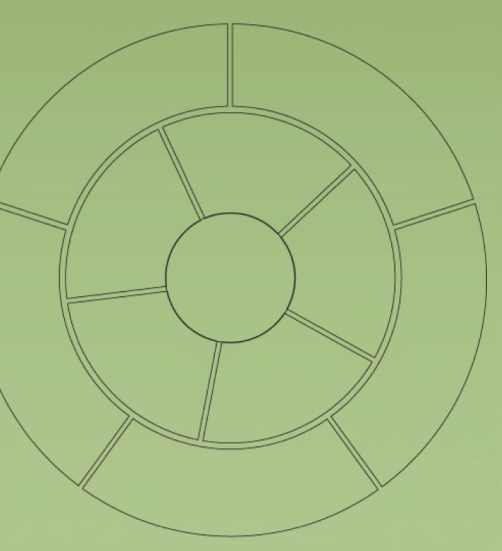


Is alcohol neuroprotective in methamphetamine-associated neuropsychological impairment?

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Background & Significance

- Methamphetamine (MA) misuse is associated with neurotoxicity and neurocognitive deficits.
- MA use parameters (e.g., cumulative lifetime exposure) generally fail to predict MA-related brain dysfunction (e.g., neurocognitive impairment)¹.
- Alcohol is the most commonly used secondary substance among primary MA users².
- Given that MA and alcohol independently disrupt overlapping neurobiological mechanisms, one may expect a synergistic neurotoxic effect of combined MA and alcohol misuse.

Aim/Hypothesis

Aim

To examine the relationships between an estimate of lifetime alcohol consumption and neurocognitive functioning among MA-dependent (MA+) and MA-nonusing (MA-) individuals.

Hypothesis

Greater reported lifetime alcohol consumption will contribute to poorer neurocognitive functioning regardless of MA-dependence, but will exhibit significantly larger effects among MA+ compared to MA- persons.

Methods

Participants

87 MA+ and 117 MA- adults underwent neuropsychological and substance use assessments. MA+ individuals met DSM-IV criteria for lifetime MA-dependence, with use within the last 18 months. 14 MA- individuals reported no habitual MA use (<10 lifetime total days of use). Exclusion criteria included other substance dependence, except alcohol or cannabis, within 5 years, or abuse within the past 12 months.

Substance Use Assessment

A timeline follow-back interview assessed alcohol MA, and cannabis use parameters: age of first use, days since last use, estimated lifetime consumption: grams (MA and cannabis) and drinks (alcohol), estimated lifetime days of use, and a density metric capturing average grams per day of use (MA and cannabis) and average drinks per drinking day (alcohol). Alcohol density, conceptualized as a proxy for typical level of alcohol use throughout the lifetime, was selected as a predictor variable in analyses.

Neurocognitive Testing

Seven ability domains were assessed: verbal fluency, executive function, processing speed, learning, recall, working memory, and motor skills. Demographically-adjusted T-scores and dichotomous impaired/unimpaired (<-1 SD cut-point) outcome variables were computed for global and domain-specific performance².

Statistical Analysis

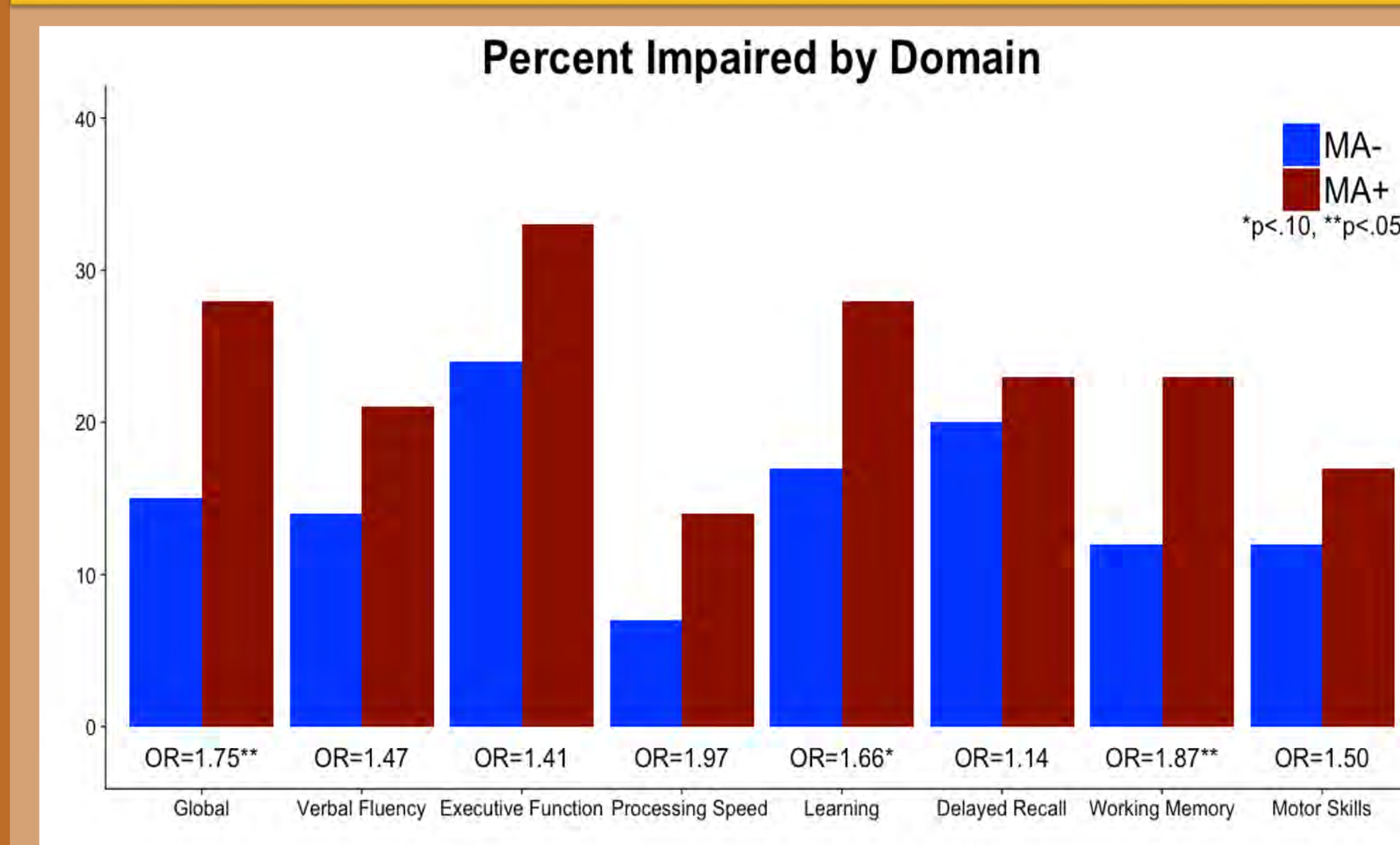
Separate regression models predicting global and domain-specific T-scores (linear) and impairment (logistic) as a function of alcohol density, MA status, and their interaction. Covariates included performance on the Reading subtest of the Wide Range Achievement (version 3 or 4; WRAT), days since last alcohol use, current depressive symptoms (BDI-II), lifetime major depressive disorder, and cannabis use density.

Table 2. Study sample characteristics

Variable	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 [2122-22554]	<.001
Density (average drinks per drinking 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
Density (average grams per day of use)	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%)	-

Abbreviations: WRAT=Wide Range Achievement Test; MDD=major depressive disorder. Note. Alcohol dependence greater than 12 months ago; other drug dependence greater than 5 years ago; cannabis may be recent.

Figure 1. Neurocognitive Performance by MA status



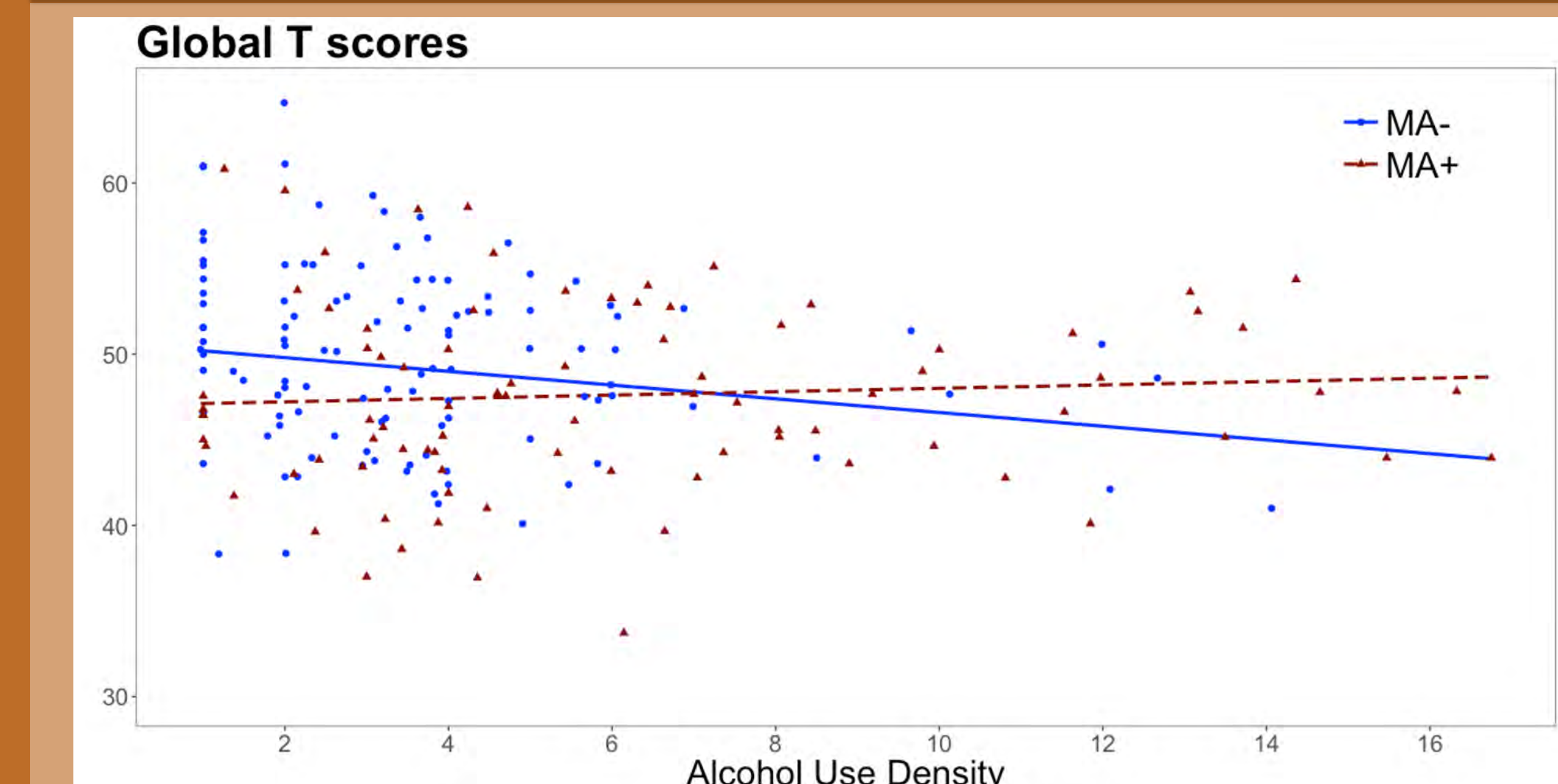
Tables 3 & 4. Coefficients for linear (beta) and logistic (odds ratio) models

Predictors	Outcome Variables: Neurocognitive Domain T Scores							
	Global	Verbal Fluency	Executive Function	Processing Speed	Learning	Delayed Recall	Working Memory	Motor Skills
Alcohol use density	-0.40**	-0.60*	-0.52*	-0.49*	-0.24	-0.06	-0.01	-0.53
MA ^a	-1.23	-1.56	-1.46	-0.29	-2.63*	0.33	-2.91*	-0.66
Alcohol use density*MA ^a	0.50**	0.74*	0.65*	0.57	0.38	0.12	0.32	0.34
Days since last alcohol use	0.00	0.00	0.00	0.00	-0.00	-0.00	-0.00	0.00
Cannabis use density	-0.42	0.48	-0.82	-0.86	0.05	-0.59	-0.15	-0.62
WRAT	0.07*	0.03	0.14**	0.03	0.19**	0.06	0.14**	-0.02
BDI-II	-0.04	-0.00	-0.05	-0.08	0.01	-0.05	0.02	-0.10
Lifetime MDD	1.10	0.53	0.77	1.15	2.53*	1.70	0.66	-0.26

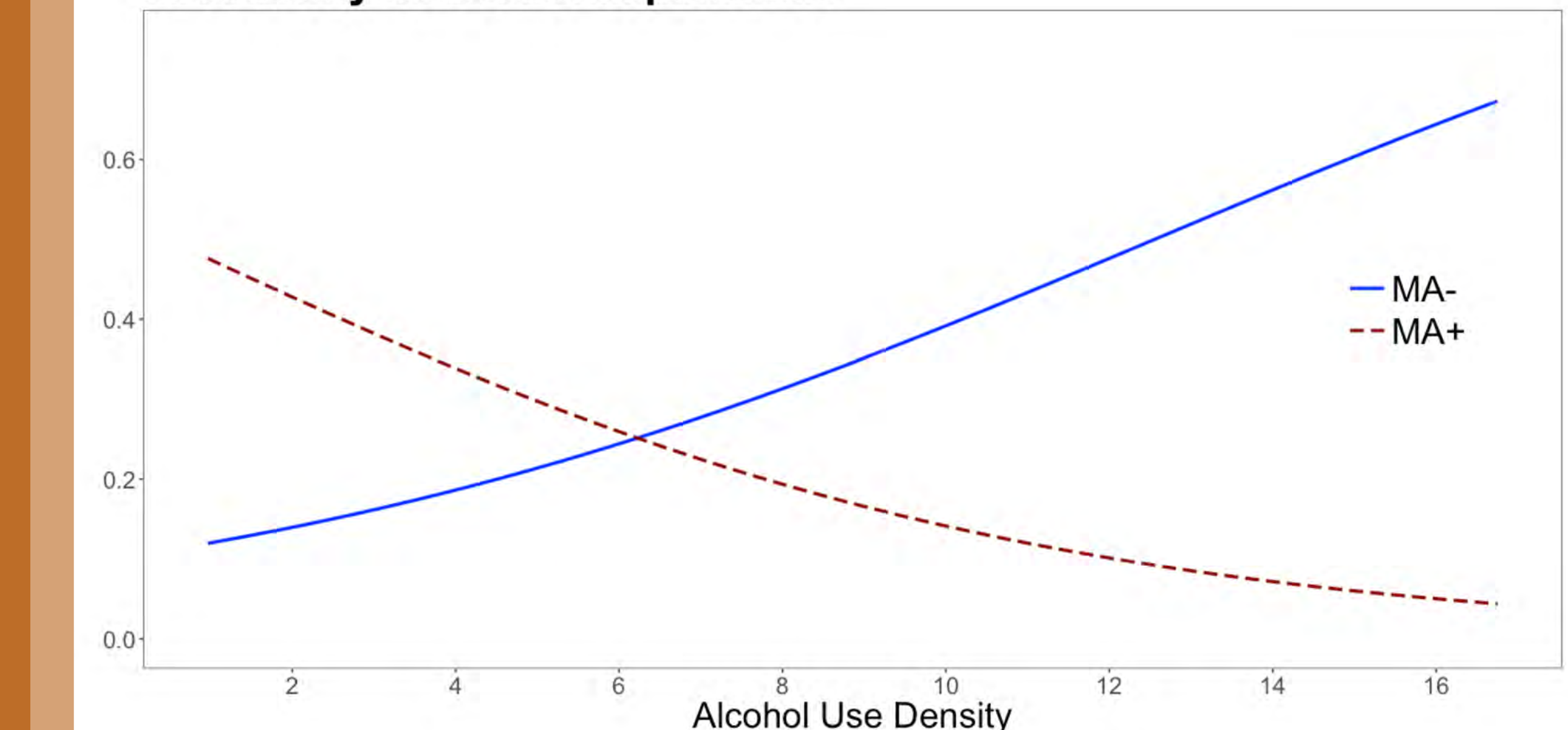
Predictors	Outcome Variables: Neurocognitive Domain Impairment Rates							
	Global	Verbal Fluency	Executive Function	Processing Speed	Learning	Delayed Recall	Working Memory	Motor Skills
Alcohol use density	1.19*	1.15	1.14	0.91	1.15	1.16*	0.98	0.98
MA ^a	1.73	1.69	1.03	2.38	1.83	1.20	1.57	1.26
Alcohol use density*MA ^b	0.70**	0.77**	0.88	0.97	0.80*	0.86	0.89	1.06
Days since last alcohol use	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Cannabis use density	0.78	1.07	1.14	0.87	0.65	0.69	1.00	0.85
WRAT	0.97	1.00	0.98	1.00	0.96**	1.01	0.93***	0.94***
BDI-II	1.03	1.00	1.02	1.03	1.01	1.02	1.02	0.98
Lifetime MDD	0.54	0.55	0.85	0.50	0.53	0.66	0.74	2.13

^aMA+ compared to MA-
^bALC Density*MA interaction values represent ratios of odds ratios
 *p<0.10; **p<0.05; ***p<0.01

Figures 2 & 3. Alcohol moderates the effect of MA status on global cognition



Probability of Global Impairment



- Alcohol use density negatively related to global functioning (b=-0.40, p=.046) among MA- persons, but did not significantly predict any domain T-scores among MA+ participants.
- Greater alcohol consumption significantly increased the likelihood of global (OR=1.21) and verbal fluency impairment (OR=1.15) in MA- persons, but significantly decreased the likelihood of global (OR=0.83) and verbal fluency impairment (OR=0.88) in MA+ individuals.

Conclusions

- Unexpectedly, alcohol use density reduced risk of global impairment in the MA+ group.
- Given the known neurotoxic and neurobehavioral consequences of heavy alcohol use, these results must be interpreted with caution.
- Our results are consistent with prior research demonstrating that singly addicted stimulant abusers exhibit poorer neurocognitive performance than poly-abusers of stimulants and alcohol³.
- 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, heat dissipation).
- Examination of neurophysiologic mechanisms (e.g., neurovascular) underlying alcohol use in MA-dependence are warranted to elucidate whether alcohol confers a degree of neuroprotection in MA-dependence.

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