., Heaton, R.K., Moore, D.J., Schweinsburg, B.C., Cherner, M., & Grant, I. (2004). Neurocognitive performance of methamphetamine users discordant for history of marijuana exposure. *Drug and Alcohol Dependence*, *76*(2), 181–190. doi: 10.1016/j.drugalcdep.2004.04.014

Gorelick, P.B. (1987). Alcohol and stroke. *Stroke*, *18*(1), 268–271.

Gottschalk, P.C. & Kosten, T.R. (2002). Cerebral perfusion defects in combined cocaine and alcohol dependence. *Drug and Alcohol Dependence*, *68*(1), 95–104.

Grant, I. (1987). Alcohol and the brain: Neuropsychological correlates. *Journal of Consulting and Clinical Psychology*, *55*(3), 310–324. doi: 10.1037/0022-006X.55.3.310

Gross, A.L., Rebok, G.W., Ford, D.E., Chu, A.Y., Gallo, J.J., Liang, K.Y., Meoni, L.A., Shihab, H.M., Wang, N.Y., & Klag, M.J. (2011). Alcohol consumption and domain-specific cognitive function in older adults: Longitudinal data from the Johns Hopkins Precursors study. *The Journals of Gerontology. Series B, Psychological Sciences and Social Sciences*, *66*(1), 39–47. doi: 10.1093/geronb/gbq062

Halkitis, P.N., Green, K.A., & Mourgues, P. (2005). Longitudinal investigation of methamphetamine use among gay and bisexual men in New York City: Findings from Project BUMPS. *Journal of Urban Health*, *82*(1 Suppl 1), i18–25. doi: 10.1093/jurban/jti020

Hart, C.L., Marvin, C.B., Silver, R., & Smith, E.E. (2012). Is cognitive functioning impaired in methamphetamine users? A critical review. *Neuropsychopharmacology*, *37*(3), 586–608. doi: 10.1038/npp.2011.276

Heaton, R.K., Miller, S.W., Taylor, M.J., & Grant, I. (2004). *Revised Comprehensive Norms for an Expanded Halstead Reitan Battery: Demographically Adjusted Neuropsychological Norms for African American and Caucasian Adults*. Lutz, FL: Psychological Assessment Resources, Inc.

Heaton, R.K., Taylor, M.J., & Manly, J. (2003). Demographic effects and use of demographically corrected norms with the WAIS-III and WMS-III, In *Clinical interpretation of the WAIS-III and WMS-III*, (pp. 181–210). San Diego, CA, USA: Academic Press.

Ho, E.L., Josephson, S.A., Lee, H.S., & Smith, W.S. (2009). Cerebrovascular complications of methamphetamine abuse. *Neurocrit Care*, *10*(3), 295–305. doi: 10.1007/s12028-008-9177-5

Horowitz, J.M. & Torres, G. (1999). Cocaethylene: Effects on brain systems and behavior. *Addiction Biology*, *4*(2), 127–140. doi: 10.1080/13556219971632

Janis, L.S., Hoane, M.R., Conde, D., Fulop, Z., & Stein, D.G. (1998). Acute ethanol administration reduces the cognitive deficits associated with traumatic brain injury in rats. *Journal of Neurotrauma*, *15*(2), 105–115. doi: 10.1089/neu.1998.15.105

Johanson, C.E., Frey, K.A., Lundahl, L.H., Keenan, P., Lockhart, N., Roll, J., Galloway, G.P., Koeppe, R.A., Kilbourn, M.R., Robbins, T., & Schuster, C.R. (2006). Cognitive function and nigrostriatal markers in abstinent methamphetamine abusers. *Psychopharmacology (Berlin)*, *185*(3), 327–338. doi: 10.1007/s00213-006-0330-6

Kalapatapu, R.K., Ventura, M.I., & Barnes, D.E. (2017). Lifetime alcohol use and cognitive performance in older adults. *Journal of Addictive Diseases*, *36*(1), 38–47. doi: 10.1080/10550887.2016.1245029

Kalechstein, A.D., Newton, T.F., & Green, M. (2003). Methamphetamine dependence is associated with neurocognitive impairment in the initial phases of abstinence. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *15*(2), 215–220. doi: 10.1176/jnp.15.2.215

Kirkpatrick, M.G., Gunderson, E.W., Levin, F.R., Foltin, R.W., & Hart, C.L. (2012). Acute and residual interactive effects of repeated administrations of oral methamphetamine and alcohol in humans. *Psychopharmacology (Berl)*, *219*(1), 191–204. doi: 10.1007/s00213-011-2390-5

Kiyatkin, E.A. & Sharma, H.S. (2009). Acute methamphetamine intoxication: Brain hyperthermia, blood–brain barrier, brain edema, and morphological cell abnormalities. *International Review of Neurobiology*, *88*, 65–100. doi: 10.1016/s0074-7742(09)88004-5

Lawton-Craddock, A., Nixon, S.J., & Tivis, R. (2003). Cognitive efficiency in stimulant abusers with and without alcohol dependence. *Alcoholism: Clinical and Experimental Research*, *27*(3), 457–464. doi: 10.1097/01.ALC.0000056620.98842.E6

Lee, J.A., Schoener, E.P., Nielsen, D.W., Kelly, A.R., Lin, W.N., & Berman, R.F. (1990). Alcohol and the auditory brain-stem response, brain temperature, and blood alcohol curves: Explanation of a paradox. *Electroencephalography and Clinical Neurophysiology*, *77*(5), 362–375.

Liang, M., Liu, Y., Zheng, N., Ananda, S., & Liu, L. (2012). Distribution of methamphetamine and its metabolite amphetamine in acute and subacute ethanol-methamphetamine combination abuse model rats. *Journal of Analytical Toxicology*, *36*(1), 30–35. doi: 10.1093/jat/bkr007

Mahoney, J.J., Kalechstein, A.D., De Marco, A.P., Newton, T.F., & De La Garza, R. (2017). The relationship between premorbid IQ and neurocognitive functioning in individuals with cocaine use disorders. *Neuropsychology*, *31*(3), 311–318. doi: 10.1037/neu0000344

McCann, U.D., Kuwabara, H., Kumar, A., Palermo, M., Abbey, R., Brasic, J., Ye, W., Alexander, M., Dannals, R.F., Wong, D.F., & Ricaurte, G.A. (2008). Persistent cognitive and dopamine transporter deficits in abstinent methamphetamine users. *Synapse*, *62*(2), 91–100. doi: 10.1002/syn.20471

Mendelson, J., Jones, R.T., Upton, R., & Jacob, P., 3rd (1995). Methamphetamine and ethanol interactions in humans. *Clinical Pharmacology & Therapeutics*, *57*(5), 559–568. doi: 10.1016/0009-9236(95)90041-1

National Institute on Alcohol Abuse and Alcoholism (U.S.) (2005). *Helping Patients Who Drink Too Much. A Clinician's Guide*. Washington, D.C.: National Institutes of Health, U.S. Department of Health and Human Services.

Neafsey, E.J. & Collins, M.A. (2011). Moderate alcohol consumption and cognitive risk. *Neuropsychiatric Disease and Treatment*, *7*, 465–484. doi: 10.2147/NDT.S23159

Norman, M.A., Moore, D.J., Taylor, M., Franklin, D., Jr., Cysique, L., Ake, C., Lazarretto, D., Vaida, F., Heaton, R.K., & HNRC Group

(2011). Demographically corrected norms for African Americans and Caucasians on the Hopkins verbal learning test-revised, brief visuospatial memory test-revised, stroop color and word test, and Wisconsin Card Sorting Test 64-Card Version. *Journal of Clinical and Experimental Neuropsychology*, *33*(7), 793–804. doi: 10.1080/13803395.2011.559157

Oscar-Berman, M. & Marinkovic, K. (2003). Alcoholism and the brain: An overview. *Alcohol Research & Health*, *27*(2), 125–133.

Oscar-Berman, M., Valmas, M.M., Sawyer, K.S., Ruiz, S.M., Luhar, R.B., & Gravitz, Z.R. (2014). Profiles of impaired, spared, and recovered neuropsychologic processes in alcoholism. *Handbook of Clinical Neurology*, *125*, 183–210. doi: 10.1016/B978-0-444-62619-6.00012-4

Park, D. & Nordahl, T. (2014). Methamphetamine and Dave's story. *Journal of Addiction Research and Therapy*, *5*(1). doi: 10.4172/2155-6105.1000e123

Perez-Reyes, M., White, W.R., McDonald, S.A., & Hicks, R.E. (1992). Interaction between ethanol and dextroamphetamine: Effects on psychomotor performance. *Alcoholism: Clinical and Experimental Research*, *16*(1), 75–81.

Piano, M.R. (2017). Alcohol's effects on the cardiovascular system. *Alcohol Research*, *38*(2), 219–241.

Potvin, S., Stavro, K., Rizkallah, E., & Pelletier, J. (2014). Cocaine and cognition: A systematic quantitative review. *Journal of Addiction Medicine*, *8*(5), 368–376. doi: 10.1097/adm.0000000000000066

Renaud, S.C. & Ruf, J.C. (1996). Effects of alcohol on platelet functions. *Clinica Chimica Acta*, *246*(1–2), 77–89.

Rippeth, J.D., Heaton, R.K., Carey, C.L., Marcotte, T.D., Moore, D.J., Gonzalez, R., &Group, H. (2004). Methamphetamine dependence increases risk of neuropsychological impairment in HIV infected persons. *Journal of the International Neuropsychological Society*, *10*(1), 1–14. doi: 10.1017/S1355617704101021

Robinson, J.E., Heaton, R.K., & O'Malley, S.S. (1999). Neuropsychological functioning in cocaine abusers with and without alcohol dependence. *Journal of the International Neuropsychological Society*, *5*(1), 10–19.

Rodgers, B., Windsor, T.D., Anstey, K.J., Dear, K.B., Jorm, A.F., & Christensen, H. (2005). Non-linear relationships between cognitive function and alcohol consumption in young, middle-aged and older adults: The PATH Through Life Project. *Addiction*, *100*(9), 1280–1290. doi: 10.1111/j.1360-0443.2005.01158.x

Rosselli, M. & Simmers, C.P. (2016). Effects of alcohol in chronic cocaine abuse: A follow up study. *Journal of Drug Abuse*, *2*(1), 1–11.

Roussotte, F.F., Bramen, J.E., Nunez, S.C., Quandt, L.C., Smith, L., O'Connor, M.J., Bookheimer, S.Y., & Sowell, E.R. (2011). Abnormal brain activation during working memory in children with prenatal exposure to drugs of abuse: The effects of methamphetamine, alcohol, and polydrug exposure. *Neuroimage*, *54*(4), 3067–3075. doi: 10.1016/j.neuroimage.2010.10.072

Sajja, R.K., Rahman, S., & Cucullo, L. (2016). Drugs of abuse and blood–brain barrier endothelial dysfunction: A focus on the role of oxidative stress. *Journal of Cerebral Blood Flow & Metabolism*, *36*(3), 539–554. doi: 10.1177/0271678X15616978

Scott, J.C., Woods, S.P., Matt, G.E., Meyer, R.A., Heaton, R.K., Atkinson, J.H., & Grant, I. (2007). Neurocognitive effects of methamphetamine: A critical review and meta-analysis. *Neuropsychology Review*, *17*(3), 275–297. doi: 10.1007/s11065-007-9031-0

Sowell, E.R., Leow, A.D., Bookheimer, S.Y., Smith, L.M., O'Connor, M.J., Kan, E., Rosso, C., Houston, S., Dinov, I.D., & Thompson, P.M. (2010). Differentiating prenatal exposure to methamphetamine and alcohol versus alcohol and not methamphetamine using tensor-based brain morphometry and discriminant analysis. *The Journal of Neuroscience*, *30*(11), 3876–3885. doi: 10.1523/JNEUROSCI.4967-09.2010

Spitzer, R., Williams, J., Gibbon, M., & First, M. (1995). *Structured Clinical Interview for DSM-IV*. Washington, DC: American Psychiatric Press.

Stavro, K., Pelletier, J., & Potvin, S. (2013). Widespread and sustained cognitive deficits in alcoholism: A meta-analysis. *Addiction Biology*, *18*(2), 203–213. doi: 10.1111/j.1369-1600.2011.00418.x

Sullivan, E.V., Harris, R.A., & Pfefferbaum, A. (2010). Alcohol's effects on brain and behavior. *Alcohol Research & Health*, *33*(1–2), 127–143.

Syapin, P.J., Hickey, W.F., & Kane, C.J.M. (2005). Alcohol brain damage and neuroinflammation: Is there a connection? *Alcoholism: Clinical & Experimental Research*, *29*(6), 1080–1089. doi: 10.1097/01.alc.0000167961.39176.e6

Taylor, A.N., Romeo, H.E., Beylin, A.V., Tio, D.L., Rahman, S.U., & Hovda, D.A. (2002). Alcohol consumption in traumatic brain injury: Attenuation of TBI-induced hyperthermia and neurocognitive deficits. *Journal of Neurotrauma*, *19*(12), 1597–1608. doi: 10.1089/089771502762300256

Topiwala, A., Allan, C.L., Valkanova, V., Zsoldos, E., Filippini, N., Sexton, C., Mahmood, A., Fooks, P., Singh-Manoux, A., Mackay, C.E., Kivimäki, M., & Ebmeier, K.P. (2017). Moderate alcohol consumption as risk factor for adverse brain outcomes and cognitive decline: Longitudinal cohort study. *BMJ*, *357*, j2353. doi: 10.1136/bmj.j2353

Turowski, P. & Kenny, B.A. (2015). The blood–brain barrier and methamphetamine: Open sesame? *Frontiers in Neuroscience*, *9*, 156. doi: 10.3389/fnins.2015.00156

Vahed, M.M. (2014). The effect of escalating dose, multiple binge methamphetamine regimen and alcohol combination on spatial memory and oxidative stress markers in rat brain. *Journal of Alcoholism & Drug Dependence*, *02*(03), 159. doi: 10.4172/2329-6488.1000159

Walter, E.J. & Carraretto, M. (2016). The neurological and cognitive consequences of hyperthermia. *Critical Care*, *20*(1), 199. doi: 10.1186/s13054-016-1376-4

Wang, L., Min, J.E., Krebs, E., Evans, E., Huang, D., Liu, L., Hser, Yl., &Nosyk, B. (2017). Polydrug use and its association with drug treatment outcomes among primary heroin, methamphetamine, and cocaine users. *International Journal of Drug Policy*, *49*, 32–40. doi: 10.1016/j.drugpo.2017.07.009

Wilkinson, G. & Robertson, G. (2006). *Wide Range Achievement Test-4 (WRAT-4)*. Lutz, FL: Psychological Assessment Resources Inc.

Wilson, L., Taylor, J.D., Nash, C.W., & Cameron, D.F. (1966). The combined effects of ethanol and amphetamine sulfate on performance of human subjects. *Canadian Medical Association Journal*, *94*(10), 478–484.

Woicik, P.A., Moeller, S.J., Alia-Klein, N., Maloney, T., Lukasik, T.M., Yeliosof, O., Wang, G.J., Volkow, N.D., & Goldstein, R.Z.

(2009). The neuropsychology of cocaine addiction: Recent cocaine use masks impairment. *Neuropsychopharmacology*, *34*(5), 1112–1122. doi: 10.1038/npp.2008.60

Wood, S., Sage, J.R., Shuman, T., & Anagnostaras, S.G. (2014). Psychostimulants and cognition: A continuum of behavioral and cognitive activation. *Pharmacological Reviews*, *66*(1), 193–221. doi: 10.1124/pr.112.007054

Yamamura, T., Hishida, S., Hatake, K., Taniguchi, T., & Ouchi, H. (1992). Effects of methamphetamine and ethanol on learning and brain neurotransmitters in rats. *Pharmacology Biochemistry and Behavior*, *42*(3), 389–400.

Yen, D.J., Wang, S.J., Ju, T.H., Chen, C.C., Liao, K.K., Fuh, J.L., & Hu, H.H. (1994). Stroke associated with methamphetamine inhalation. *European Neurology*, *34*(1), 16–22.

Yu, S., Zhu, L., Shen, Q., Bai, X., & Di, X. (2015). Recent advances in methamphetamine neurotoxicity mechanisms and its molecular pathophysiology. *Behavioural Neurology*, *2015*, 103969. doi: 10.1155/2015/103969