



Neurochemical and behavioral comparisons of contingent and non-contingent methamphetamine exposure following binge or yoked long-access self-administration paradigms

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Received: 22 April 2019 / Accepted: 26 March 2020 / Published online: 9 May 2020
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Abstract

Rationale Abuse of the psychostimulant methamphetamine (METH) can cause long-lasting damage to brain monoaminergic systems and is associated with profound mental health problems for users, including lasting cognitive impairments. Animal models of METH exposure have been useful in dissecting the molecular effects of the drug on cognition, but many studies use acute, non-contingent “binge” administrations of METH which do not adequately approximate human METH use. Long-term METH exposure via long-access (LgA) self-administration paradigms has been proposed to more closely reflect human use and induce cognitive impairments.

Objective To better understand the role of contingency and patterns of exposure in METH-induced cognitive impairments, we analyzed behavioral and neurochemical outcomes in adult male rats, comparing non-contingent “binge” METH administration with contingent (LgA) METH self-administration and non-contingent yoked partners.

Results Binge METH (40 mg/kg, i.p., over 1 day) dramatically altered striatal and hippocampal dopamine, DOPAC, 5-HT, 5-HIAA, BDNF, and TrkB 75 days after drug exposure. In contrast, 6-h LgA METH self-administration (cumulative 24.8–48.9 mg METH, i.v., over 16 days) altered hippocampal BDNF in both contingent and yoked animals but reduced striatal 5-HIAA in only contingent animals. Neurochemical alterations following binge METH administration were not accompanied by cognitive deficits in Morris water maze, novel object recognition, or Y-maze tests. However, contingent LgA METH self-administration resulted in impaired spatial memory in the water maze.

Conclusions Overall, substantial differences in neurochemical markers between METH exposure and self-administration paradigms did not consistently translate to deficits in cognitive tasks, highlighting the complexity of correlating METH-induced neurochemical changes with cognitive outcomes.

Keywords Methamphetamine · Cognitive performance · Neurotoxicity · Spatial working memory · Self-administration

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Introduction

Methamphetamine (METH) is an addictive psychostimulant abused worldwide. Chronic METH use is associated with depression, anxiety, aggression, and psychosis (Meredith et al. 2005; Rusyniak 2013), as well as cognitive deficits including impaired executive function, episodic, verbal and working memory, and deficits in motor performance (Kalechstein et al. 2003; Marshall et al. 2007; Rusyniak 2013). The cognitive impairment associated with long-term, heavy drug use presents a unique challenge in addiction treatment, exacerbating maladaptive behavioral choices. Psychostimulants, such as cocaine and amphetamines, can reduce cognitive flexibility, attention, and impulse control (Cadet and Bisagno 2015; Gould 2010). However, because most clinical studies that evaluate the links between drug use and cognition are retrospective, they cannot adequately measure a subject's cognitive abilities prior to heavy drug use, nor comprehensively evaluate the role of genetic and environmental influences on this chronic drug-using population.

Researchers have thus developed a variety of animal models to better understand METH-induced changes in behavior and cognition. These studies have important differences in drug contingency—i.e., the association of the reinforcer (METH) with a particular behavior. Most studies to date have used acute, non-contingent “binge”-like administrations of METH to elicit impairments in sequential motor learning in the radial arm maze (Daberkow et al. 2005), increased impulsivity (Richards et al. 1999), impaired object recognition (Belcher et al. 2005; Bisagno et al. 2002; Camarasa et al. 2010; He et al. 2006; Herring et al. 2008; Marshall et al. 2007; Melo et al. 2012; Reichel et al. 2011, 2012; Schroder et al. 2003), and impaired spatial memory in the Morris water maze (Camarasa et al. 2010). However, these experimenter-administered regimens of drug do not adequately approximate human METH use: “binge” dosing involves non-contingent administration of one or more large doses of METH to drug-naïve animals, whereas human METH users volitionally self-administer the drug. While the use of the term “binge” to describe experimenter-administered drug rather than volitional, rapid, and unrestrained intake is somewhat counterintuitive, we have chosen to use this terminology for simplicity and to remain consistent with the literature.

There are substantial differences in neurological and biochemical adaptations in animals that receive addictive drugs via passive versus active routes (Jacobs et al. 2003); drug self-administration studies allow for contingent (i.e., reinforced) drug exposure and are considered a gold-standard of drug addiction research. Long-access METH self-administration studies, in which extended daily self-administration training periods produce escalating drug intake, may better mimic the behavioral and physiological effects of heavy METH use in humans than traditional short-access training regimens or

binge regimens (Edwards and Koob 2013). There are relatively few studies that have examined the cognitive impacts of long-access METH self-administration in rats: following chronic long-access (i.e., 6-h) METH self-administration, Parsegian et al. (2011) and Cox et al. (2016) reported selected deficits in attentional set-shifting and reversal learning, Recinto et al. (2012) reported impairment in spatial and working memory, and Rogers et al. (2008) reported impairment in object recognition, but not spatial recognition.

In addition to cognitive deficits, the ability of METH to cause long-lasting damage to brain monoaminergic systems has been well documented. First reported in the 1970s by Seiden et al. (1976) and Wagner et al. (1979) and demonstrated many times in the following decades (e.g., Chapman et al. 2001; Friedman et al. 1998; Herring et al. 2008; Seiden et al. 1993), acute non-contingent high-dose METH causes long-term depletions in brain dopamine and serotonin levels. Recent studies examining the neurochemical effects of METH self-administration have reported variable results in neurochemical markers, dependent on the pattern of METH exposure, particularly the length of self-administration sessions, and the biochemical markers evaluated (e.g., Kousik et al. 2014; Krasnova et al. 2010; McFadden et al. 2012; Schwendt et al. 2009), but few also evaluated cognitive outcomes. Thus, while many studies have individually evaluated the effects of METH exposure on neurochemical markers and cognitive outcomes, what is difficult to determine from the literature is the *comparative* impact of long-access METH self-administration versus binge METH on brain monoaminergic systems and cognitive deficits. Given this gap in understanding, we sought to directly compare the behavioral and neurochemical outcomes of contingent long-access METH self-administration (with yoked METH and yoked saline controls) against the effects of non-contingent binge METH administration.

Methods

Animals

Forty-eight adult male Wistar rats were individually housed in a climate-controlled room on a reverse light/dark cycle (lights off at 07:00, lights on at 19:00) with ad libitum access to food and water. All experiments were conducted in accordance with the Guide for the Care and Use of Laboratory Animals (US National Academy of Sciences) and were approved by the Animal Care and Use Committee of the National Institute on Drug Abuse under protocols 09-CNRB-25 and 13-BNRB-48. The animal facility was fully accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International. All cognitive-behavioral tasks were performed by experimenters blinded to animal treatment conditions.

Methamphetamine administration

Binge model

A cohort of animals was tested for behavioral and neurochemical effects following a neurotoxic regimen of METH exposure, modeled after procedures used by Xi et al. (2009) and Herring et al. (2008) and further described by Kobeissy et al. (2012). This “binge” cohort of animals received four i.p. injections of 10 mg/kg (+)-METH HCl (binge METH, $n = 12$) or saline every 2 h (binge saline, $n = 12$). Core body temperature was monitored via an ear thermometer (Vet-Temp VT150 Instant Infrared Ear Thermometer, Advanced Monitors Corp., San Diego, CA). All animals were weighed prior to the initial dose and 24 h after the final dose.

Yoked METH self-administration

A separate cohort of animals was tested for behavioral and neurochemical effects following contingent or non-contingent METH exposure in a long-access (LgA) self-administration paradigm, using methods and equipment described previously (Keck et al. 2013, 2014).

Catheter implantation Intravenous (i.v.) catheterization of the right external jugular vein was performed under sodium pentobarbital (60 mg/kg, i.p.) anesthesia, utilizing standard aseptic surgical techniques. After exiting the jugular, the catheter passed subcutaneously to the top of the skull, where it exited into a connector (a modified 24-G cannula; Plastics One, Roanoke, VA, USA) mounted to the skull with a jeweler’s screws and a dental acrylic. During experimental sessions, the catheter was connected to the injection pump via tubing, encased in a protective metal spring, from the head-mounted connector to the top of the experimental chamber. Catheters were flushed daily with a gentamicin–heparin–saline solution (0.1 mg/mL gentamicin, 30 IU/mL heparin; ICN Biochemicals, Cleveland, OH, USA).

Apparatus and general behavioral procedures Yoked self-administration experiments were conducted in operant response test chambers (32 × 25 × 33 cm) from MED Associates Inc. (Fairfax, VT, USA) with two retractable levers located 6.5 cm above the floor; for contingent self-administration, the left lever was active and the right lever inactive. After recovery from surgery, each rat was placed into a test chamber and allowed to lever press freely. The house light was turned on at the start of each 6-h test session and the levers were extended.

Yoked self-administration procedure The “LgA” cohort was divided into three groups: one group was allowed to self-administer (+)-METH on a fixed ratio 1 (FR1) reinforcement

schedule, 6 h/day for 16 days. These LgA contingent METH animals served as leads in a yoked paradigm for two other yoked animals, one receiving (+)-METH (LgA yoked METH) and one receiving saline (LgA yoked saline).

Upon a self-administered infusion of (+)-METH for the LgA contingent METH animals, LgA yoked METH animals would receive an identical non-contingent dose of (+)-METH, and LgA yoked saline animals would receive a non-contingent infusion of saline. All drug or saline infusions, contingent or non-contingent, were delivered in a volume of 0.08 mL/infusion over 4.65 s and was paired with the simultaneous presentation of a stimulus light and tone (each lasting 4.65 s). (+)-METH was dissolved in sterile saline at a concentration of 0.5 mg/mL; thus, the delivered unit dose was 40 µg/infusion; this is equivalent to a dose of 0.1 mg/kg/infusion in a 400-g rat, typical of the size of rats used in these studies; however, loss of daily weight records for these yoked experiments prevents completely equivalent comparison of pharmacological exposure to METH across groups due to likely body weight variations over the course of these experiments. For LgA contingent METH animals, depression of the active lever activated the infusion pump and depression of the inactive lever was counted but had no consequence. Depression of the active lever during an infusion was counted but also had no consequence. For LgA yoked METH and LgA yoked saline animals, presses of left or right levers were counted but had no consequences.

Novel object recognition

Novel object recognition procedures were adapted from Mathiasen and DiCamillo (2010) and Bevins and Besheer (2006). Both binge and LgA cohorts began novel object recognition testing 3–4 days after the final METH exposure. On day one, all animals were habituated to the testing apparatus, given 3 min to explore the chamber in the absence of any objects. On day two, animals were placed in a chamber with two identical objects, each secured to the chamber floor, and allowed to explore for 3 min. Following a 1-h delay, one of the objects was replaced with a novel object, and animals were placed in the chamber and allowed to explore for 3 min. On day three, animals were placed in the chamber with a pair of identical objects, different from the objects used in the previous training or testing and allowed to explore for 3 min. On day four, following a 24-h delay, one of the objects was replaced with a novel object, and animals were placed in the chamber and allowed to explore for 3 min. Chambers were wiped down with paper towels between each animal. Animal movements were recorded via a video camera and analyzed with ANY-maze software (Stoelting Co., Wood Dale, IL). The exploration time for each object was determined by an observer blinded to methamphetamine treatment condition; exploration was defined as the rat placing its nose within 2 cm of the

Western blot Hippocampal brain-derived neurotrophic factor (BDNF) and tropomyosin-related kinase B (TrkB) expression levels were evaluated via Western blot, using procedures adapted from those reported previously (Krasnova et al. 2013). Tissue samples were sonicated in lysis buffer (50 mM Tris-HCl, 5 mM EDTA, 1% sodium deoxycholate, 150 mM NaCl, 500 μ M Na_3VO_4 , 10 mM NaF, 0.5% Triton X-100) containing protease inhibitors and centrifuged at 12,000g for 15 min at 4 °C. Protein samples were collected from the supernatant and quantitated using the Bradford protein assay. 20 μ g of protein was separated by 10% and 10–20% TGX SDS-polyacrylamide gel electrophoresis for TrkB and BDNF, respectively. Proteins were electrophoretically transferred to a polyvinylidene difluoride membrane and blocked in 3% BSA in 0.1% TBS-T overnight or 6 h for TrkB and BDNF, respectively. Membranes were probed with antibodies against TrkB (1:1000, BioVision Research Products) and BDNF (1:500, Santa Cruz Biotechnology, Inc.) in 3% BSA in 0.1% TBS-T overnight at 4 °C. Immune complexes were labeled with HRP-linked secondary antibody and ECL Prime chemiluminescence reagents (GE Healthcare). To confirm equal protein loading, blots were re-probed with anti- α -tubulin antibody (1:6000, Sigma) for 2 h at room temperature. Optical densities were quantified using Kodak Molecular Imaging Software (Carestream Health, Inc.). Samples from matched treatment regimens were run on the same gel (i.e., all binge saline and binge METH samples were run on one gel, all contingent/yoked saline and METH samples were run on one gel); data were normalized to the average intensity of the respective saline control groups in order to compare data across blots.

Statistical analyses

All data are presented as means \pm SEM and were analyzed in GraphPad Prism 6 (San Diego, CA, USA). For analysis of variance (ANOVA) tests, whenever a significant main effect was found, individual group comparisons were carried out using pre-planned Bonferroni *t* tests.

Results

Binge METH administration acutely elevates body temperature and decreases body weight

Body weight and temperature are well established to dramatically change during and after high-dose METH exposures. These outcomes were recorded in the binge cohort during and after METH exposure (Fig. 1) in order to monitor the health of the animals during the procedure. Rats that received 4 doses of 10 mg/kg METH, i.p., had significantly elevated body temperatures compared with saline controls (Fig. 1a). One-way

repeated measures ANOVA revealed significant effects of METH treatment ($F_{(5, 55)} = 35.19$, $p < 0.0001$) with significantly elevated body temperatures during METH exposure compared with baseline, as measured by planned Bonferroni analyses ($t > 6.5$, $p < 0.001$ for 1.5-, 3.5-, 5.5-, and 7.5-h time points, $t < 1.84$, $p > 0.05$ for -0.5- and 23.5-h time-points). Saline treatment had no significant effect on body temperature ($F_{(5, 55)} = 1.67$, $p > 0.15$). METH treatment but not saline treatment significantly reduced body weight 24 h after the first injection (Fig. 1b; saline: paired *t* test: $t_{(11)} = 0.982$, $p > 0.34$; METH: paired *t* test: $t_{(11)} = 5.44$, $p = 0.0002$).

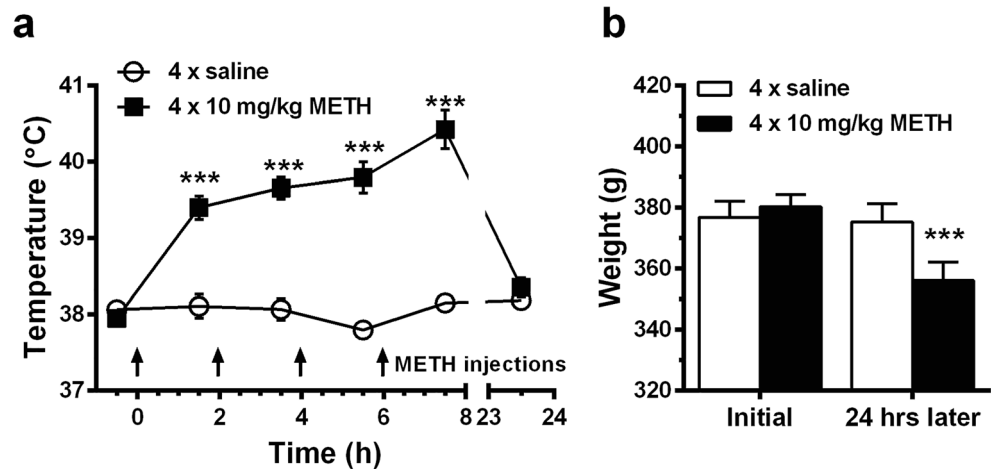
Contingent and yoked non-contingent long-access METH self-administration led to consistent drug intake

Contingent LgA METH animals rapidly learned to self-administer METH, and daily METH intake escalated over the first 8 days of the 16-day training period (open circles, Fig. 2a), consistent with previous reports using similar METH self-administration paradigms (Tunstall et al. 2018). Variability in the active lever presses seen in particularly days 4–9 was the result of a single animal that lever-pressed substantially during the drug infusion period, producing active lever counts without additional infusions. The cumulative i.v. METH intake during the 16-day training period ranged from cumulative 24.8 to 48.9 mg (Fig. 2b). Yoked LgA METH animals received a METH dose equal to their matched contingent animals.

METH exposure showed no consistent effect on novel object recognition

The novel object recognition task was performed using 1-h and 24-h probe times (Fig. 3). Across all groups of animals, METH exposure did not consistently affect novel object exploration time or total exploration time. When considering time spent exploring the novel versus familiar object during the 1-h-delay choice trial (Fig. 3a), a two-way ANOVA with drug treatment as the between-subject factor and object as the within-subject factor revealed no significant effects of drug treatment but a significant difference in object preference (drug treatment: $F_{(4, 43)} = 1.08$, $p > 0.38$; object: $F_{(1, 43)} = 31.99$, $p < 0.0001$; interaction: $F_{(4, 43)} = 0.19$, $p > 0.94$). Planned Bonferroni analyses revealed that only the binge METH group spent significantly more time exploring the novel object over the familiar object (binge saline: $t = 2.29$ and $p > 0.05$; binge METH: $t = 3.47$ and $p < 0.01$; yoked saline: $t = 2.17$ and $p > 0.05$; yoked METH: $t = 2.51$ and $p > 0.05$; contingent METH: $t = 2.39$ and $p > 0.05$). Similarly, when considering time spent exploring the novel versus familiar object during the 24-h-delay choice trial (Fig. 3b), a two-way ANOVA with drug treatment as the between-subject

Fig. 1 Binge METH effects on body temperature and body weight. **a** Body temperature was significantly elevated in rats that received 4×10 mg/kg METH, i.p., compared with saline controls. **b** Similarly, body weight was significantly reduced 24 h after initial METH exposure in rats that received 4×10 mg/kg METH, i.p., but not in saline controls. Data presented as means \pm SEM; *** $p < 0.001$ compared with baseline ($n = 12$ binge METH, $n = 12$ binge saline)



factor and object as the within-subject factor revealed no significant effects of drug treatment but a significant difference in object preference (drug treatment: $F_{(4, 43)} = 2.27$, $p > 0.07$; object: $F_{(1, 43)} = 15.06$, $p < 0.001$; interaction: $F_{(4, 43)} = 0.035$, $p > 0.99$). Planned Bonferroni analyses revealed that no group spent significantly more time exploring the novel object over the familiar object (binge saline: $t = 2.22$ and $p > 0.05$; binge METH: $t = 1.89$ and $p > 0.05$; yoked saline: $t = 1.36$ and $p > 0.05$; yoked METH: $t = 1.68$ and $p > 0.05$; contingent METH: $t = 1.68$ and $p > 0.05$).

Further analysis of these data used a Discrimination Index (DI), which uses the difference in exploration time for novel and familiar object, then dividing this value by the total amount of object exploration (i.e., $DI = (T_N - T_F)/(T_N + T_F)$). Positive scores (between 0 and 1) indicate a novel object preference, negative scores (between 0 and -1) indicate a familiar object preference, and a zero score indicates a null preference. (Antunes and Biala 2012) These results, which can normalize

differences in exploratory time that could otherwise complicate interpretations of the analyses presented above, are presented in Fig. 3c. A two-way repeated measures ANOVA, with drug treatment as the between-subject factor and time as the within-subject factor, revealed no significant effects of drug treatment or time (drug treatment: $F_{(4, 43)} = 0.097$, $p > 0.98$; time: $F_{(1, 43)} = 1.03$, $p > 0.31$; interaction: $F_{(4, 43)} = 0.26$, $p > 0.90$). Planned Bonferroni analyses revealed no significant group differences in DI (all comparisons: $t < 0.52$ and $p > 0.05$).

Contingent long-access METH self-administration associated with impairment in Morris water maze performance

Animals were tested in the Morris water maze (Morris 1984) to determine whether the drug administration had affected

Fig. 2 Long-access contingent METH self-administration training. **a** LgA contingent METH rats readily learned to lever press for METH delivery. **b** Cumulative METH delivered to LgA contingent METH and matched LgA yoked METH animals during the 16-day training period. Data in the left panel presented as means \pm SEM; line in the right panel indicates mean drug taken over 16-day training period ($n = 8$)

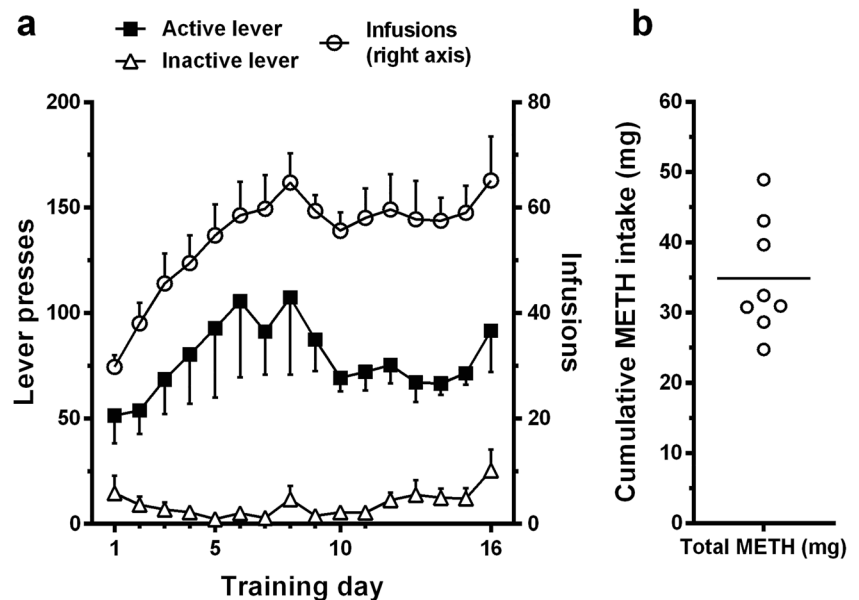
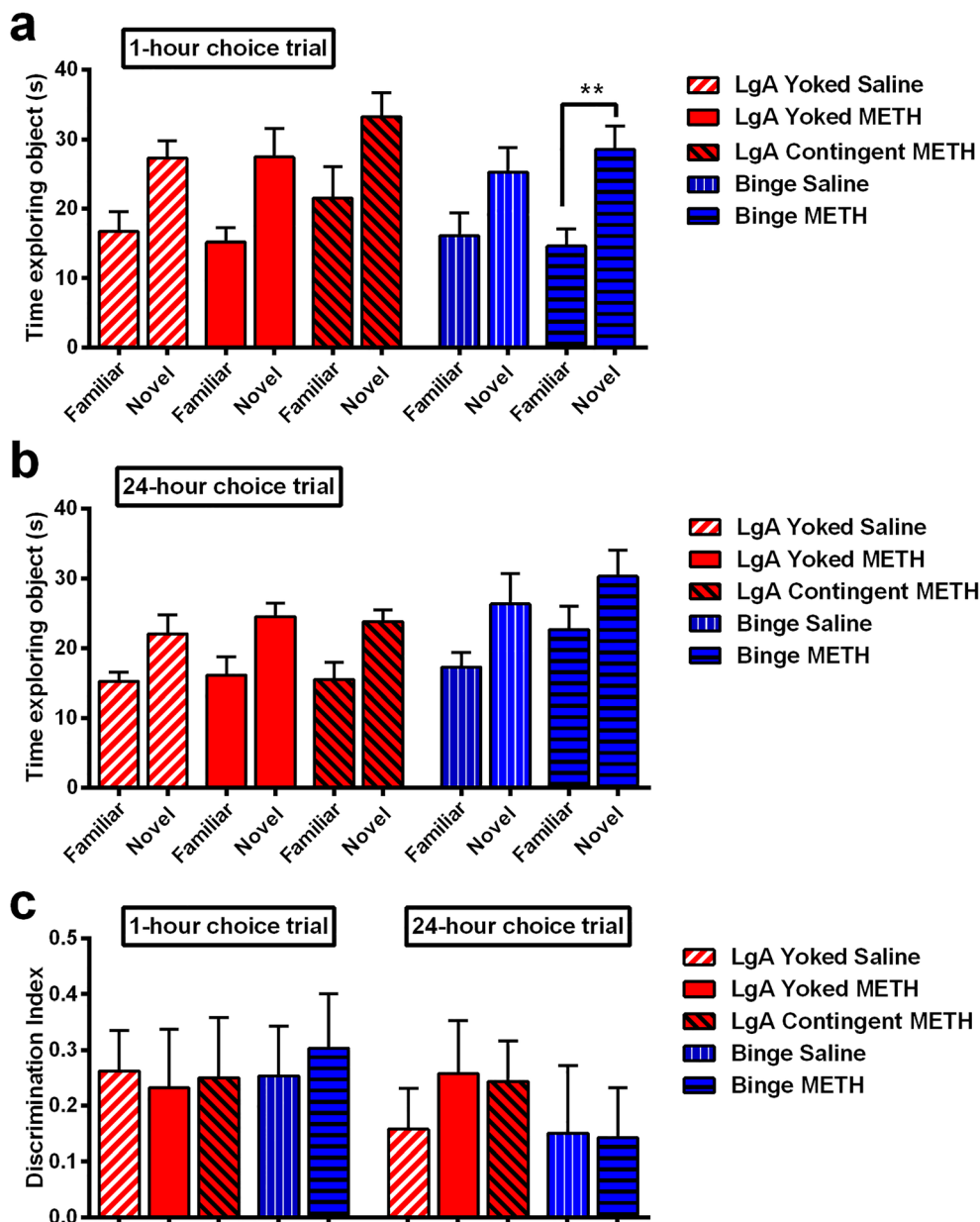


Fig. 3 Novel object recognition. **a** In a 1-h-delay choice trial, LgA yoked saline, LgA yoked METH, binge METH, and saline groups spent significantly more time exploring a novel object, but not the LgA contingent METH group. **b** In a separate 24-h-delay choice trial, binge METH and saline groups did not spend significantly more time exploring a novel object, but LgA yoked saline, LgA yoked METH, and LgA contingent METH groups all three groups spent significantly more time exploring a novel object. **c** In a Discrimination Index analysis, there was no significant difference between groups regarding their preference for the novel object across treatments and time. All groups began novel object recognition testing 3–4 days after the final METH exposure. Data presented as means \pm SEM; $**p < 0.01$ ($n = 12$ for binge METH and binge saline; $n = 8$ for LgA yoked saline, LgA yoked METH, LgA contingent METH)



spatial learning and memory (Fig. 4). All animals effectively learned the location of the platform over 5 days of training, showing no statistical difference between the control and drug groups in latency to reach the hidden platform (Fig. 4a, c). A two-way repeated measures ANOVA, with drug treatment as the between-subject factor and training session as the within-subject factor, revealed significant effects of training session but not drug treatment (drug treatment: $F_{(4, 43)} = 0.415$, $p > 0.79$; training session: $F_{(4, 172)} = 50.1$, $p < 0.0001$; interaction: $F_{(16, 172)} = 1.27$, $p > 0.22$). Performance in the probe trials, in which the platform was removed, was analyzed with a one-way ANOVA across quadrants, followed by specific comparisons (pre-planned Bonferroni analyses) between the target quadrant and each other quadrant. Only if there was a

significant difference between the target quadrant and each of the three remaining quadrants was a significant preference for the target quadrant indicated. Except for the LgA contingent METH group, all other groups displayed retention of platform location, spending significantly more time in the platform training (SW) quadrant (Fig. 4b, d), represented in red (SW versus NW, SW versus NE, and SW versus SE post-tests: binge saline: $p < 0.001$ for all comparisons; binge METH: $p < 0.01$ for all comparisons; yoked saline: $p < 0.0001$ for all comparisons; yoked METH: $p < 0.01$ for all comparisons; LgA contingent METH: post-tests: SW versus NE, and SW versus SE, $p < 0.0001$, SW versus NW, $p > 0.05$).

No significant drug exposure effect was seen in Morris water maze reversal training and testing (Fig. 5). All animals

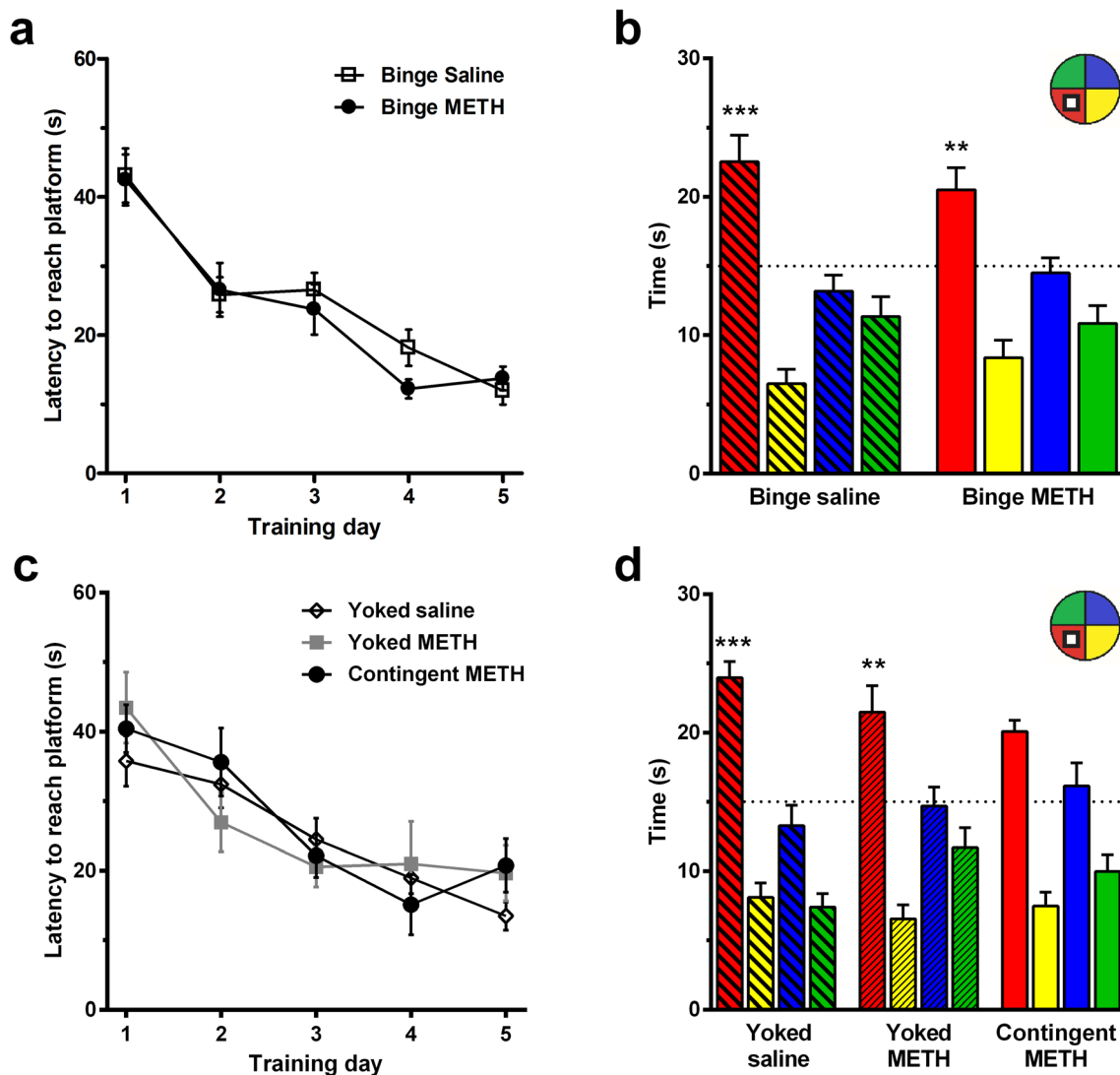


Fig. 4 Morris water maze training and probe trial. METH treatment does not affect the acquisition of spatial memory, but contingent long-access METH self-administration impairs retention of memory. **a, c** During water maze training, no differences were seen between all METH- and saline-treated groups seen in the latency to reach the hidden platform. **b** In a probe trial following training, in which the platform had been removed from the target quadrant, both binge saline- and METH- treated groups spent significantly more time in the target quadrant than in the other three quadrants. **d** LgA yoked saline and LgA yoked METH groups also spent significantly greater time in the target quadrant than in the other

three quadrants. In contrast, LgA contingent METH animals did not spend significantly more time in the target quadrant than in the other three quadrants, suggesting a deficit in spatial memory retention. Training for all animals began 8–10 days after the final METH exposure. Data presented as means \pm SEM; ** $p < 0.01$, *** $p < 0.001$ for SW quadrant (red) versus all other quadrants ($n = 12$ for binge METH and binge saline; $n = 8$ for LgA yoked saline, LgA yoked METH, LgA contingent METH). Dashed lines in panels **b** and **d** represent chance-level expected quadrant time

effectively learned the new location of the platform over 4 days of reversal training, showing no statistical difference between the latency to reach the hidden platform (Fig. 5a, c). A two-way repeated measures ANOVA, with drug treatment as the between-subject factor and training session as the within-subject factor, revealed significant effects of training session but not drug treatment (drug treatment: $F_{(4, 43)} = 0.065$, $p > 0.99$; training session: $F_{(3, 129)} = 22.6$, $p < 0.0001$; interaction: $F_{(12, 129)} = 1.25$, $p > 0.25$). Performance in the probe trials, in which the platform was removed, was analyzed with a one-way ANOVA across quadrants, followed by specific

comparisons (pre-planned Bonferroni analyses) between the target quadrant and each other quadrant. Only if there was a significant difference between the target quadrant and each of the three remaining quadrants was a significant preference for the target quadrant indicated. All treatment groups displayed retention of platform location, spending significantly more time in the reversal training (NE) quadrant (Fig. 5b, d), represented in blue (NE versus NW, NE versus SW, and NE versus SE post-tests: binge saline: $p < 0.0001$ for all comparisons; binge METH: $p < 0.0001$ for all comparisons; yoked saline: $p < 0.0001$ for all comparisons; yoked METH: $p < 0.001$ for

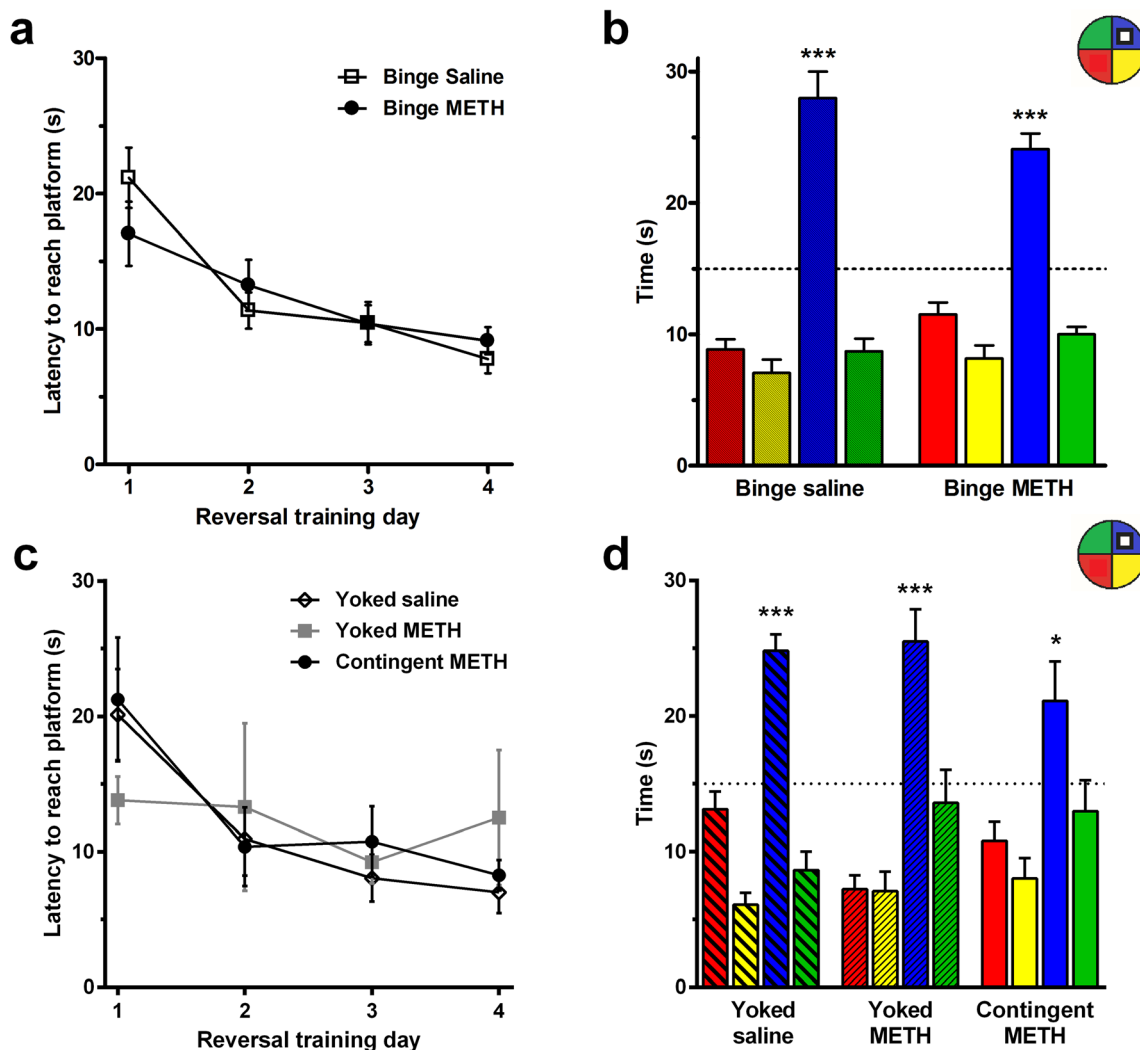


Fig. 5 Morris water maze reversal training and probe trial. **a, c** During water maze reversal training, in which the platform was moved to the opposite quadrant of initial training, no differences were seen between any METH- or saline-treated groups in the latency to reach the hidden platform. **b, d** In a probe trial following reversal training, in which the platform had been removed from the new target quadrant, all METH-

and saline-treated groups spent significantly more time in the target quadrant than in the other three quadrants. Data presented as means ± SEM; **p* < 0.05, ****p* < 0.001 for NE quadrant (blue) versus all other quadrants (*n* = 12 for binge METH and binge saline; *n* = 8 for LgA yoked saline, LgA yoked METH, LgA contingent METH). Dashed lines in panels **b** and **d** represent chance-level expected quadrant time

all comparisons; LgA contingent METH: *p* < 0.05 for all comparisons).

No effect of METH administration on Y-maze performance

All treatment groups displayed spontaneous alternation behavior in the Y-maze task (Fig. 6), and no differences between METH-treated animals and saline controls were observed in a one-way ANOVA ($F_{(4, 172)} = 0.196, p > 0.93$). All groups significantly preferred to enter the Y-maze arm least-recently visited, as measured by one-sample *t* tests with a theoretical

value of 50% (binge saline, $t_{(11)} = 5.79, p = 0.001$; binge METH, $t_{(11)} = 5.12, p = 0.003$; LgA yoked saline, $t_{(7)} = 4.6, p = 0.026$; LgA yoked METH, $t_{(7)} = 4.6, p = 0.028$; LgA contingent METH, $t_{(7)} = 4.7, p = 0.022$).

METH administration associated with long-term depletion of hippocampal and striatal monoamine levels

The effects of METH administration on hippocampal DA, DOPAC, 5-HT, and 5-HIAA levels are presented in Fig. 7. No significant effects of a contingent or non-contingent LgA

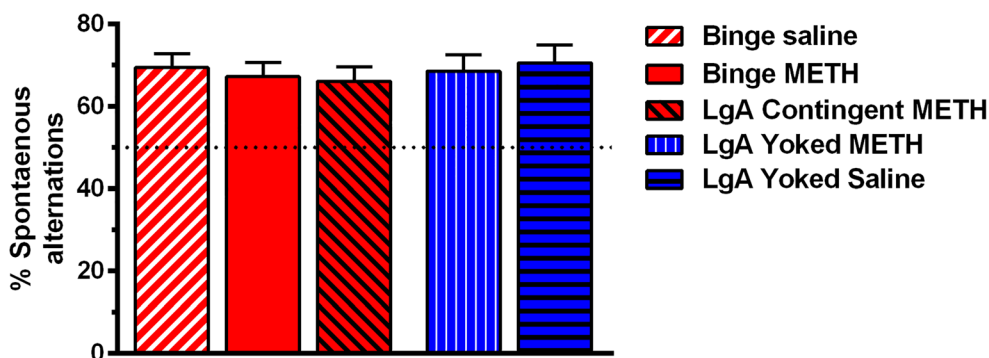


Fig. 6 Y-maze. METH treatment had no effect on spatial memory performance as evaluated by Y-maze test of spontaneous alternation behavior. LgA animals and binge animals showed no difference across treatment groups in percentage of spontaneous alternations. Testing was conducted on day 24 or 33 days after final METH exposure for the LgA

and binge cohorts, respectively. Data presented as means ± SEM ($n = 12$ for binge METH and binge saline; $n = 8$ for LgA yoked saline, LgA yoked METH, LgA contingent METH). Dashed line represents chance-level expected alternations

METH exposure on hippocampal DA, DOPAC, 5-HT, or 5-HIAA were observed (one-way ANOVAs; DA: $F_{(2, 21)} = 2.38$, $p > 0.1$; DOPAC: $F_{(2, 21)} = 2.23$, $p > 0.1$; 5-HT: $F_{(2, 21)} = 0.51$, $p > 0.6$; 5-HIAA: $F_{(2, 21)} = 2.57$, $p > 0.1$). Binge METH treatment caused significant reductions in hippocampal 5-HT and 5-HIAA, but not DA or DOPAC, compared with saline

controls (two-tailed t tests; DA: $t_{(22)} = 1.20$, $p > 0.2$; DOPAC: $t_{(22)} = 1.23$, $p > 0.2$; 5-HT: $t_{(22)} = 2.35$, $p = 0.028$; 5-HIAA: $t_{(22)} = 2.94$, $p = 0.0076$).

The effects of METH administration on striatal monoamine levels are presented in Fig. 8. No significant effect of LgA METH exposure on striatal DA, DOPAC, or 5-HT was

Fig. 7 Hippocampal monoamine levels 75 days post-METH exposure as determined by HPLC with electrochemical detection. **a** Hippocampal DA levels. No significant effect of treatment across all treatment groups. **b** Hippocampal DOPAC levels. No significant effect of METH across all treatment groups. **c** Hippocampal 5-HT levels. No significant effect of treatment across LgA treatment groups, but a significant decrease in hippocampal 5-HT observed in binge METH-treated animals compared with saline. **d** Hippocampal 5-HIAA levels. No significant effect of treatment across LgA treatment groups, but a significant decrease in hippocampal 5-HIAA observed in binge METH-treated animals compared with saline. Data presented as means ± SEM; * $p < 0.05$, ** $p < 0.01$ ($n = 12$ for binge METH and binge saline; $n = 8$ for LgA yoked saline, LgA yoked METH, LgA contingent METH)

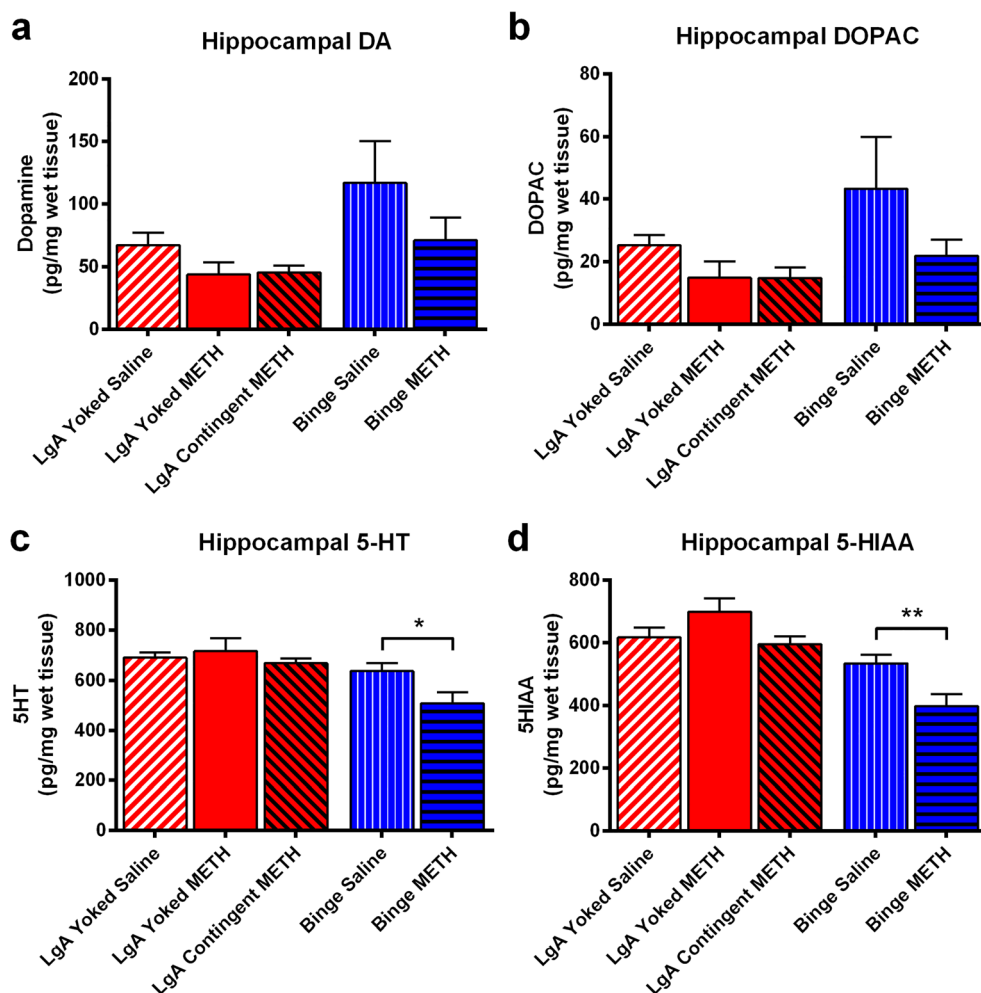
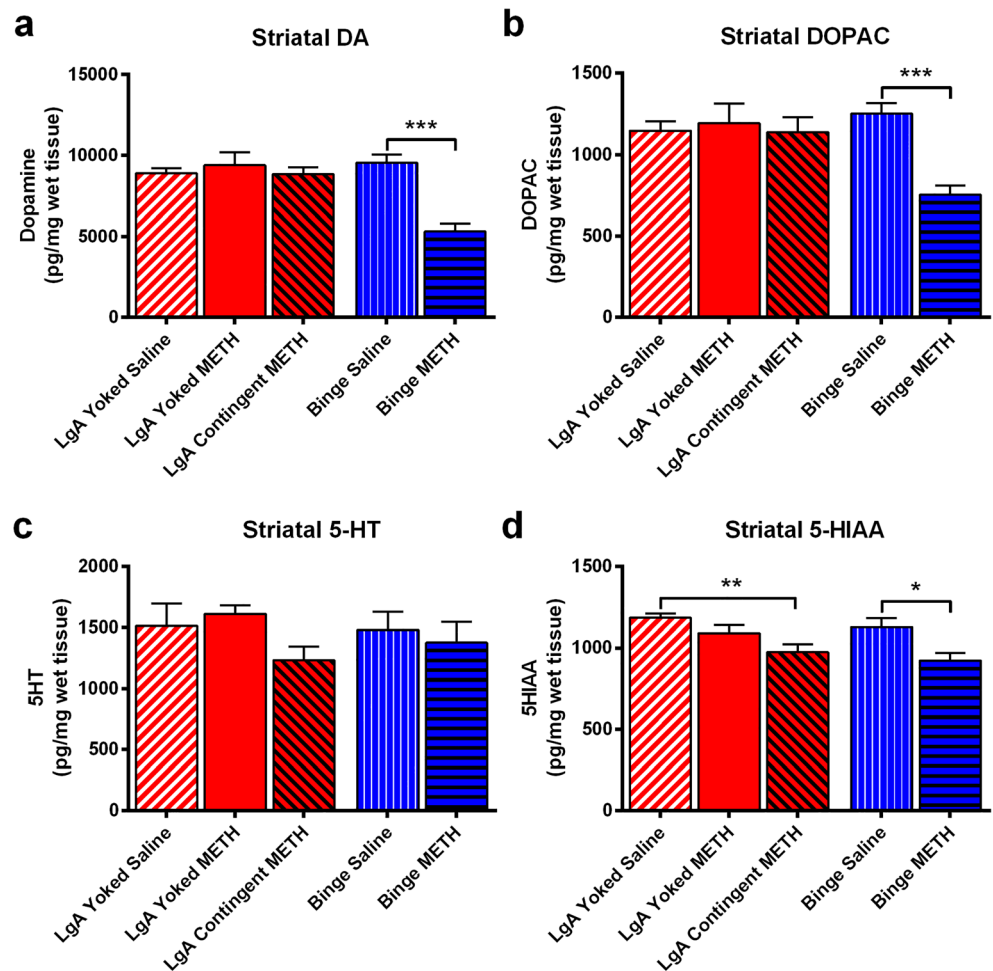


Fig. 8 Striatal monoamine levels 75 days post METH exposure as determined by HPLC with electrochemical detection. **a** Striatal DA levels. No significant effect of treatment across LgA treatment groups, but a significant decrease in striatal DA observed in binge METH-treated animals compared with saline. **b** Striatal DOPAC levels. No significant effect of treatment across LgA treatment groups, but a significant decrease in striatal DOPAC observed in binge METH-treated animals compared with saline. **c** Striatal 5-HT levels. No significant effect of METH on striatal 5-HT levels across all treatment groups. **d** Striatal 5-HIAA levels. Significant decrease in striatal 5-HIAA observed in LgA contingent METH animals compared with saline and a significant decrease in striatal 5-HIAA observed in binge METH-treated animals compared with saline. Data presented as means \pm SEM; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ ($n = 12$ for binge METH, binge saline; $n = 8$ for LgA yoked saline, LgA yoked METH, LgA contingent METH)



observed, but LgA contingent METH animals did show decreased striatal 5-HIAA levels compared with yoked saline controls (one-way ANOVAs; DA: $F_{(2, 21)} = 0.28$, $p > 0.7$; DOPAC: $F_{(2, 21)} = 0.10$, $p > 0.9$; 5-HT: $F_{(2, 21)} = 2.28$, $p > 0.1$; 5-HIAA: $F_{(2, 21)} = 6.15$, $p = 0.0079$, LgA yoked saline versus LgA contingent METH: $t = 3.5$ and $p < 0.01$, other comparisons: $t < 1.96$ and $p > 0.05$). Binge METH treatment caused significant reductions in hippocampal DA, DOPAC, and 5-HIAA, but not 5-HT, compared with saline controls (two-tailed t tests; DA: $t_{(22)} = 6.11$, $p < 0.0001$; DOPAC: $t_{(22)} = 5.85$, $p < 0.0001$; 5-HT: $t_{(22)} = 0.46$, $p > 0.6$; 5-HIAA: $t_{(22)} = 2.82$, $p = 0.0101$).

Long-access and binge METH administration associated with long-term decreases in hippocampal BDNF, with binge paradigm also increasing TrkB

Hippocampal TrkB and BDNF protein levels were measured at 75 days post-METH exposure using Western blot (Fig. 9). Hippocampal TrkB levels (Fig. 9a) were not affected by LgA METH exposure ($F_{(2, 18)} = 2.22$, $p > 0.1$), but

significantly increased in the binge METH group compared with saline controls ($t_{(16)} = 5.97$, $p < 0.0001$). Hippocampal BDNF levels (Fig. 9b) were reduced by METH exposure in the LgA cohort, compared with yoked saline controls ($F_{(2, 20)} = 26.01$, $p < 0.0001$; post-tests: LgA yoked saline versus LgA yoked METH, $t > 5.5$ and $p < 0.001$; LgA yoked saline versus LgA contingent METH, $t > 6.8$ and $p < 0.001$; LgA yoked METH versus LgA contingent METH, $t = 1.3$ and $p > 0.05$). Binge METH treatment also significantly reduced hippocampal BDNF expression compared with saline controls ($t_{(21)} = 2.53$, $p = 0.0197$). For both TrkB and BDNF analyses, control tubulin protein levels did not significantly vary across treatment groups nor did tubulin level vary across the multiple blots used for these analyses (TrkB: $F_{(4, 35)} = 2.17$, $p = 0.093$; BDNF: $F_{(4, 39)} = 2.16$, $p = 0.092$). 6 of 48 total protein samples were excluded from our final TrkB ($n = 1$ LgA yoked saline, $n = 2$ LgA yoked METH, $n = 1$ binge saline) and BDNF ($n = 1$ LgA yoked saline, $n = 1$ binge METH) analyses as outliers (more than two standard deviations above or below group means in TrkB, BDNF, or control tubulin levels).

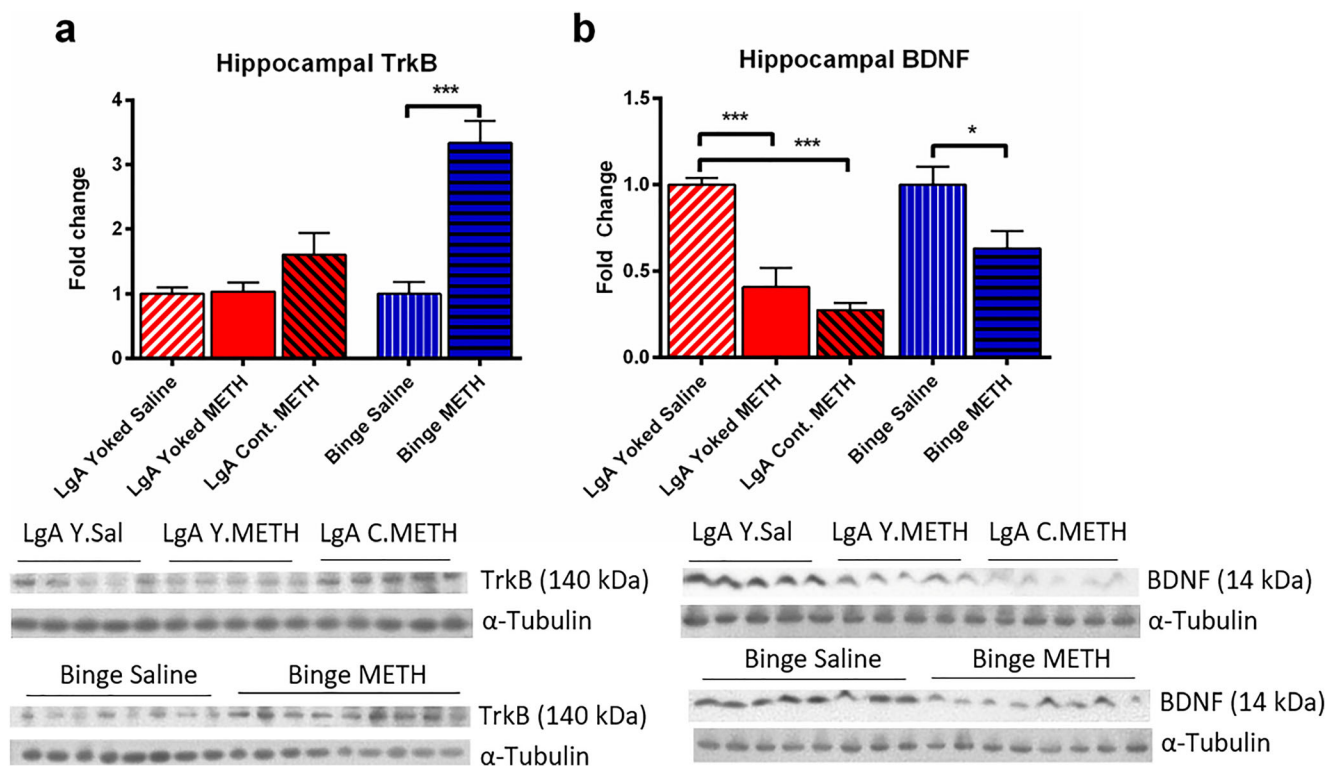


Fig. 9 Hippocampal TrkB and BDNF protein levels 75 days post-METH exposure as evaluated by Western blot. **a** No significant effect of treatment across LgA groups on hippocampal TrkB protein levels, but binge METH treatment significantly increased TrkB levels ($n = 7$ LgA yoked saline, $n = 6$ LgA yoked METH, $n = 8$ LgA contingent METH; $n = 11$ binge saline, $n = 12$ binge METH). **b** LgA METH exposure, both yoked and contingent, significantly reduced hippocampal BDNF expression.

Binge METH treatment also significantly reduced hippocampal BDNF levels ($n = 7$ LgA yoked saline, $n = 8$ LgA yoked METH, $n = 8$ LgA contingent METH; $n = 12$ binge saline, $n = 11$ binge METH). Data were normalized to the average intensity of the respective saline control groups in order to compare data across blots. Data presented as means \pm SEM; * $p < 0.05$, *** $p < 0.001$

Discussion

In this study, we sought to evaluate and compare the cognitive and neurochemical effects of two different METH exposure paradigms. By directly comparing a classical neurotoxic dosing regimen (the “binge” model) with 6-h long-access METH self-administration (LgA) animals and yoked non-contingent counterparts, we could evaluate the effects of drug exposure patterns and contingency on a variety of behavioral and neurological outcomes. We used several behavioral tasks that have been tested previously in various studies of METH-induced neurotoxicity. Overall, METH exposure produced clear neurochemical alterations detectable 75 days after last drug exposure, though the outcomes were considerably more dramatic in the binge model than in LgA self-administration. In a battery of cognitive-behavioral tests, effects were only modest. In addition, deficits did not unambiguously correlate with drug exposure patterns or neurochemical outcomes, though some intriguing observations are noted below.

Impairment in the novel object recognition (NOR) task is the most widely replicated cognitive effect associated with the “binge” METH treatment in rats (Belcher et al. 2005; Bisagno et al. 2002; Camarasa et al. 2010; He et al. 2006; Herring et al.

2008; Marshall et al. 2007; Melo et al. 2012; Reichel et al. 2011, 2012; Schroder et al. 2003). Somewhat unexpectedly, we observed no clear METH-associated impairments in NOR in either the LgA animals or the binge METH-treated animals. When data are analyzed via a Discrimination Index, no statistically significant group differences were detectable. The broadly similar performance of the binge saline, binge METH, and LgA yoked saline groups is more consistent with the literature, in which longer times separating training from probe trials diminished recognition of the familiar object as *familiar*, leading to a reduced preference for a newly introduced object. Given that the METH-exposed LgA groups had reduced novel object preference in the 1-h trial but a clearer novel object preference in the 24-h trial could suggest some METH-associated deficit in short-term object recognition that can be overcome by additional time, possibly a result of diminished synaptic plasticity or altered long-term potentiation.

While these results make it difficult to interpret clear differences in cognitive impairment between METH dosing regimens, they do suggest that the binge METH-induced NOR impairment reported in the literature may not be as robust an effect as previously thought. For example, a recent study

comparing three methamphetamine dosing regimens similarly found no impairment in short-term novel object recognition performance (Seyedhosseini Tamijani et al. 2018). Additionally, North et al. (2013) found that 14 days of daily neurotoxic dose of METH does not alter short-term memory as measured by NOR. Furthermore, the findings of Belcher et al. (2005) indicate that the METH-induced impairment in NOR observed by some groups could be independent of METH-induced damage to DA and 5-HT systems: they administered PCA, a drug that preferentially damages 5-HT terminals, and d-AMPH, a drug that preferentially damages DA terminals, and found that neither caused impairments in the NOR task while METH did.

There are limited published reports of METH's effect on spatial working memory. Previous studies reported METH-induced spatial working memory impairment in Y-maze performance following LgA METH self-administration (Recinto et al. 2012), daily dosing regimens over 7, 10, or 14 days (Seyedhosseini Tamijani et al. 2018), or a single 30-mg/kg METH injection but not a chronic escalating METH injection paradigm (Simoes et al. 2007). We found no significant impact of METH exposure on Y-maze performance across all treatment groups, although variations in experimental procedures could account for differences in our treatment results (e.g., Simoes et al. (2007) used a single 30 mg/kg dose; this study used four 10 mg/kg doses). We report no effects of binge or LgA METH treatment on the acquisition of the water maze task as evaluated by Morris water maze. This corresponds with the results of Herring et al. (2008), who found no impairment in Morris water maze performance following a binge dosing regimen. Our observations are also consistent with those of Friedman et al. (1998) and Gutierrez et al. (2017) who reported METH-associated impairments only during single training sessions. Interestingly, we observed impairment in the LgA contingent METH animals' retention of platform location in the probe trial after the initial 5-day acquisition training—but not after the reversal training—and no impairment in the LgA yoked METH animals, as measured by a lack of statistically significant preference for the platform quadrant. This may indicate a potential role of contingency in cognitive impairments associated with METH use.

Long-term serotonergic and dopaminergic deficits following a neurotoxic regimen of methamphetamine administration have been widely reported, often using “binge” exposure models similar to this study (Chapman et al. 2001; Friedman et al. 1998; Herring et al. 2008; Seiden et al. 1993). Few reports have evaluated the effects of long-access METH self-administration on brain monoaminergic systems. In this study, we sought to explore the potential long-term neurotoxic effects of 6-h LgA METH self-administration compared with a traditional binge dosing regimen. We observed reduced hippocampal DA, 5-HT, and 5-HIAA levels as well as reduced striatal DA, DOPAC, and 5-HIAA levels in the binge METH-

treated animals as measured 75 days post-METH treatment, indicating long-term neurotoxic effects of this dosing regimen consistent with previously reported studies. In the same time frame (75 days following last METH exposure), we saw minimal long-term monoaminergic deficits in the LgA METH animals (only significantly decreased striatal 5-HIAA in the LgA contingent METH animals), suggesting that this METH treatment did not elicit robust neurotoxicity as measured by monoaminergic depletion.

The neurotrophin BDNF signals through TrkB and is involved in neuronal growth, survival, and plasticity. BDNF has complex effects on receptor expression, signaling cascades, and neural morphology that vary across brain regions, affecting drug-taking and drug-seeking behaviors in animal models of psychostimulant addiction and withdrawal (Anderson et al. 2017; Guillin et al. 2001; Li et al. 2013; Li and Wolf 2015; McGinty et al. 2010; Ren et al. 2015). In this study, we report a long-term decrease in hippocampal BDNF protein levels observed 75 days post-METH exposure in all drug-exposed groups compared with saline controls. This follows observations by Krasnova et al. (2013) of short-term increases in striatal BDNF levels followed by decreases in BDNF levels observed 1 month post-METH exposure. The long-term decrease in BDNF is consistent with studies of human METH users in which serum BDNF levels are initially elevated and subsequently decrease following prolonged withdrawal (Ren et al. 2016, 2017), with serum BDNF levels correlating to the duration of drug abstinence (Hilburn et al. 2011). We also observed a significant increase in hippocampal TrkB protein levels 75 days post-METH exposure in only the binge METH group, which could reflect a compensatory mechanism related to the more substantial neurotoxicity seen in this group as determined by monoamine depletion and could help prevent cognitive deficits. Braun et al. (2011) reported an acute increase in BDNF and TrkB levels following neurotoxic methamphetamine exposure, which may be linked to acute DA increases also observed following METH. In turn, our observed decreases in both BDNF and DA levels following the neurotoxic binge dose at a late 75-day time point may support this BDNF-mediated mechanism of DA homeostasis in the drug-exposed brain. Importantly, Johansen and McFadden (2017) recently reported increases in hippocampal BDNF in male but not female rats 1 day after the completion of a long-access METH self-administration paradigm, indicating that there may be important sex differences in neurochemical outcomes that were not addressed in the design of this study and many others cited above.

Overall, the binge METH paradigm used in this study, in which 40 mg/kg METH was given i.p. over the course of 1 day, induced neurochemical effects readily detectable 75 days after drug exposure, including reduced striatal DA and DOPAC, reduced hippocampal 5-HT, 5-HIAA, and BDNF, and increased hippocampal TrkB. LgA METH self-

administration, in which METH intake ranged from 24.8 to 48.9 mg (equivalent to 62.0–122.3 mg/kg in a 400-g rat) over the 16-day training period, produced a much more limited set of neurochemical effects 75 days after drug exposure, including reduced hippocampal BDNF in both LgA contingent METH and yoked METH animals and reduced striatal 5-HIAA in only LgA contingent METH animals. The variable amount of administered METH across LgA contingent and yoked pairs, and the lower daily mean intake of 2.18 mg/day (equivalent to 5.45 mg/kg in a 400-g rat) spread over 6 h, is likely the reason LgA METH is less neurotoxic by these measures.

There are several previous reports that describe contingency of psychostimulant administration dramatically affects the type and magnitude of neuroadaptive responses (e.g., Dworkin et al. 1995; Frankel et al. 2011; Jacobs et al. 2003; Stefanski et al. 1999, 2004; Wiskerke et al. 2016). We found no reports that specifically evaluated the effects of drug contingency on cognitive-behavioral outcomes following METH exposure. In this study, there was a mild performance deficit in the LgA contingent METH animals in the Morris water maze compared with yoked METH and yoked saline controls. However, the neurochemical alterations measured in this group were only modestly different from those of the yoked METH group. More importantly, very clear neurochemical differences were seen in the binge METH group compared with saline controls, but testing in NOR, Y-maze, and Morris water maze tasks showed no consistent deficits in these cognitive tasks in binge METH-exposed animals. A possible explanation for the behavioral difference between binge and self-administration groups could be the large compensatory increase in TrkB receptor levels in binge but not self-administration groups.

Possibly the most parsimonious explanation for these data is that there is no causative relationship between the neurochemical effects measured and performance in these behavioral assays. While this may be explained by various procedural differences between this study and previous reports, a broader view of the literature suggests that METH-induced neurotoxicity does not *reliably* produce cognitive-behavioral deficits in rodents. For example, Seiden et al. (1993) performed a battery of tests following neurotoxic-level METH administration (12.5-, 25-, or 50-mg/kg/injection, s.c., every 12 h for 4 days) and found no effects of METH treatment in any of the 17 behavioral outcomes measured (including food and water intake, schedule-controlled behavior, open field, one-way avoidance, two-way avoidance, swim test, and morphine analgesia), despite observing significant monoamine depletions as far as 18 months post-METH exposure. These results, coupled with our own, highlight the likelihood that while many METH-induced cognitive-behavioral effects have been reported to correlate with measures of neurotoxicity and loss of monoaminergic terminals, a causative link between

reduced performance in cognitive tasks and CNS monoamine neurotoxicity has not been clearly established.

Both METH exposure models used in this paper are limited in their approximations of human patterns of drug use. Human METH use is variable, but many patients report long periods of drug intake that may be followed by a “crash” (Cornett and Goeders 2013; Kuczenski et al. 2009; Shabani et al. 2016). Experimenter-administered “binge” METH may readily induce a cyclic drug exposure pattern reminiscent of human intake, but lack any self-titration of drug dose one would expect from a self-administering animal possibly resulting in exaggerated physiological consequences. Typical short-access METH self-administration models (e.g., 2-h drug access) produce low, stable METH self-administration unlike reported patterns of human METH intake; this observation has driven the development of multiple self-administration models that attempt to better model binge-and-crash intake cycles by increasing drug access periods, e.g., 6 (Jang et al. 2013), to 15 (Krasnova et al. 2010), to 96 h (Cornett and Goeders 2013) of METH self-administration access, with complex comparative neurochemical and behavioral consequences reported in these models. Furthermore, while humans chronically using METH or other drugs can show alterations in neurophysiology, recent critical reviews of the clinical literature argue that available studies are not sufficient to support the claim that *recreational* METH use causes loss of DA neurons in humans (Kish et al. 2017) and that reported METH-associated deficits in cognitive performance occur in only a small number of measures and may be clinically insignificant (Hart et al. 2012) or clinically significant in only a subset of patients (Cadet and Bisagno 2015; Dean et al. 2013). Indeed, the spectrum of behavioral and neurochemical effects produced by METH is highly dependent upon dose, with low-to-moderate doses producing well-established pro-cognitive effects (Wood et al. 2014).

Overall, this study demonstrated substantial differences in neurochemical outcomes can be seen between rats undergoing a standard “binge” METH exposure paradigm compared with a LgA METH self-administration paradigm. Inclusion of yoked LgA controls suggests these neurochemical differences may be affected in part due to the contingency of the METH administration. It is worth noting that the operant training paradigm used herein included a compound cue (light, tone, drug/saline delivery) for all rats; therefore, all yoked rats, though unable to affect their drug/saline delivery, were effectively in Pavlovian conditioning sessions. The consequences of this are unclear but could contribute to findings in which the yoked LgA rats displayed contingent-like results, such as reductions in BDNF levels. Dramatic alterations in monoamine, BDNF, and TrkB levels did not appear to correlate to deficits in three cognitive tasks in the binge METH group. While LgA contingent METH animals showed modest deficits in the retention of spatial memory in the water maze—possibly a result

of a lack of compensatory TrkB upregulation—this effect is possibly most simply explained by a general lack of strong causative relationships between the measured neurochemical outcomes and performance in these behavioral assays.

Funding information The authors received support from the NIDA-IRP and the NIA-IRP for this research. TMK was supported by an IRTA postdoctoral fellowship. CAS and CB were supported by IRTA post-baccalaureate fellowships. AHN is supported by Z1A DA000424.

Compliance with ethical standards

All experiments were conducted in accordance with the Guide for the Care and Use of Laboratory Animals (US National Academy of Sciences) and were approved by the Animal Care and Use Committee of the National Institute on Drug Abuse under protocols 09-CNRB-25 and 13-BNRB-48.

Conflict of interest The authors declare that they have no conflict of interest.

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