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A prior history of binge-drinking increases sensitivity to the motivational valence of methamphetamine in female C57BL/6J mice

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ABSTRACT: Methamphetamine (MA) and alcohol use disorders exhibit a high degree of co-morbidity and sequential alcohol-MA mixing increases risk for co-abuse. Recently, we reported greater MA-conditioned reward in male C57BL/6J mice with a prior history of binge alcohol-drinking (14 days of 2-hour access to 5, 10, 20 and 40% alcohol). As female mice tend to binge-drink more alcohol than males and females tend to be more sensitive than males to the psychomotor-activating properties of MA, we first characterized the effects of binge-drinking upon MA-induced place-conditioning (four pairings of 0.25, 0.5, 1, 2, or 4 mg/kg IP) in females and then incorporated our prior data to analyze for sex differences in MA-conditioned reward. Prior binge-drinking history did not significantly affect locomotor hyperactivity or its sensitization in female mice. However, the dose-response function for place-conditioning was shifted to the left of water-drinking controls, indicating an increase in sensitivity to MA-conditioned reward. The examination of sex differences revealed no sex differences in alcohol intake, although females exhibited greater MA-induced locomotor stimulation than males, irrespective of their prior drinking history. No statistically significant sex difference was apparent for the potentiation of MA-conditioned reward produced by prior binge-drinking history. If relevant to humans, these data argue that both males and females with a prior binge-drinking history are similarly vulnerable to MA abuse and it remains to be determined whether or not the neural substrates underpinning this increased vulnerability reflect common or sex-specific adaptations in reward-related brain regions.

KEYWORDS: binge-drinking, females, sex differences, place-conditioning, reward, methamphetamine, co-abuse

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Introduction

Globally, a very high rate of co-abuse of alcohol and methamphetamine (MA) exists in humans, with over 60% of MA users reporting regular alcohol co-abuse.^{1,2} In addition, MA is the third most co-abused drug for men suffering from Alcohol Use Disorder (AUD), and the fourth most co-abused drug for women suffering from AUD,³ with recent excessive alcohol consumption reported to augment the incidence of MA-alcohol co-abuse 4 to 5-fold.^{4–10} Of major concern, treatment admission rates for MA abuse is rising annually world-wide² and alcohol-MA co-abuse is a risk factor for treatment discontinuation and non-compliance in MA-dependent individuals.⁴

Despite the international recognition that MA and alcohol are often co-administered, the impact of such co-administration upon brain and behavior has received little experimental consideration. In human subjects, MA's positive subjective effects are potentiated by the consumption of an alcoholic beverage.^{11–14} Akin to these findings in humans, male, drug-naïve, C57BL/6J (B6) mice prefer to consume a mixed solution of MA and alcohol over either solution alone and alcohol-experienced B6 mice exhibit greater oral MA intake than alcohol-naïve animals.¹⁵ Further, in male B6 mice, a prior history of binge alcohol-drinking shifts the dose-response function for

oral MA intake to the left¹⁵ and shifts the dose-response function for MA-induced place-conditioning upwards,¹⁶ relative to alcohol-naïve controls. These latter findings from male mice argue that a history of excessive alcohol-drinking induces pharmacodynamic changes in the brain that increase the rewarding/reinforcing properties of MA.

Clinically, sex-drug interactions exist regarding the onset and severity of both MA and alcohol use disorders, as well as the neuropsychiatric consequences of addiction co-morbidity.^{3–10} Yet, to the best of our knowledge, there has been no direct examination of sex differences in the biobehavioral consequences of MA-alcohol mixing. With the closing of the gender gap in heavy drinking^{17–19} and evidence that the development of an AUD & related psychiatric disturbances tends to follow an accelerated course in females than in males,^{19–28} it is imperative that we gain a deeper scientific understanding of how excessive alcohol intake by female subjects alters their MA responsiveness. To this end, the present study characterized the effect of a history of binge-drinking upon the dose-response function for MA-induced place-conditioning and psychomotor activation in female mice. The data obtained were then directly compared to those previously acquired for male mice under very similar testing conditions.¹⁶



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The results indicate that a prior history of binge alcohol-drinking increases sensitivity to the positive motivational valence of MA also in females and that the psychopharmacological mechanisms underpinning the increased MA sensitivity of females may be different from that for males.

Materials and methods

Subjects

Subjects were adult (8-10 weeks old) female C57BL/6J (B6) mice, obtained from the Psychological and Brain Sciences vivarium at UCSB. The mice were raised under a 12-hour regular light cycle (lights on: 0700 hour) and transferred to an adjacent colony room under a 12-hour reverse light cycle (lights on: 2200 hour) a minimum of 14 days prior to the onset of binge-drinking procedures (see below). After the final day of drinking, mice were transferred back to the regular light cycle and allowed to re-acclimatize for 5 days prior to CPP testing. This was done to lower the spontaneous activity of the animals and augment the probability of detecting MA-induced locomotor hyperactivity. Mice were housed in groups of four on a ventilated rack and only separated from their cage-mates during experimental procedures. All procedures were approved by the Institutional Animal Care and Use Committee of the University of California Santa Barbara and conducted in accordance with the Guide to the Care and Use of Laboratory Animals (2014).

Binge alcohol-drinking procedures

As in our prior study of MA-alcohol interactions in male B6 mice,^{15,16} females underwent a 2-week, four-bottle-choice version of the Drinking-in-the-Dark (DID) binge alcohol-drinking paradigm (5, 10, 20 and 40% alcohol, v/v). At approximately 1 hour prior to bottle presentation (which occurred at 3 hour into the dark phase of the cycle), mice were transferred to a dark, non-colony, testing room and singly housed in their respective drinking cages to habituate the animals to the drinking environment. The four bottles were then placed on the cage, with the order of concentrations randomized across animals and days, and mice were allowed to consume the solutions over a 2-hour period. The bottles were then removed from the drinking cage and weighed. The mice were returned to their home cage and transported back to their colony room. The amount of alcohol consumed was calculated daily as the change in bottle weight over the 2-hour drinking period, divided by the animals' body weight, which was determined weekly. The amount of alcohol consumed was corrected for spillage induced by bottle-handling on empty test cages. Control, alcohol-naïve, mice consumed water only.

MA-induced place-conditioning and locomotor activity

Following the end of the binge-drinking phase of the study, the mice were relocated to a colony room under a regular light

cycle (light on: 0700 hour) and allowed to acclimatize for 1 week prior to starting place-conditioning procedures. The procedures and behavioral testing equipment employed to induce MA-induced place-conditioning and to monitor locomotor activity in female B6 mice were identical to those described in our study of males.¹⁶ To elicit place-conditioning, mice were conditioned in a two-compartment polycarbonate apparatus where the compartments (each measuring 23 cm long × 24 cm high × 22 cm wide) were tactilely (floor texture; smooth vs. metal hole board) and visually (wall pattern; wood vs. marbled pattern) distinct and the time spent and distance traveled in each compartment was recorded using a digital video-tracking system (ANY Maze, Stoelting). Conditioning commenced with a 15 minute habituation session to familiarize the animals to the entire apparatus. Briefly, the mice underwent two conditioning sessions per day, with the saline-conditioning sessions occurring in the morning (starting ~0830 hour) and the MA-conditioning sessions occurring in the mid-afternoon (starting ~1300 hour). Different groups of mice were conditioned with one of five MA doses (0.25, 0.5, 1, 2 or 4 mg/kg, IP; vol = 10 ml/kg). Testing commenced with a 15-minute pre-conditioning test (PreTest) in which mice had free-access to both compartments of the 2-chamber apparatus. While individual mice exhibited a bias for one compartment over the other, when all mice were considered, there was no compartment bias on the PreTest. No mice were excluded due to strong initial compartment biases. For the next 4 days, 15-minute conditioning sessions were conducted with mice confined to one compartment following saline injection and the opposite compartment following MA injection. The MA-paired compartment was assigned such that the initial compartment bias was similar between water and binge-drinking mice. Following the conditioning phase of the study, a 15-minute post-conditioning test (Posttest) was conducted in which mice again had free-access to both compartments. The difference in the time spent on the MA- versus saline-paired compartment (CPP Score) served to index the direction and magnitude of the conditioned response. Locomotor activity was monitored throughout the study using digital video-recording and the difference in the distance traveled between the first and fourth MA-conditioning session was used to index behavioral sensitization, while the distance traveled on the PreTest indexed spontaneous reactivity to a novel environment and that on the first saline-conditioning session indexed saline-induced locomotion.

Statistical analyses

The data obtained from female subjects were analyzed either by independent subjects *t*-tests or by analyses of variance (ANOVAs), with the between-subjects factors of History (water vs. binge alcohol), MA dose (0.5-4 mg/kg), or with the within-subjects factor of Test (PreTest vs. PostTest), when appropriate. To determine whether or not sex differences exist

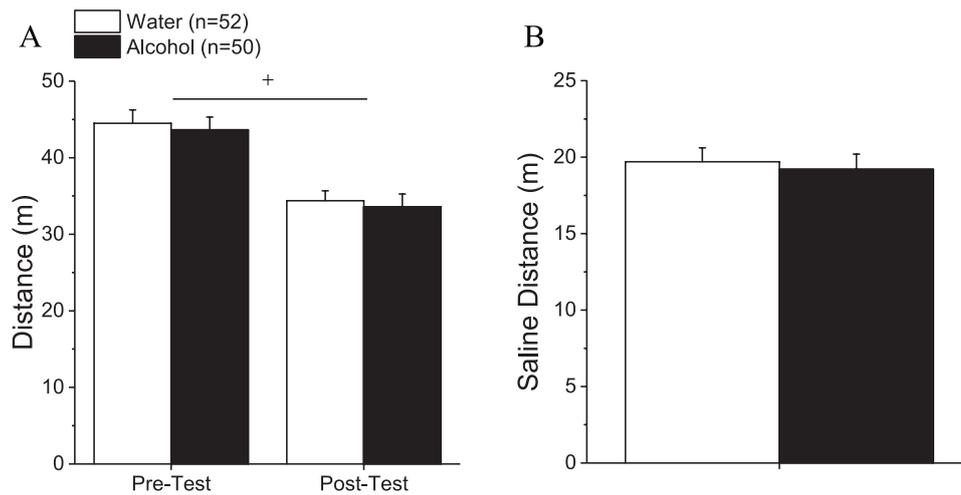


Figure 1. Binge-drinking history does not impact spontaneous or saline-induced locomotor activity in female B6 mice. (A) Summary of the distance traveled (in m) during the 15-minute pre-conditioning and post-conditioning tests (respectively, PreTest and PostTest). (B) Summary of the distance traveled during the first saline-conditioning session. Data represent the means \pm SEMs of the number of animals indicated in panel A. $+P < .05$ vs. PreTest.

with respect to alcohol-MA interactions, the data for females were combined with those from our prior study of male mice¹⁶ and analyzed using ANOVA, with the additional between-subjects factor of Sex. Alpha was set to 0.05 for all analyses.

Results

Alcohol intake

The female B6 mice in the present study consumed, on average, 5.50 ± 0.3 g/kg alcohol during the 2-hour drinking period. In the subset of mice assayed, alcohol intake was positively correlated with blood alcohol concentrations ($r^2 = 0.80$, $n = 11$) and based on prior correlational work,^{29,30} this amount of alcohol intake corresponds to blood alcohol concentrations ≥ 100 mg%. Thus, the female mice in this study were, by definition,³¹ engaged in binge alcohol-drinking prior to MA-conditioning procedures.

Spontaneous/saline-induced locomotor activity

An analysis of the locomotor activity expressed by the female mice during the pre- and post-conditioning tests indicated a test-dependent reduction in activity, but no effect of prior binge-drinking history upon spontaneous locomotion (Figure 1A) [History effect: $F(1,92) = 0.16$, $P = .69$; Test effect: $F(1,92) = 134.88$, $P < .0001$; History \times Test interaction: $F(1,92) = 0.009$, $P = .93$]. The lowered locomotor activity on post-conditioning test was also not related to the prior MA experience of the mice as indicated by no MA dose effect or interactions with the Dose factor [Dose effect: $F(4,92) = 1.05$, $P = .39$; Dose \times Test: $F(1,92) = 1.99$, $P = .10$; History \times Dose: $F(4,92) = 0.41$, $P = .80$; Dose \times Test \times History: $F(1,92) = 1.55$, $P = .20$]. Thus, the reduction in locomotor activity from the pre- to the post-conditioning tests likely reflects a mere habituation

to the testing apparatus. Further, analysis of the locomotor response to the first saline-conditioning session indicated no effect of prior binge-drinking history (Figure 1B; $t(100) = 0.35$, $P = .72$).

MA-induced locomotor activity

The capacity of acute MA to stimulate locomotor activity increased in a dose-dependent manner [Dose effect: $F(1,101) = 16.69$, $P < .0001$]. However, prior binge-drinking history did not alter the dose-response function for the acute locomotor stimulatory effects of MA (Figure 2A) [History effect: $F(1,101) = 0.09$, $P = .76$; History \times Dose: $F(4,101) = 0.71$, $P = .59$]. The difference in MA-induced locomotion observed during the first and the fourth MA-conditioning session was calculated as an index of locomotor sensitization. Although inspection of Figure 2B suggested less MA-induced locomotor sensitization in binge-drinking females conditioned with the 4 mg/kg MA dose, the dose-response function for MA-induced locomotor sensitization was not significantly affected by prior binge-drinking history [Dose effect: $F(4,101) = 7.38$, $P < .0001$; History effect: $F(4,101) = 1.69$, $P = .20$; interaction: $F(4,101) = 1.90$, $P = .12$]. Thus, prior binge-drinking history does not alter the locomotor stimulatory or sensitizing effects of MA in female B6 mice.

MA-induced place-conditioning

The dose-response function for MA-induced place-conditioning was shifted markedly in female mice by a prior history of binge-drinking as indicated by a significant History \times Dose \times Side interaction [$F(1,92) = 5.59$, $P < .0001$]. The place-conditioning data were expressed as a CPP Score (time on MA-paired side minus the time on the saline-paired side), which rendered

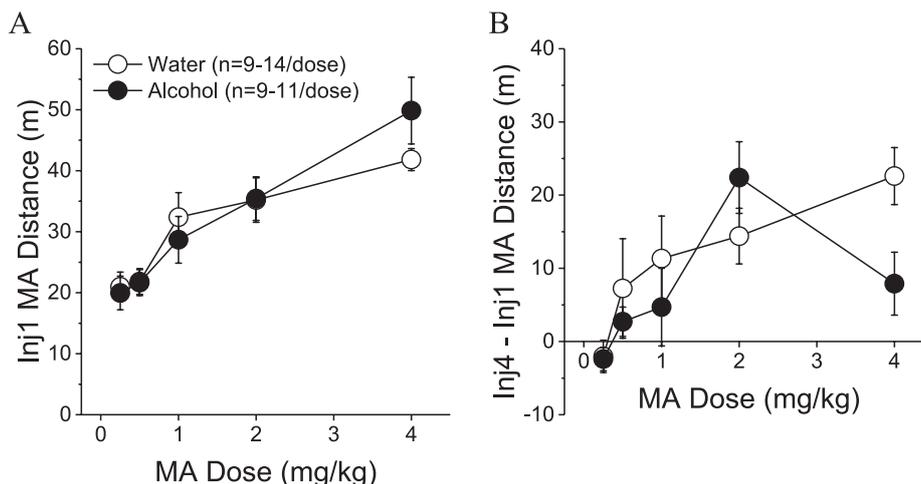


Figure 2. Binge-drinking history does not significantly impact MA-induced locomotion or locomotor sensitization in female B6 mice. (A) Summary of the distance traveled (in m) during the first MA-conditioning session. (B) Summary of the change in the distance traveled from the first to the fourth MA-conditioning session as an index of locomotor sensitization. Data represent the means \pm SEMs of the number of animals indicated in panel A.

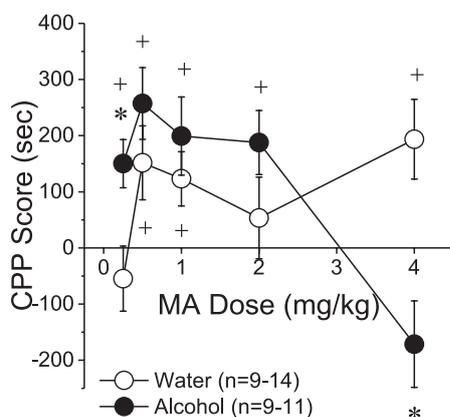


Figure 3. Binge-drinking history shifts the dose-response function for MA-induced place-conditioning to the left of water controls. Summary of the difference in time spent in the MA- versus saline-paired chamber across the different MA-conditioning doses. Data represent the means \pm SEMs of the number of animals indicated in the figure. * $P < .05$ for MA-paired versus saline-paired (ie, conditioned response); + $P < .05$ versus Water.

the interaction between prior drinking history and MA dose more obvious (Figure 3). Indeed, analysis of the CPP Scores confirmed the shift in the dose-response function by prior binge-drinking history [History \times Dose: $F(1,101) = 5.59$, $P < .0001$]. Deconstructing this interaction along the Dose factor indicated that binge-drinking females exhibited a greater CPP Score at 0.25 mg/kg MA than water controls [$t(18) = 2.85$, $P = .01$] and water-drinking controls exhibited a greater CPP Score at 4 mg/kg MA than binge-drinking mice [$t(16) = 3.50$, $P = .003$]. No alcohol-water differences in CPP Scores were apparent at the 0.5 and 1.0 mg/kg doses (t -tests, $P_s > .45$). *A priori* contrasts between the time spent on the saline versus MA-paired compartment (see Table 1) confirmed a significant place-preference in water controls at the 0.5, 1 and 4 mg/kg doses, while binge-drinkers exhibited a significant place-preference at the 0.25, 0.5,

Table 1. Results of the *a priori* comparisons of the time spent in the MA-paired versus -unpaired compartment of the place-conditioning chamber on the PostTest to confirm the presence or absence of a conditioned response.

MA DOSE (MG/KG)	WATER-DRINKING	ETOH-DRINKING
0.25	$t(9) = 0.95$, $P = .37$	$t(9) = 3.50$, $P = .007^*$
0.5	$t(9) = 2.31$, $P = .04^*$	$t(9) = 4.02$, $P = .003^*$
1.0	$t(8) = 2.54$, $P = .03^*$	$t(9) = 2.87$, $P = .02^*$
2.0	$t(13) = 0.73$, $P = .48$	$t(10) = 3.29$, $P = .008^*$
4.0	$t(8) = 2.73$, $P = .03^*$	$t(8) = 2.23$, $P = .05^*$

*denotes a conditioned response.

1 and 2 mg/kg doses and a significant place-aversion at the 4 mg/kg MA dose. These data indicate that a prior history of binge-drinking increases behavioral sensitivity to the conditioned-rewarding properties of MA in female B6 mice.

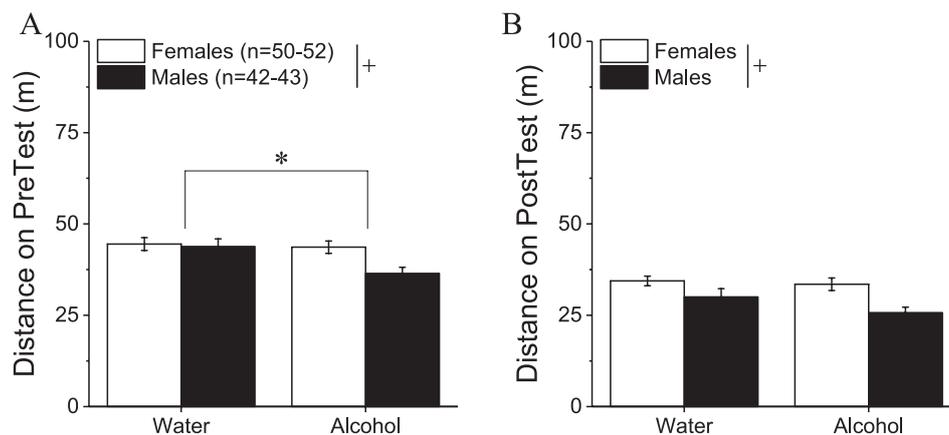
Direct examination of sex differences in the effects of binge-drinking upon spontaneous and MA-induced changes in behavior

The data from the female mice presented above were then compared directly to the data obtained previously from male mice undergoing identical binge-drinking and MA-induced place-conditioning procedures.¹⁶ The results of these analyses are detailed below.

Alcohol intake. Surprisingly, the average total alcohol intake exhibited by the males in our prior study and that of the females herein was identical (Table 2) [$t(91) = 0.001$, $P = 1.0$; $n = 43$ for males and $n = 50$ for females].

Table 2. Comparison of the means \pm SEMs obtained from our prior study of MA-alcohol interactions in male B6 mice and those observed in the present study of female subjects.

DEPENDENT VARIABLE	FEMALES	MALES
Total Alcohol Intake (g/kg)	5.50 \pm 0.30	5.50 \pm 0.19
Injection 1 Saline Distance (m); Water	19.70 \pm 0.94	19.85 \pm 1.07
Injection 1 Saline Distance (m); Alcohol	19.21 \pm 1.00	17.72 \pm 0.84
Locomotor Habituation (m); Water	-4.63 \pm 1.07	-1.55 \pm 1.66
Locomotor Habituation (m); Alcohol	-4.01 \pm 1.13	-3.41 \pm 1.04

**Figure 4.** Females exhibit more spontaneous locomotor hyperactivity than males, irrespective of binge-drinking history. (A) Summary of the distance traveled (in m) by male and female during the 15-minute pre-conditioning test. (B) Summary of the distance traveled during the 15-minute post-conditioning test in these same animals. Data represent the means \pm SEMs of the number of animals indicated in panel A. * $P < .05$ versus Water, + indicates main effect of Sex ($P < .05$).

Spontaneous and saline-induced locomotion. Next, we examined for sex differences in the effect of prior binge-drinking upon the spontaneous locomotor activity expressed during the Pre-Test. Overall, females locomoted more than males on the Pre-Test when the mice were first exposed to the place-conditioning apparatus [Sex effect: $F(1,186) = 4.70$, $P = .03$]. When both sexes were considered, mice with prior binge-drinking history exhibited lower spontaneous locomotor activity during the PreTest, than water controls [History effect: $F(1,186) = 5.14$, $P = .03$]. Although both the binge-drinking and sex effects appeared to be driven by the low locomotor activity of the binge-drinking males (Figure 4A), the interaction between these factors was not statistically significant [History \times Sex: $F(1,186) = 3.26$, $P = .07$]. Sex differences in the effect of prior binge-drinking upon the locomotor response to the initial saline injection were analyzing also using a Sex \times History ANOVA and no group differences were apparent for this measure (Table 2) [Sex effect: $F(1,186) = 0.47$, $P = .49$; History effect: $F(1,186) = 1.80$, $P = .18$; interaction: $F(1,186) = 0.71$, $P = .40$]. Likewise, a Sex \times History ANOVA conditioned on the difference in saline-induced locomotion from the first to the fourth saline-conditioning session also indicated no group differences (Table 2) [Sex effect: $F(1,186) = 2.24$, $P = .14$;

History effect: $F(1,186) = 0.26$, $P = .61$; interaction: $F(1,186) = 1.01$, $P = .32$]. Finally, a Sex \times History ANOVA conducted on the spontaneous locomotor activity of the mice during the post-conditioning test indicated more locomotor activity in female than in males (Figure 4B) [Sex effect: $F(1,186) = 12.71$, $P < .0001$], irrespective of prior drinking history [History effect: $F(1,186) = 2.29$, $P = .13$; Sex \times History interaction: $F(1,186) = 1.08$, $P = .30$].

MA-induced locomotion. Overall, females exhibited greater acute MA-induced locomotion than males (Figure 5A) [Sex effect: $F(1,186) = 15.06$, $P < .0001$; Dose effect: $F(1,186) = 33.20$, $P < .0001$]. Although there was a trend toward a sex difference in the overall impact of binge-drinking upon acute MA-induced locomotion [Sex \times History interaction: $F(1,186) = 2.81$, $P = .095$] that reflected larger sex differences in alcohol-experienced mice, no other interactions approached statistical significance [History \times Dose: $F(4,186) = 1.28$, $P = .28$; Sex \times Dose: $F(4,186) = 1.03$, $P = .40$; Sex \times History \times Dose: $F(4,186) = 0.73$, $P = .57$]. An examination of the differences in MA-induced locomotion from injections 1 to 4 of conditioning yielded no sex difference or interaction for the sensitized locomotor response to MA (Figure 5B) [Dose effect: $F(4,186) = 16.41$,

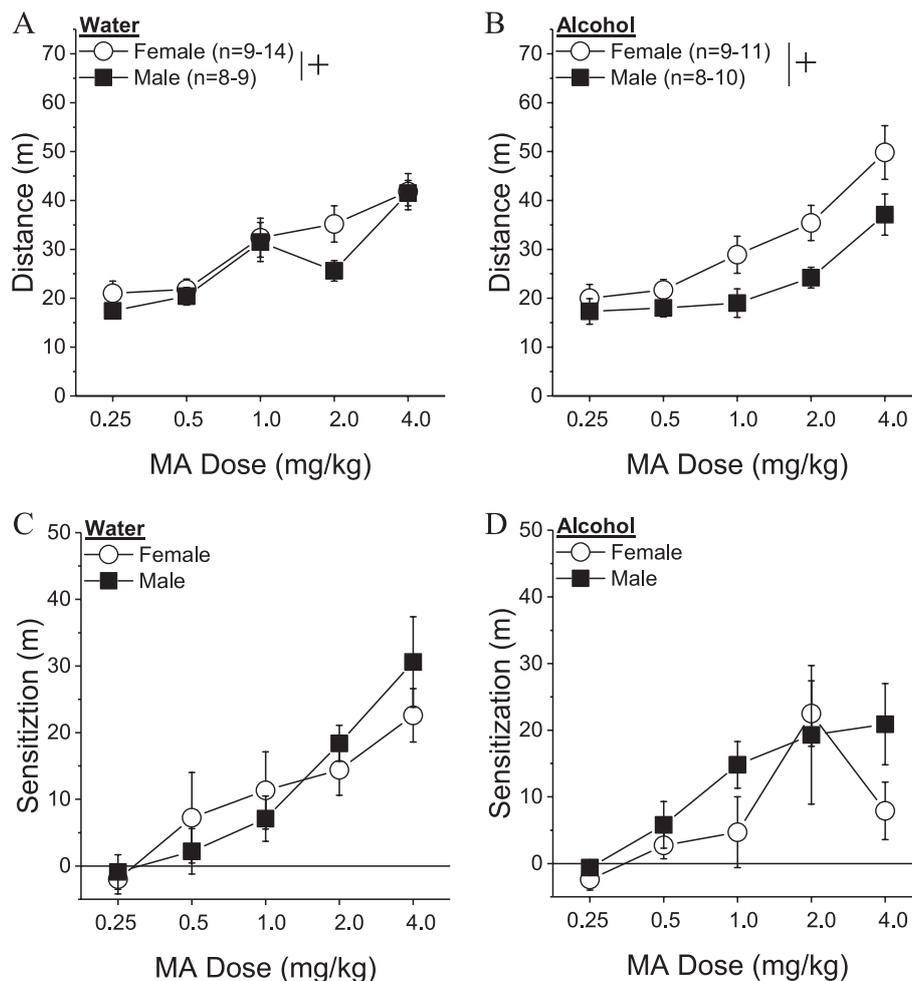


Figure 5. Females exhibit more MA-induced locomotor hyperactivity than males, irrespective of binge-drinking history. (A) Summary of the distance traveled (in m) by water-drinking male and female mice during the first MA-conditioning session. (B) Summary of the distance traveled (in m) by alcohol-drinking male and female mice during the first MA-conditioning session. (C) Summary of the change in the distance traveled from the first to the fourth MA-conditioning session by water-drinking male and female mice. (D) Summary of the change in the distance traveled from the first to the fourth MA-conditioning session by alcohol-drinking male and female mice. Data represent the means \pm SEMs of the number of animals indicated in panel A for water-drinking mice and in panel B for alcohol-drinking mice. + indicates main effect of Sex ($P < .05$).

$P < .0001$; Sex effect: $F(1,186) = 1.90$, $P = .17$; History effect: $F(1,186) = 0.55$, $P = .46$; Sex \times History: $F(1,186) = 1.03$, $P = .31$; Dose \times History: $F(4,186) = 1.18$, $P = .14$; Sex \times Dose: $F(4,186) = 0.91$, $P = .46$; Sex \times Dose \times History: $F(4,186) = 0.78$, $P = .54$].

MA-induced place-conditioning. To facilitate data analyses, the place-conditioning data were expressed as a CPP Score. A history of binge-drinking shifted the dose-response function for place-conditioning in both male and female mice [History \times Dose: $F(4,186) = 3.51$, $P = .009$; Sex \times History \times Dose: $F(4,186) = 2.06$, $P = .09$]. Although a visual inspection of the shape of the MA dose-conditioning function in alcohol-experienced males appeared to be quite different from that of females (particularly at the 4.0 mg/kg MA-conditioning dose; Figure 6), all of the other interactions with the Sex factor did not reach statistical significance [Sex \times History: $F(1,186) = 3.67$, $P = .06$; Sex \times Dose: $F(4,186) = 2.31$, $P = .06$].

Discussion

In humans, recent excessive alcohol consumption increases risk for methamphetamine co-abuse⁴⁻¹⁰ and a prior binge-drinking history increases the positive motivational valence of MA in male B6 mice.¹⁶ Herein, we extend our prior study of MA-alcohol interactions to female B6 mice and show that a prior binge-drinking history shifts the dose-response function for MA-induced place-conditioning to the left of alcohol-naïve controls. Indicative of an increased sensitivity to MA's motivational valence, conditioning with 0.25 mg/kg MA was sufficient to elicit a significant place-preference only in alcohol-experienced females and the magnitude of that conditioned response was comparable to that elicited by higher MA doses in water-drinking controls (eg, 0.5 and 1.0 mg/kg; see Figure 3). In humans, higher MA doses elicit negative subjective states that are considered aversive.³² Interestingly, conditioning with 4.0 mg/kg MA elicited a significant conditioned place-preference in water controls, while this same conditioning regimen

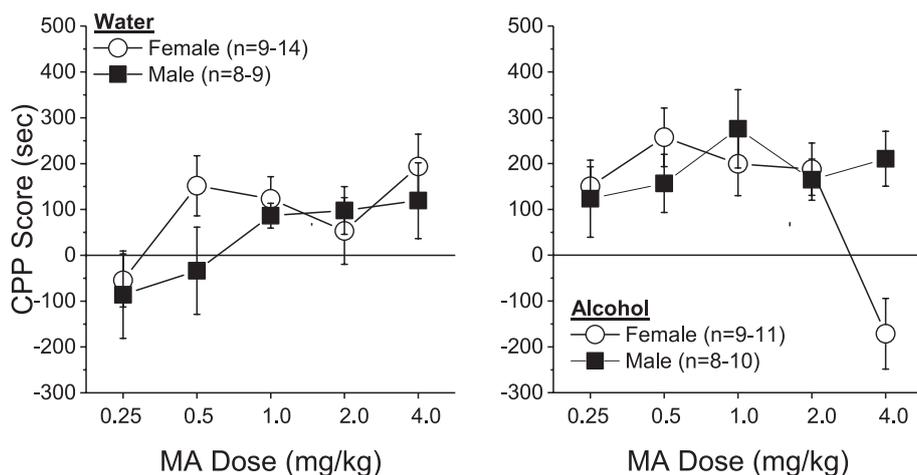


Figure 6. No detectable sex difference exists in the shift in the dose-response function for MA-induced place-conditioning by binge-drinking history. Summary of the difference in time spent in the MA- versus saline-paired chamber across the different MA-conditioning doses in water- and alcohol-drinking mice (left and right, respectively). Data represent the means \pm SEMs of the number of animals indicated in the figure.

elicited a place-aversion of comparable magnitude (~200 seconds) in their binge-drinking counterparts (Figure 3). As reported for males,¹⁶ the effect of prior binge-drinking upon MA-conditioned reward in female mice was independent of any significant alcohol effects upon spontaneous or MA-induced locomotor activity, arguing against an effect of binge-drinking upon MA pharmacokinetics to explain the increased sensitivity to MA-conditioned reward observed herein. This being said, it is interesting to note that the magnitude of locomotor sensitization induced by conditioning with the 4.0 mg/kg MA in alcohol-experienced females was less than half that exhibited by the water controls (see Figure 2B). Although the magnitude of this alcohol-water difference was insufficient to influence the results of the omnibus ANOVA for the sensitization data, MA induces focused stereotyped behaviors at doses >3 mg/kg, particularly following repeated administration.^{29,30,33,34} While stereotypy was not measured herein to avoid disturbing the conditioning, we speculate that the alcohol-water difference in sensitized behavior at the 4.0 mg/kg dose reflects the induction of stereotyped behavior in alcohol-experienced mice – a finding indicative of increased sensitivity to MA's psychoactive effects. Such an interpretation would be consistent with the results of a recent study by Tschumi et al³⁵ indicating that prior alcohol consumption increases the psychomotor-activating effects MA, but only at high doses (>5 mg/kg). Thus, a prior history of binge-drinking increases sensitivity to the motivational valence of MA in female mice, which may reflect greater sensitivity to its psychomotor-sensitizing effects, particularly at higher MA doses.

What psychopharmacological mechanisms might account for the relatively selective effect of a prior binge-drinking history upon the conditioned-rewarding (and perhaps also the behavioral-sensitizing) effects of MA in female mice? One possibility might relate to an effect of binge alcohol experience and/or withdrawal on MA pharmacokinetics. However, recent studies do not support any effect of either contingent or

non-contingent alcohol consumption upon striatal levels of MA following injection.^{36,37} Further, a change in MA pharmacokinetics would be predicted to shift the MA dose-behavior functions upwards, rather than to the right (Figure 3) and to exert a generalized effect upon all MA-induced behaviors. Thus, a pharmacokinetic mechanism does not likely account for the MA-alcohol interactions observed herein. The fact that alcohol history did not alter the acute locomotor response to MA argues that binge-drinking history (or withdrawal from said history) is insufficient unto itself to increase MA's potency to induce a conditioned response. As drug potency is often reflected by increased binding affinity, by extension, binge-drinking history alone is likely insufficient to increase the affinity of MA-binding sites in the brain (eg, monoamine transporters, monoamine oxidase or TAAR1 receptor) c.f.³⁸⁻⁴²

The direct statistical comparison of the place-conditioning data from the present study and those published previously for males¹⁶ failed to detect a significant sex difference in the effects of binge-drinking upon the shape of the dose-response function for MA-conditioned reward. However, in contrast to the binge-induced leftward shift in the dose-response function for MA-induced place-conditioning observed herein (Figure 3), the MA dose-conditioned response function is clearly shifted upwards by in males with prior binge-drinking history.¹⁶ Thus, while prior binge-drinking history increases the sensitivity of females to MA-conditioned reward without impacting drug efficacy, prior binge-drinking history increases the efficacy of MA to elicit conditioned reward in males, without influencing sensitivity to this effect. While obviously limited by the fact that our studies of male versus female mice were conducted in series rather than simultaneously, and procedural differences exist for the duration of the acclimation period prior to MA-conditioning (7 days in females, 10 days in males), we are unaware of any other investigation examining how alcohol-MA interactions might vary by sex of relevance to understanding the purported

sex differences in MA addiction severity.^{43–45} Although female mice tend to binge-drink larger amounts of alcohol than males under limited- or scheduled-access procedures,^{46–51} sex differences in binge-drinking are not reported in all studies of B6 mice for example,^{52,53} and were not observed herein (see Table 2). As such, the sex-related differences in the binge-induced shift in the MA dose-conditioned reward function cannot reflect differential alcohol intake. This being said, sex differences are reported for alcohol pharmacokinetic parameters, including absorption, distribution and metabolism^{54–57} that, in theory, could impact how binge-drinking alters subsequent MA responsiveness. The ability to detect sex differences in alcohol pharmacokinetics is highly dependent upon the route of alcohol administration, with recent studies of binge-drinking failing to detect sex differences in blood alcohol levels upon the consumption of comparable amounts of alcohol by male and female mice.^{48,52,53} As blood alcohol levels were not assayed in our studies of MA-alcohol interactions, an important aspect of future work will be to examine more systematically whether or not sex differences in alcohol pharmacokinetics relate to subsequent MA reward sensitivity and intake.

Authors Contribution

KKS designed the experiments, supervised the project, analyzed the data and composed the final manuscript. KRS, EKF and MAC conducted the experiments and collected the data. KRS and EKF composed initial versions of the manuscript. CDB advised the experimental design and assisted in data interpretation. All authors edited and approved the final manuscript and its subsequent revisions.

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