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ORIGINAL INVESTIGATION

# The effects of yohimbine and amphetamine on fear expression and extinction in rats

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**Abstract**
*Rationale* Psychostimulants, such as yohimbine and amphetamine, can enhance learning and memory. Extinction of conditioned fear involves new learning, so we asked whether psychostimulants could enhance this learning. Previous work suggests that yohimbine facilitates extinction, using freezing as a fear measure. However, psychostimulant-induced alterations in locomotion can confound freezing measurements. Furthermore, the effects of amphetamine on fear extinction have never been examined.
*Objective* We evaluated the effectiveness of yohimbine and amphetamine in enhancing fear extinction. In addition to freezing, we measured bar-press suppression, which is less sensitive to changes in locomotion. We asked: Do psychostimulants reduce fear during extinction training when drug is present? Does learning extinction with psychostimulants result in better extinction retention?
*Materials and methods* Rats received fear conditioning on day 1 followed by partial extinction training on days 2 and 3. Yohimbine (1.0, 2.0, or 5.0 mg/kg, i.p.), amphetamine (1.0 mg/kg, i.p.), or vehicle were injected prior to extinction on day 2.
*Results* Yohimbine dose-dependently reduced freezing during extinction training on day 2, whereas bar-press suppression was reduced at the highest dose only. When tested drug-free, yohimbine-treated rats showed equivalent levels of freezing and suppression to controls. Amphetamine also decreased freezing during extinction, but did not decrease suppression. During the drug-free test, there was no difference between amphetamine-treated rats and controls in either measure.
*Conclusions* Although yohimbine and amphetamine are capable of decreasing freezing, neither drug strengthened retention of fear extinction. Based on these rodent findings, psychostimulants may not be suitable adjuncts to extinction-based therapies for the treatment of anxiety disorders.

**Keywords** Fear conditioning · Psychostimulant · Norepinephrine · Fear extinction · Bar-press suppression · Freezing · $\alpha_2$-Adrenoceptor antagonist · Reuptake blocker · Anxiety disorders

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## Introduction

Psychostimulants can enhance learning and memory in a variety of tasks. Two psychostimulant drugs known to

strengthen learning and retention are yohimbine, an $\alpha_2$-adrenoceptor antagonist, and amphetamine, a monoaminergic reuptake blocker. In humans, administration of yohimbine during presentation of an emotional story enhances subsequent free recall and recognition memory in a drug-free test (O'Carroll et al. 1999). Similarly, amphetamine given to people before or after a verbal learning task enhances later recall and recognition (Soetens et al. 1993, 1995). In rats, amphetamine facilitates learning and retention of aversive memories such as conditioned taste aversion (Fenu and Di Chiara 2003) and conditioned avoidance (Davies et al. 1974; Blaiss and Janak 2007).

Although the formation of aversive memories is enhanced by psychostimulants, the question remains whether these drugs can enhance extinction of these memories. In fear extinction, fear responses are reduced upon repeated presentation of conditioned stimuli, resulting in the formation of a new inhibitory memory (Rescorla 2004; Myers and Davis 2007; Quirk and Mueller 2008). Previous work has shown that yohimbine administered prior to extinction can enhance subsequent recall of extinction (Cain et al. 2004; Morris and Bouton 2007), an effect attributed to increased norepinephrine release. In addition, pre-extinction administration of tricyclic antidepressants, which block reuptake of norepinephrine, enhances recall of extinction the next day (Telegdy et al. 1983; Kikusui et al. 2001). Amphetamine also blocks reuptake of norepinephrine, as well as other monoamines, and is already in use clinically to treat attention disorders. Decades of research implicate noradrenergic signaling in enhancing memory formation (McGaugh 2000), and memory for extinction is impaired by lesions of the locus coeruleus which deprive the cortex of norepinephrine (Mason and Fibiger 1979; McCormick and Thompson 1982). Recently, we have shown that fear extinction is dependent on noradrenergic signaling in the prefrontal cortex (Mueller et al. 2008). Because psychostimulants increase extracellular concentrations of norepinephrine (Goldberg and Robertson 1983; Berridge 2006), we asked whether systemic administration of psychostimulants could enhance acquisition and/or retention of fear extinction.

Most prior work on conditioned fear has used freezing as a measure of fear. Amphetamine has been shown to increase locomotor activity (Dews 1953), whereas yohimbine has been observed to increase (Mason et al. 1998) or decrease (Chopin et al. 1986) locomotor activity, which could confound freezing measurements. To determine whether these drugs enhance extinction acquisition or simply reduce freezing responses, we trained rats to bar-press for food and assessed both freezing and bar-press suppression to a conditioned auditory stimulus. Because bar-press suppression is normalized for baseline press rates (Bouton and Bolles 1980; Mast et al. 1982), it is less likely to be confounded by psychostimulant-induced changes in baseline activity. We administered yohimbine or amphetamine prior to extinction training and then tested the rats drug-free the following day, thus allowing us to evaluate whether the drugs accelerated the acquisition of extinction and/or improved retention of extinction. Characterizing the effects of psychostimulants in rodent studies of fear extinction is a first step in determining whether these drugs might be useful as pharmacological adjuncts to exposure therapy for anxiety disorders (Pine and Cohen 2002; Myers and Davis 2007).

## Materials and methods

### Subjects

One hundred twenty male Sprague–Dawley rats weighing 270–320 g were housed and handled as previously described (Quirk et al. 2000). Rats were restricted to 18 g of standard rat chow daily and were subsequently trained to press a bar for food on a variable interval schedule (VI 60 s). All procedures were approved by the local Institutional Animal Care and Use Committee in accordance with the National Institute of Health guidelines.

### Apparatus

Fear conditioning and extinction were carried out in four identical operant conditioning chambers (Coulbourn Instruments, Allentown, PA, USA). The floor consisted of stainless steel bars separated by 1.8 cm, connected to a shock scrambler (Coulbourn). A response lever was located 6.5 cm above the floor, and a speaker was positioned on the opposite wall. The chamber was ventilated and illuminated by a single house light and housed in a sound-attenuating box (Med Associates, Burlington, VT, USA). Locomotor activity was measured in an open field (91.5×91.5×61 cm) divided into peripheral (within 15.25 cm of the walls) and central (61×61 cm) regions of approximately equal area.

### Drugs

All drugs were purchased from Sigma (St. Louis, MO, USA). Yohimbine was dissolved in distilled water to avoid the formation of a precipitate, and D-amphetamine was dissolved in physiological saline. Solutions were prepared the same day they were used and administered in a volume of 1.0 mL/kg. Doses of yohimbine and amphetamine were chosen based on previous studies (Cain et al. 2004; Morris and Bouton 2007; Martinez et al. 1980).

### Fear conditioning and extinction

On day 1, rats were presented with five tones (30 s, 75 dB, 4 kHz) in the absence of shocks and were subsequently fear-conditioned with seven presentations of the tone that coterminated with a foot shock (0.43 mA, 0.5 s). The intertrial interval varied and averaged 3 min. Groups of rats were matched on freezing during conditioning. On day 2, rats were injected with yohimbine (5.0, 2.0, or 1.0 mg/kg, i.p.), amphetamine (1.0 mg/kg, i.p.), or vehicle 20–30 min prior to extinction training. Extinction consisted of either six or eight presentations of the tone in the absence of shock, administered in the same chamber as conditioning. On days 3 and 4, rats were given additional extinction trials (drug-free) to test for extinction memory, again in the same chamber (AAA design). A variant of this design was used to test whether yohimbine would enhance fear extinction when extinction and testing occurred in a novel environment. Rats were fear-conditioned in context A (as above) on day 1. On day 2, rats were administered yohimbine (1.0 mg/kg, i.p.) prior to eight trials of extinction in a novel chamber (context B). On day 3, rats were tested drug-free in context B (ABB design). Context A consisted of the operant conditioning chamber with grid floors. Context B differed in that the flooring consisted of vinyl sheets, the walls of the operant conditioning chamber were striped, and a novel almond odor was present.

### Locomotor activity

Following fear conditioning and extinction procedures, rats were no longer food-restricted and had access to food in their home cages ad libitum. After 2–3 days, rats were assigned to either the drug or vehicle condition based on drug exposure during extinction, such that each group consisted of 50% drug-experienced and 50% drug-naïve rats. Rats were then assessed for drug-induced locomotor activity in an open field for 10 min. Open-field testing was performed during the light cycle under lit conditions and was recorded onto videotapes.

### Data analysis

Digital video files were analyzed offline with the Freeze-scan software (Clever Systems, Reston, VA, USA), which calculated the percent time rats were motionless during tone presentations. We also assessed suppression of bar-pressing as an additional measure of conditioned fear. The rate of bar-pressing during the 30-s tone was compared to the rate in the 60 s prior to the tone to calculate a suppression ratio as follows: suppression = (pretone rate − tone rate)/(pretone rate + tone rate). A suppression ratio of 0 indicates no suppression of bar-pressing, and a ratio of 1.0 indicates maximal suppression. For the open-field experiments, locomotion (line crossings) was scored manually from videotape by observers blind to the treatment of the rats. All group comparisons were made using analysis of variance (ANOVA) and Student's *t* tests. Significant main effects of ANOVA were followed by Tukey's post hoc comparisons.

## Results

### Yohimbine decreased freezing, but did not enhance fear extinction

Fear conditioning was conducted on day 1, and on day 2, rats injected with yohimbine (5.0 mg/kg, i.p.) expressed significantly lower levels of freezing on average than rats injected with distilled water (vehicle) throughout the extinction session (yohimbine=34%, vehicle=84%, $n$=12 and 11; Fig. 1a). ANOVA revealed a main effect of group ($F_{1,21}$= 24.0, $p$<0.001) and a group by trial interaction ($F_{5,105}$=2.6, $p$=0.029), indicating that yohimbine-treated rats expressed less freezing overall and a higher rate of extinction during the session than vehicle-treated controls. Yohimbine-treated rats also showed significantly less bar-press suppression on average than vehicle-treated rats during extinction training (yohimbine=0.26, vehicle=0.88; effect of group: $F_{1,21}$= 27.0, $p$<0.001; Fig. 1a). Thus, yohimbine decreased fear expression and appeared to facilitate extinction learning. In a drug-free test the following day, however, both groups expressed similar levels of freezing (yohimbine=77%, vehicle=66%; $F_{1,21}$=0.6, $p$=0.45) and similar bar-press suppression (yohimbine=0.76, vehicle=0.82; $F_{1,21}$=0.1, $p$= 0.82). These findings indicate that this dose of yohimbine does not improve long-term retention of extinction.

At a lower dose of yohimbine (2.0 mg/kg, i.p.), yohimbine-treated rats expressed significantly less freezing on average than vehicle-treated rats throughout extinction training (yohimbine=49%, vehicle=74%, $n$=10 and 12; $F_{1,20}$=4.39, $p$=0.049; Fig. 1b). In contrast, bar-press suppression did not differ between the groups (yohimbine= 0.55, vehicle=0.69, $p$=0.21). In a drug-free test the following day, both the yohimbine- and vehicle-injected groups showed equivalent levels of freezing (yohimbine= 62%, vehicle=61%, $p$=0.95) and bar-press suppression (yohimbine=0.51, vehicle=0.48, $p$=0.80). Thus, a dose of 2.0 mg/kg yohimbine reduced fear expression in only one of two measures and did not enhance long-term extinction retention.

Rats that were injected with 1.0 mg/kg yohimbine prior to extinction training did not show significantly reduced freezing compared to controls (yohimbine=59%, vehicle= 74%, $n$=12 and 12, $p$=0.16). However, extinction of the

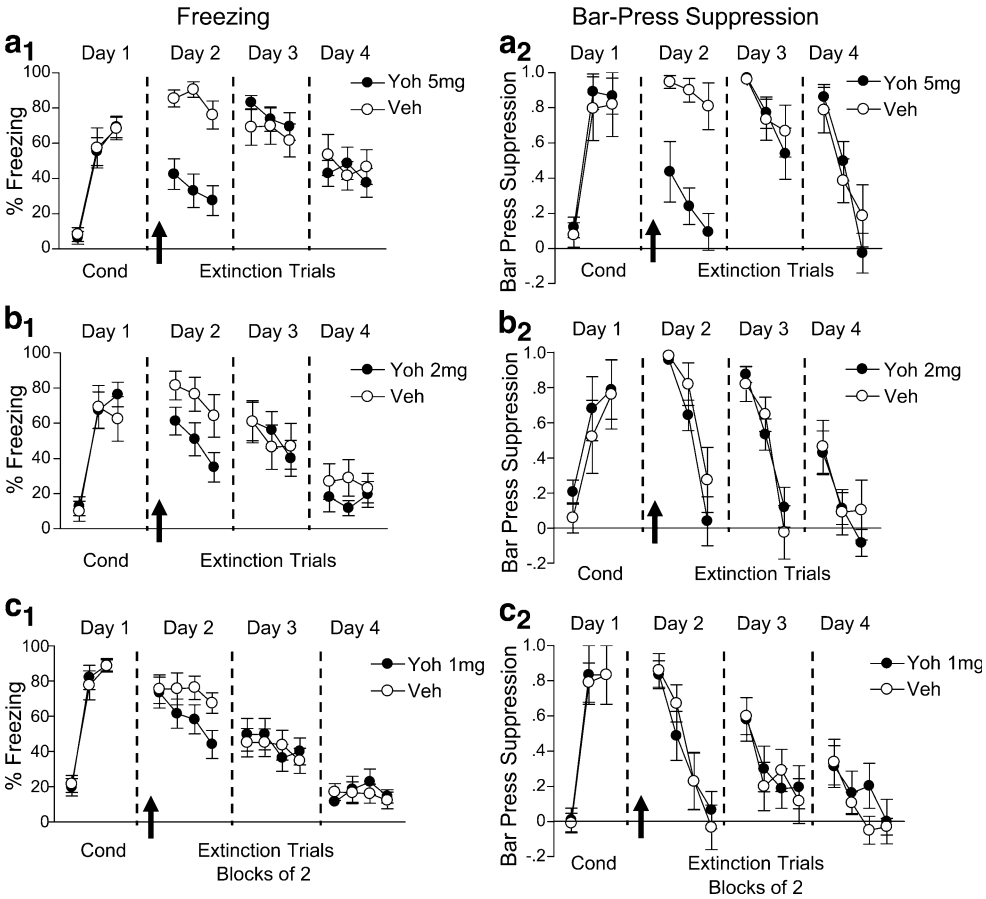


**Fig. 1** Effects of yohimbine on conditioned freezing, bar-press suppression, and long-term extinction retention as a function of dose. Freezing and bar-press suppression are depicted following a high (**a**), medium (**b**), or low (**c**) dose of yohimbine. Data are shown in blocks of two trials. *$p<0.05$

freezing response proceeded at a faster rate in yohimbine-treated rats, as evidenced by a significant group by trial interaction ($F_{7,154}=2.47$, $p=0.02$; Fig. 1c). In contrast, bar-press suppression was similar between groups (yohimbine=0.40, vehicle=0.43, $p=0.82$) and no group by trial interaction was observed ($p=0.91$), suggesting that fear expression was still intact. During a drug-free test the following day, there was no difference between groups in freezing (yohimbine=44%, vehicle=42%, $p=0.85$) or bar-press suppression (yohimbine=0.32, vehicle=0.30, $p=0.90$).

These yohimbine results are summarized in Fig. 2. Yohimbine dose-dependently reduced freezing during extinction training (Fig. 2a). In addition, we assessed the effects of yohimbine on locomotion in an open field. Yohimbine did not reduce locomotor activity at any one dose, although we observed an overall significant reduction across all doses tested ($F_{3,30}=3.67$, $p=0.02$; Fig. 2b), suggesting that yohimbine induced a mild motor impairment. To assess this possibility further, we examined the effect of yohimbine on spontaneous bar-pressing prior to the first extinction tone. Yohimbine significantly reduced bar-pressing only at the highest dose ($F_{3,65}=4.74$, $p=0.005$, Tukey's post hoc, $p=0.005$; Fig. 2c). Thus, the pronounced reduction in freezing and suppression with the 5.0 mg/kg dose of yohimbine were likely due to nonspecific effects on motivational state, rather than to a reduction in fear expression. Under no conditions did yohimbine enhance long-term extinction retention.

We examined the effects of yohimbine when extinction and testing were done in a novel chamber (ABB design) and found that rats injected with yohimbine (1.0 mg/kg, i.p.) did

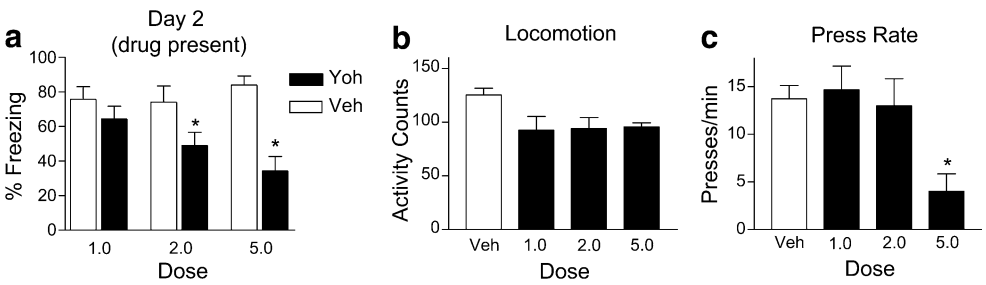


**Fig. 2** Summary of yohimbine-induced effects on freezing responses and locomotor activity. (**a**) Average freezing across trials during extinction. Effects of yohimbine on (**b**) total locomotor activity and (**c**) bar-pressing for food

not show significantly reduced freezing compared to controls (yohimbine=63%, vehicle=69%, $n$=8 and 8, $p$=0.48), although extinction of the freezing response proceeded at a faster rate in yohimbine-treated rats, as evidenced by a significant group by trial interaction ($F_{7,98}$=2.72, $p$=0.013). In contrast, bar-press suppression was similar between groups (yohimbine=0.32, vehicle=0.45, $p$=0.44; Fig. 3) and no group by trial interaction was observed ($p$=0.22), suggesting that fear expression was still intact. During a drug-free test the following day, there was no difference between groups in freezing (yohimbine=55%, vehicle=54%, $p$=0.91) or bar-press suppression (yohimbine=0.28, vehicle=0.25, $p$=0.83). Thus, yohimbine did not enhance long-term extinction retention regardless of the contextual design of the experiment.

### Amphetamine decreased freezing, but did not enhance fear extinction

We injected amphetamine (1.0 mg/kg, i.p.) prior to extinction training and observed that amphetamine-treated rats expressed lower levels of freezing on average than saline-treated rats throughout the extinction session (amphetamine=27%, saline=87%, $n$=6 and 6; Fig. 4a). ANOVA confirmed that amphetamine decreased freezing compared to saline ($F_{1,10}$=34.67, $p$<0.001) and showed that amphetamine decreased freezing responses at a faster rate than saline as indicated by a significant treatment by trial interaction ($F_{5,50}$=3.66, $p$=0.007). In contrast to freezing, bar-press suppression showed no effect of amphetamine, as there were no differences between treatment groups during extinction training (amphetamine=0.81, saline=0.87, $p$=0.66). Preserved bar-press suppression suggests that amphetamine-induced reductions in freezing are not due to reduced fear expression. In a drug-free test the next day, no differences were observed between the amphetamine- and saline-treated groups for freezing (amphetamine=57%, saline=37%, $p$=0.28) or suppression (amphetamine=0.66, saline=0.56, $p$=0.64). In an additional drug-free test (day 4), however, amphetamine-treated animals froze significantly more than saline-treated animals during the first block of two tones (amphetamine=45%, saline=15%; $t_{10}$=3.10, $p$=0.011). Thus, a single injection of amphetamine prior to extinction did not enhance long-term extinction retention, but rather partially impaired it.

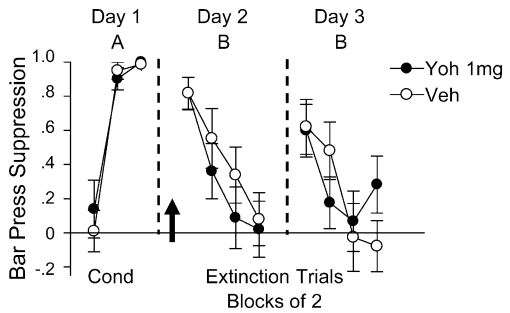


**Fig. 3** Effects of yohimbine on freezing and bar-press suppression when fear conditioning and extinction occurred in different contexts. Data are shown in blocks of two trials

Although a single injection of amphetamine did not enhance extinction, we asked whether repeated injections across multiple extinction training sessions might facilitate extinction learning. Amphetamine was administered before each of the first two extinction sessions (Fig. 4b). Amphetamine-injected rats showed significantly less freezing than controls in both the first extinction session (amphetamine=37%, saline=71%, $n$=12 and 11) and the second extinction session (amphetamine=4%, saline=45%; $F_{1,21}$=14.27, $p$=0.001). In contrast, no effects were observed for bar-press suppression during the first (amphetamine=0.69, saline=0.63, $p$=0.62) or second (amphetamine=0.37, saline=0.57, $p$=0.08) extinction sessions. When tested drug-free the following day, there was no difference in freezing (amphetamine=15%, saline=22%, $p$=0.45) or bar-press suppression (amphetamine=0.27, saline=0.27, $p$=0.98). Thus, amphetamine administered across 2 days of extinction did not enhance long-term extinction retention.

To determine whether this dose of amphetamine affected locomotion, we performed an open-field test (Fig. 4c). Amphetamine-treated rats exhibited significantly greater locomotor activity than saline-treated rats ($t_{21}$=5.15, $p$<0.001). We also examined the effect of amphetamine on bar-pressing prior to the first extinction tone (Fig. 4d). Amphetamine did not alter bar-pressing compared to saline treatment ($p$=0.44). These results, together with the lack of effect on bar-press suppression, suggest that amphetamine simply interfered with freezing responses rather than facilitating extinction learning.

## Discussion

We examined the effects of two psychostimulant drugs, yohimbine and amphetamine, on the acquisition and retention of fear extinction. In agreement with previous findings (Cain et al. 2004; Morris and Bouton 2007), we found that yohimbine reduces freezing during extinction training, suggesting a decrease in fear expression. Upon further analysis, however, we found that the apparent decrease in fear expression was not evident when examining a second measure of fear (bar-press suppression) that is less affected by baseline locomotion. At high doses, both locomotion and bar-pressing were impaired by yohimbine, suggesting that this drug induces a mild ataxia (Majczynski et al. 2006) and/or reduces motivation for exploration and food reinforcement. A reduction in exploration is consistent with the known anxiogenic-like effects of yohimbine. For

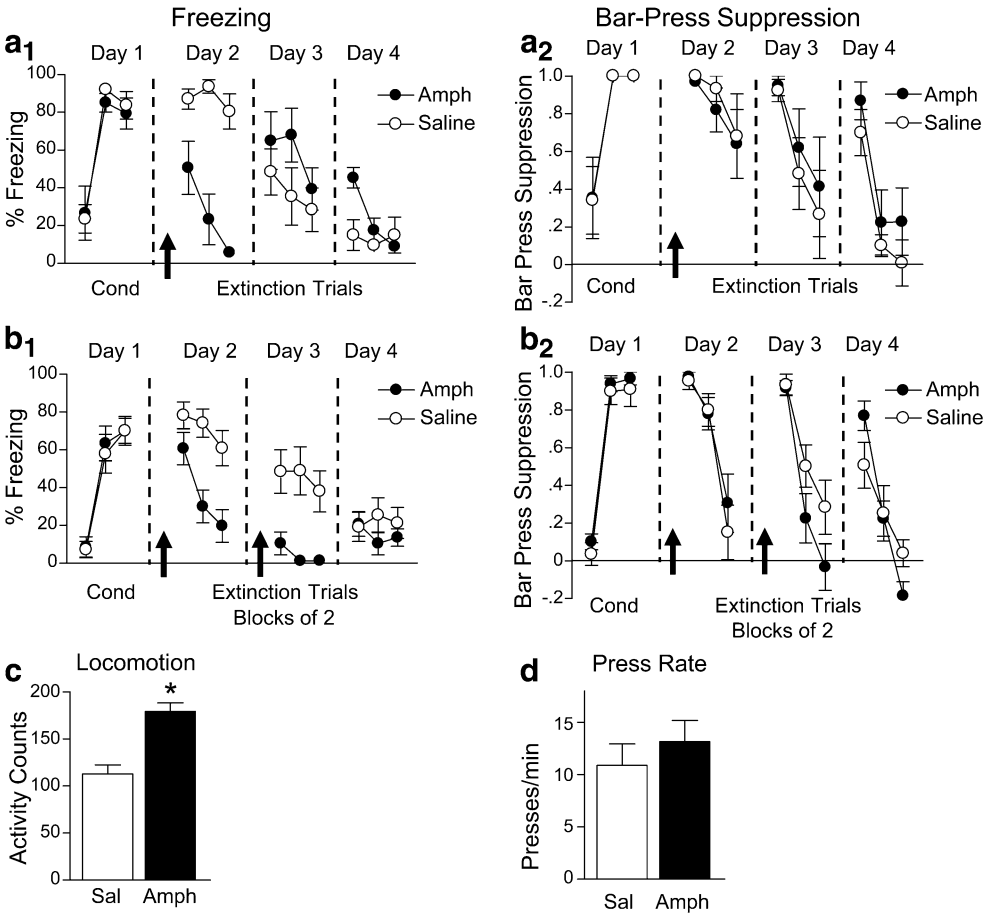


**Fig. 4** Effects of amphetamine on conditioned freezing and bar-press suppression after a single exposure of amphetamine during extinction (**a**) or exposure to amphetamine prior to each of 2 days of extinction (**b**). Effects of amphetamine on total locomotor activity (**c**) and bar-pressing for food (**d**). Data are shown in blocks of two trials. *$p<0.05$

example, systemic administration of yohimbine has previously been shown to hinder exploration of the open arms of an elevated plus-maze (Johnston and File 1989).

In our hands, yohimbine failed to enhance long-term retention of extinction at all doses examined and regardless of the contextual design. Our finding that the highest dose of yohimbine (5.0 mg/kg) was ineffective at enhancing extinction is in agreement with Morris and Bouton (2007). In that study, however, a lower dose of 1.0 mg/kg of yohimbine facilitated both acquisition and retention of extinction. We observed that this lower dose was ineffective in enhancing retention of extinction. Yohimbine has also been shown to effectively facilitate retention of extinction in mice after five extinction trials (Cain et al. 2004), but not after ten or more trials. The discrepancy between our results and those showing enhanced extinction with yohimbine (Cain et al. 2004; Morris and Bouton 2007; Hefner et al. 2008) does not appear to be due to the contextual design of the experiments. Unlike those previous studies, however, we incorporated a second measure of fear (bar-press suppression). It is possible that the appetitive motivation to bar-press for food could affect extinction learning or that the effect of food restriction alters the effectiveness of a drug (Cabib et al. 2000). It has been suggested that yohimbine increases the learning of contextual inhibition of responding to a fear-conditioned stimulus (Morris and Bouton 2007). Thus, yohimbine may be less effective in situations where the context is ambiguous. Clinically, however, it has been argued that extinction-based exposure therapy should be conducted in the original context in which the person was exposed to trauma to maximally protect them from context-induced renewal (Bouton 2002; Tobena et al. 1993).

Similar to yohimbine, amphetamine appeared to facilitate extinction acquisition, as tone-evoked freezing was rapidly reduced across trials. The lack of an effect on bar-press suppression and the large increase in locomotion, however, suggests that the reduction in freezing did not reflect a reduction in fear. Rather, freezing behavior was likely masked by amphetamine-induced hyperactivity. Furthermore, amphetamine treatment during extinction did not enhance subsequent extinction recall, indicating that this drug does not facilitate extinction. In agreement with our findings, previous research has demonstrated that amphetamine either has no effect or impairs retention of extinction in other paradigms. For instance, amphetamine did not affect retention of extinction of Pavlovian-conditioned approach when only five trials of extinction were given (Blaiss and Janak 2007). Furthermore, amphetamine was found to impair extinction retention of passive avoidance (Kumar 1971) and

of fear-potentiated startle (Borowski and Kokkinidis 1998). Thus, we conclude that amphetamine does not enhance extinction acquisition or retention at the dose used in the present study. Recently, it was shown that much lower doses of amphitamine (e.g., 0.025 mg/kg) enhance acquisition of fear to a tone in mice (Wood and Anagnostaras 2008). Perhaps very low doses of amphetamine could be used to enhance extinction.

Psychostimulant drugs enhance norepinephrine release, and high levels of norepinephrine have been associated with anxiety disorders such as post-traumatic stress disorder (Geracioti et al. 2001). Patients with this disorder exhibit resistance to extinction (Orr et al. 2000; Milad et al. 2008) and exaggerated norepinephrine release in response to traumatic stimuli (Geracioti et al. 2006), suggesting that heightened norepinephrine release may be responsible for impairing extinction learning. Furthermore, yohimbine can cause panic attacks in post-traumatic stress disorder patients (Southwick et al. 1997, 1999). Thus, increasing circulating levels of norepinephrine with psychostimulants may hinder extinction memory formation. In support of this, our data suggest that amphetamine exposure during extinction, which augments circulating norepinephrine levels, which may partially impair long-term retention of extinction. Consistent with the present results, we have recently observed that blocking noradrenergic beta-receptors with systemic propranolol did not impair (or facilitate) extinction retention (Rodriguez-Romaguera et al. 2009).

Although our data suggest that psychostimulants are not able to enhance extinction in rats, whether these drugs can serve as adjuncts for extinction-based therapy in humans remains unknown. A number of other drugs have been shown to enhance extinction retention in rodents, although research in humans is lagging. These include PEPA, an AMPA receptor potentiator (Zushida et al. 2007), and AM404, an inhibitor of endocannabinoid breakdown and reuptake (Chhatwal et al. 2005). A growing body of evidence supports the use of D-cycloserine, a partial agonist of the NMDA receptor, to enhance extinction retention in rats (Walker et al. 2002; Ledgerwood et al. 2003) and exposure therapy in humans (Ressler et al. 2004; Hofmann et al. 2006; Guastella et al. 2008). Thus, research on fear extinction is paving the way for the use of pharmacological adjuncts to exposure therapy to treat anxiety disorders.

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**Conflicts of interest** The authors have no competing conflicts of interest.

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