
Repeated Intermittent Administration of Psychomotor Stimulant Drugs Alters the Acquisition of Pavlovian Approach Behavior in Rats: Differential Effects of Cocaine, *d*-Amphetamine and 3,4-Methylenedioxymethamphetamine (“Ecstasy”)

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Background: Psychomotor stimulant drugs can produce long-lasting changes in neurochemistry and behavior after multiple doses. In particular, neuroadaptations within corticolimbic brain structures that mediate incentive learning and motivated behavior have been demonstrated after chronic exposure to cocaine, *d*-amphetamine, and 3,4-methylenedioxymethamphetamine (MDMA). As stimulus–reward learning is likely relevant to addictive behavior (i.e., augmented conditioned reward and stimulus control of behavior), we have investigated whether prior repeated administration of psychomotor stimulant drugs of abuse, including cocaine, *d*-amphetamine, or MDMA, would affect the acquisition of Pavlovian approach behavior.

Methods: Water-deprived rats were tested for the acquisition of Pavlovian approach behavior after 5 days treatment with cocaine (15–20 mg/kg once or twice daily), *d*-amphetamine (2.5 mg/kg once or twice daily), or MDMA (2.5 mg/kg twice daily) followed by a 7-day, drug-free period.

Results: Prior repeated treatment with cocaine or *d*-amphetamine produced a significant enhancement of acquisition of Pavlovian approach behavior, indicating accelerated stimulus–reward learning, whereas MDMA administration produced increased inappropriate responding, indicating impulsivity. Abnormal drug-induced approach behavior was found to persist throughout the testing period.

Conclusions: These studies demonstrate that psychomotor stimulant-induced sensitization can produce long-term alterations in stimulus–reward learning and impulse control that may contribute to the compulsive drug taking that typifies

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Key Words: Sensitization, dopamine, nucleus accumbens, amygdala, incentive motivation, drug addiction

Introduction

Repeated exposure to psychomotor stimulant drugs produces long-lasting behavioral and neuronal changes, including behavioral sensitization (Post and Rose 1976; Robinson and Becker 1986; Robinson and Berridge 1993; Taylor and Horger 1999; Vanderschuren et al 1999), neuroadaptations within the corticolimbic system (Kalivas et al 1998; Nestler and Aghajanian 1998; Robinson and Kolb 1997; Grace 1995), and alterations in learning and memory (O’Brien et al 1998; Childress et al 1993; Rogers et al 1999; Harmer and Phillips 1998) that are thought to be critical to addiction (Altman et al 1996; Leshner 1998). Such long-term changes in brain substrates involved in incentive motivational processes have been hypothesized to be a critical component of addictive behavior, because progressive enhancements of the incentive qualities of drugs, and associated stimuli, may contribute to compulsive drug-seeking and drug-taking behavior (Phillips and Fibiger 1990; Robinson and Berridge 1993; Taylor and Horger 1999; Jentsch and Taylor 1999).

The ventral striatum and associated circuitry has been argued to be an important substrate for neuronal plasticity and changes underlying these long-lasting behavioral alterations. For example, the ventral striatum and its dopaminergic innervation have been implicated in the “instrumental” response to self-administered drugs (Roberts et al 1980), and intake of psychomotor stimulant drugs increases dopamine release within the ventral striatum (Kalivas and Stewart 1991; Robinson and Berridge 1993;

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Wolf 1998). This increase in striatal dopamine efflux produced by drugs of abuse may alter corticostriatal circuitry in such a way as to promote the instrumental action to self-administer the drug.

Nevertheless, psychomotor stimulant drugs also affect neurotransmission in other brain regions, and it has been hypothesized that alterations in dopamine release in the amygdala, in particular, may be important in the abnormal affective responses to drugs and drug-related stimuli in drug addiction (Harmer et al 1997; Jentsch and Taylor 1999). It is clear that stimuli associated contingently with drug intake can develop conditioned reinforcing qualities (Arroyo et al 1998; Markou et al 1999) and precipitate craving (O'Brien et al 1998) and drug seeking (McFarland and Ettenberg 1997). It is noteworthy that drugs of abuse can enhance the acquisition of conditioned approach elicited by a stimulus associated contingently with reward availability, termed *Pavlovian approach behavior* (Hitchcott et al 1997). The ability of the reinforcer-associated (conditioned) stimulus to evoke approach behavior in rats is thought to be relevant to the control of behavior by reward-associated stimuli, and consequently, this type of learning may be the mechanism by which drug-associated cues come to maintain drug-taking behavior and elicit craving (as discussed above).

Most relevant, repeated administrations of *d*-amphetamine have been shown to augment Pavlovian learning via dopaminergic mechanisms within the amygdala (Harmer et al 1997; Harmer and Phillips 1998, 1999). Specifically, Pavlovian approach behavior was transiently enhanced 11 days after 5 days of *d*-amphetamine treatment (Harmer and Phillips 1998). Based on these results, the aim of the present study was to examine further the effects of repeated administrations of psychomotor stimulant drugs, *d*-amphetamine, cocaine, and S-(+)-3,4-methylenedioxymethamphetamine (MDMA), on the subsequent acquisition of Pavlovian appetitive approach behavior after withdrawal. Specifically, we investigated whether multiple daily drug doses would result in persistently modified behavior. These studies are critical in determining how repeated administrations of psychomotor stimulant drugs affect Pavlovian learning and/or control of behavior by reward-related stimuli.

Methods and Materials

Animals

Experimentally naive male Sprague-Dawley rats (Charles River, Portage, ME) with initial weights of 200–250 g were used as subjects. All subjects had food continuously available for the duration of the experimental periods. During the drug administration and withdrawal period, the subjects had water available *ad libitum*; however, two days prior to the start of Pavlovian approach training, subjects were restricted to 30-min access to

water per day. During the testing period, water was also available in the home cage for 30 min, beginning 1 hour after the end of the Pavlovian appetitive approach testing session (see below). All rats gained ~5% body weight per week, reaching body weights of ~350–400 g at the end of the experiment. Experimental protocols were approved by the Yale University School of Medicine Animal Care and Use Committee, and all procedures were in accordance with the NIH "Guide for the Care and Use of Animals."

Drugs

d-Amphetamine sulfate, MDMA hydrochloride (Research Biochemicals Inc., Natick, MA) and cocaine hydrochloride (National Institute on Drug Abuse, Rockville, MD) were dissolved in 0.9% sterile saline and administered by intra-peritoneal injection. All injection volumes were 1.0 mL/kg. Cocaine (15–20 mg/kg) was given once or twice daily for 5 days. *d*-Amphetamine (2.5 mg/kg) was given once or twice daily for 5 days. MDMA (2.5 mg/kg) was given twice daily for 5 days. Time between drug treatment and testing was 7 days. Rats receiving saline injections on identical schedules were always used as control subjects.

Apparatus

Four aluminum operant chambers (12 × 8 × 10 inches) with grid floors were used (ENV-008CT, Med Associates Inc., E. Fairfield, VT). Each chamber was housed in a soundproof outer chamber (24 × 24.5 × 16 inches) equipped with a white noise generator and ventilating fan to minimize external noise. A liquid dipper (0.06 mL cup size) delivered water as the reinforcer into the magazine. Head entries were detected by a photocell above the reinforcer receptacle. Above this magazine was a 2.5-W, 24-V light. The chamber was illuminated by a light mounted on the back wall. A Sonalert tone (10 kHz) generator, which could emit a 65-dB tone above background noise, was mounted above the magazine. A Personal Computer with a Med Associates, Inc. (Georgia, VT) interface and software controlled the boxes.

Pavlovian Appetitive Approach Behavior

Training began after the 7-day post-drug interval. Behavior (head entries) was recorded with a photocell-equipped magazine. On the first day, 5-sec access to 0.06 mL water (the unconditioned stimulus [US]) was available in the dipper on a fixed time, 15-sec (FT-15) schedule; the session ended after the delivery of 50 reinforcers. For the second (30-min) daily session, 0.06 mL of water was made available for 5-sec periods on a FT-15 schedule, and now, head entries during the inter-US interval resulted in the FT-15 schedule being reset, resulting in a delay of subsequent reinforcement. Beginning on the third day, the subjects received 30 pairings of a 5-sec conditioned stimulus (CS; light + tone) followed immediately by 5-sec access to 0.06 mL of water; the CS + US pairings were delivered on a random time, 30-sec (RT-30) schedule. As before, head entries during the RT-30 interval (termed "inappropriate" head entries) resulted in a 3-sec delay, during which time no reinforcement was given, followed

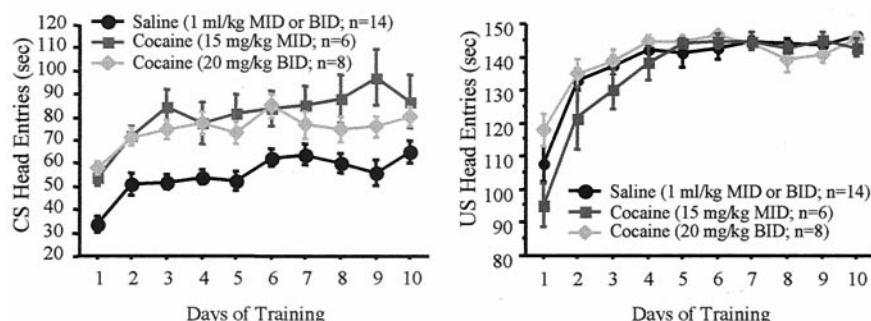


Figure 1. Repeated exposure to 15 mg/kg/day cocaine {MID} (dark gray squares) or 20 mg/kg/twice daily {BID} (light gray diamonds) produced a statistically significant increase in approach to the Conditioned Stimulus (CS) (head entries in sec, left) but not Unconditioned Stimulus (US) (right), relative to saline-treated control rats (black circles). Overall repeated measures analysis of variance revealed a significant main effect of treatment and day-by-treatment interaction ($p < .0001$). Data is shown for daily test sessions of Pavlovian approach training, which began 7 days after the final drug treatment. Data is presented as Mean $\pm$ S.E.M.

by a return to the RT-30 schedule. Training on this schedule is known to result in a discriminated pattern of approach to the head entry magazine during CS + US, but not during "inappropriate" times (see Olmstead et al 1998). Moreover, the CS becomes established as a conditioned reinforcer because of its contingent relationship with the US (Robbins 1977; Taylor and Robbins 1984).

Statistical Analysis

Dependent measures included total duration of head entries (in sec) during the cumulative 5-sec CS ("appropriate"), 5-sec US, or non-CS + US ("inappropriate") times. Repeated measures analysis of variance (training day being the repeated measure) were used to determine group effects and any interactions for any of these dependent measures; post hoc tests (Tukey-Kramer and Scheffe's tests) were used, where appropriate, to determine significant differences after analysis of variance (ANOVA) revealed any main effects or interactions.

Results

Subchronic Exposure to Cocaine or d-Amphetamine Augments Pavlovian Learning

Initial analysis revealed no significant differences between the once-daily and twice-daily saline-treated rats, so these groups were combined for subsequent analyses, resulting in five treatment groups (saline, once-daily cocaine, twice-daily cocaine, once-daily d-amphetamine, twice-daily d-amphetamine). Overall repeated measures ANOVA on CS approach during the first 10 days of training indicated a highly significant main effect of treatment [$F(4,36) = 8.36, p < .0001$] and a significant treatment $\times$ training day interaction [$F(36,324) = 2.92, p < .0001$], as shown in Figure 1. Post hoc analyses (Tukey-Kramer test) revealed that both the once- and twice-daily cocaine regimens and the twice-daily d-amphetamine treatment increased CS approach relative to the saline-exposed control rats, as

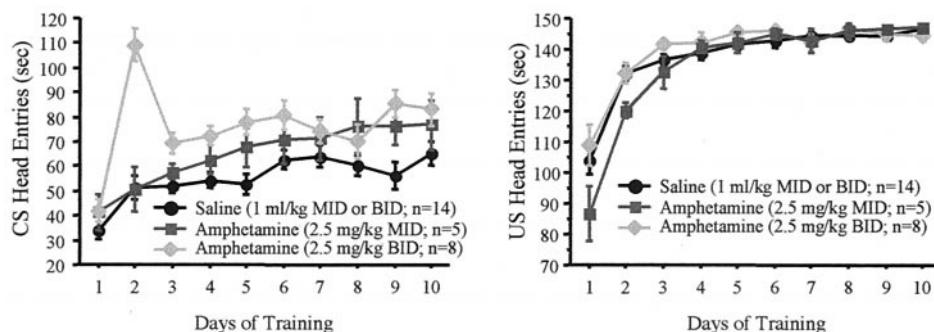


Figure 2. Repeated exposure to 2.5 mg/kg/day amphetamine {MID} (dark gray squares) or 2.5 mg/kg/twice daily {BID} (light gray diamonds) produced a statistically significant increase in approach to the Conditioned Stimulus (CS) (head entries in sec, left) but not Unconditioned Stimulus (US) (right), relative to saline-treated control rats (black circles). Overall repeated measures analysis of variance revealed a significant main effect of treatment and day-by-treatment interaction ($p < .0001$). Data is shown for daily test sessions of Pavlovian approach training given 7 days after the final treatment. Data is presented as Mean $\pm$ S.E.M.

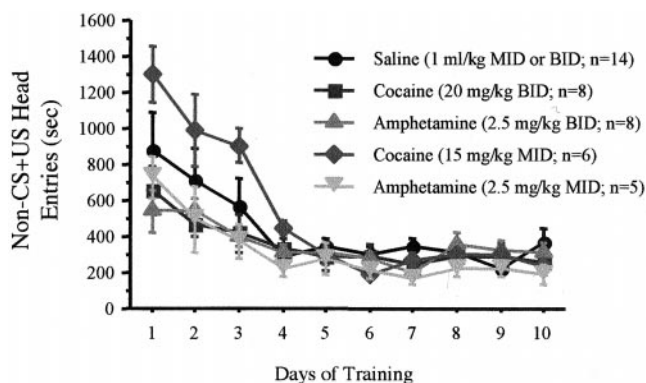


Figure 3. Repeated exposure to once-daily cocaine (light gray diamonds), twice-daily cocaine (dark gray squares), once-daily *d*-amphetamine (light gray upside-down triangles), or twice-daily *d*-amphetamine (light gray triangles) did not significantly alter head entries into the magazine during the non-conditioned stimulus + unconditioned stimulus (non-CS+US) ("inappropriate") times. Subjects were those as for Figures 1 and 2. Data is shown for daily test sessions of Pavlovian approach training given 7 days after the final treatment. Data is presented as Mean $\pm$ S.E.M.

shown in Figures 1 and 2. In contrast, no drug treatment regimen affected US approach, indicated by a lack of main effect of treatment [$F(4,36) = 1.78, p = .15$]; see Figures 1 and 2. Moreover, head entries into the magazine during the non-CS + US ("inappropriate") times were not significantly affected by drug treatment [$F(4,36) = 1.13, p = .35$], as shown in Figure 3.

Further post hoc analyses (Scheffe's test) revealed that the increases in CS approach were not just specific to the first days of training. Rather, CS approach was significantly elevated in the once-daily cocaine group on days 1–9 (Figure 1), in the twice-daily cocaine group on days 1–6 and 8–9 (Figure 1), and in the twice-daily *d*-amphetamine group on days 2–6 and 7–10 (Figure 2). This suggests that both the acquisition of CS approach, as well as some degree of performance under an established CS–US association, were potentiated by stimulant treatment.

Repeated Administrations of S-(+)-3,4-Methylenedioxymethamphetamine Preferentially Modify Inappropriate Head Entries

One week after the final of 10 subchronic doses of MDMA (2.5 mg/kg), rats were evaluated for acquisition of Pavlovian approach behavior, as shown in Figure 4. Overall ANOVA revealed no significant effect of treatment on head entries during the CS period [$F(1,14) = 1.68, p = .21$; Fig. 4A] or US period [$F(1,14) = 0.02, p = .87$; Fig. 4B]; however, inappropriate head entries were significantly elevated at all non-CS + US times [$F(1,14) =$

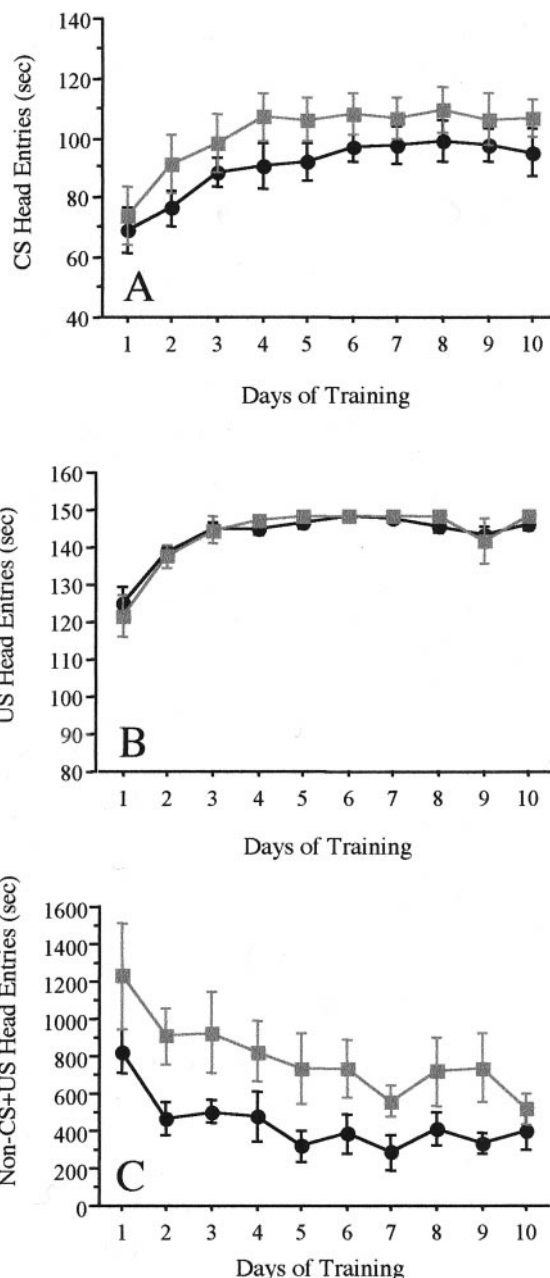


Figure 4. Repeated exposure to subchronic S-(+)-3,4-methylenedioxymethamphetamine (MDMA) (2.5 mg/kg/day) did not significantly affect head entries during the Conditioned Stimulus (CS) (panel A) or Unconditioned Stimulus (US) period (panel B) but inappropriate head entries were significantly elevated at all non-CS + US times ($p < .05$; panel C). Data is shown for daily test sessions of Pavlovian approach training given 7 days after the final treatment. There were eight subjects in each group. Data is presented as Mean $\pm$ S.E.M.

4.69, $p < .05$; Fig. 4C]. Thus, although the acquisition of CS approach was equivalent in saline- and MDMA-treated rats, the normal decrement in approach to the reward receptacle at inappropriate times exhibited by control subjects was not evident in MDMA-exposed rats.

Discussion

The current results demonstrate that the acquisition of appetitive Pavlovian approach behavior is modified in rats that had previously been treated with multiple doses of psychomotor stimulant drugs. Here we found that cocaine and *d*-amphetamine selectively augmented the acquisition of Pavlovian approach behavior to a CS that was contingently associated with water reward, whereas MDMA produced an impaired ability to diminish approach to the magazine, despite the negative consequences of this inappropriate behavior. These effects were found to be robust during learning of the CS–US association, as well as persistent throughout the testing period. These data suggest that withdrawal from repeated administrations of psychomotor stimulant drugs may produce neuroadaptations within the corticolimbic circuit that result in greater control of behavior by reward-related stimuli (cocaine and *d*-amphetamine) and/or inefficient regulation of behavior (MDMA). This increase in stimulus control of behavior likely results not only from enhanced Pavlovian learning (as demonstrated here) but also from augmentation of the reinforcing properties of stimuli associated contingently with the delivery of reinforcement (e.g., Taylor and Horger 1999) and impaired inhibitory modulation of conditioned responding (Jentsch and Taylor 1999).

Neural Circuits Underlying Acquisition of Pavlovian Approach

Recent studies have implicated the basolateral and central nuclei of the amygdala in the acquisition of appetitive Pavlovian approach behavior (reviewed in Everitt et al 1999). Parkinson et al (2000) demonstrated that lesions of the central, but not basolateral, nucleus of the amygdala impair acquisition of conditioned approach behavior. In addition, the anterior cingulate cortex and the nucleus accumbens core are implicated in the development of the conditioned approach response, and it has been hypothesized that mesocorticolimbic dopamine neurons connect the central nucleus of the amygdala with these anterior forebrain sites (Everitt et al. 1999).

Whereas lesions of the basolateral nucleus do not impair acquisition of conditioned approach behavior, manipulations of dopaminergic transmission within this site does affect appetitive Pavlovian learning. Post-training infusions of *d*-amphetamine or 7-OH-DPAT, a dopamine

D3-preferring agonist, enhance the acquisition of appetitive Pavlovian approach (Hitchcott et al 1997; Hitchcott and Phillips 1998). In contrast, pretraining infusions of 7-OH-DPAT into the basolateral nucleus do not affect this form of CS–US learning (Hitchcott et al 1997; Hitchcott and Phillips 1998). Thus, the basolateral nucleus of the amygdala has a complex involvement in Pavlovian learning and/or in the consolidation of memory about Pavlovian relationships.

Relationship to Conditioned Reinforcement

Previously, we demonstrated that subchronic cocaine exposure resulted in increased instrumental responding for a second-order (conditioned) reinforcer (Taylor and Horger 1999). In this experiment, animals were first trained on the CS–US association, subsequently drug-treated, and then tested for the acquisition of a new instrumental response for the conditioned reinforcer after withdrawal from the drug. These data were interpreted to indicate that subchronic cocaine administration had facilitated the control over behavior by the conditioned reinforcer in a manner similar to that produced by intra-accumbens administrations of *d*-amphetamine or dopamine (Taylor and Robbins 1984, 1986; Cador et al 1991); however, the current data also demonstrate that subchronic administration of *d*-amphetamine or cocaine can affect the development of the Pavlovian association that subsequently supports the conditioned reinforcing properties of the CS.

The ability of a conditioned reinforcer to support instrumental learning is a process that is thought to depend on the basolateral nucleus of the amygdala (Burns et al 1993) and its projections to the nucleus accumbens core (Parkinson et al 1999). In contrast, the modulation of the incentive salience of the conditioned reinforcer appears to depend on dopaminergic function within the nucleus accumbens shell (Taylor and Robbins 1984; Parkinson et al 1999). Taken with these findings, our results indicate that subchronic administration of psychomotor stimulant drugs can affect incentive learning and conditioned reinforcement in a manner that implicates drug actions within the basolateral and central nucleus of the amygdala, as well as the core and/or shell regions of the nucleus accumbens.

Possible Involvement in Impulsivity

We previously hypothesized that dysfunction of the frontal cortex could contribute to increased control of behavior by reward-related stimuli and that this may contribute to impulsivity in drug addicts (Jentsch and Taylor 1999). Lesions of the frontal cortex were previously found not to affect the acquisition of a new instrumental response for conditioned reinforcement (Burns et al 1993) but to

potentiate responding for cocaine and for cocaine-associated conditioned cues (Weissenborn et al 1998). It is notable in this regard that repeated administrations of MDMA were found to have no effect on acquisition of CS approach, but rather, to result in increased head entries during non-CS + US times (relative to saline-treated control rats) despite the negative consequences of this behavior. This suggests that the inhibitory modulation of the unconditioned or conditioned component of the approach response may be impaired, possibly implicating frontal cortical dysfunction. Similar behavioral effects have been found after withdrawal from repeated treatment with the psychotomimetic drug of abuse phencyclidine hydrochloride (PCP) (Jentsch et al 2000; Jentsch and Taylor 1999).

Summary and Conclusions

These studies indicate that the psychomotor stimulant drugs cocaine and *d*-amphetamine can affect appetitive Pavlovian learning in a manner that may have relevance to drug addiction. The reported effects of MDMA also suggest that some patterns of drug treatment may also produce deficits of the inhibitory modulation of reward-related behavior. These results clearly indicate that drugs of abuse can affect behavioral processes that contribute to addiction, including stimulus-reward learning and control of behavior by reward-associated cues, as well as behavioral inhibition. Furthermore, our results suggest that different drugs may influence these processes in diverse ways, giving rise to the distinct patterns of and factors that contribute to drug-taking behavior, effects possibly related to dissociable pharmacological and/or neuroanatomical mechanisms of actions of these drugs.

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