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Exploratory Studies in Sensory Reinforcement in Male Rats: Effects of Methamphetamine

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Abstract

Understanding sensory reinforcement and the effects of stimulant drugs on sensory reinforcers is potentially important for understanding their influence on addiction processes. Experiment 1 explored the reinforcing properties of a visual stimulus and the effects of methamphetamine (METH) on responding maintained by a visual reinforcer (VRF) in male rats. Snout poke responses to the active alternative produced the VRF according to variable interval (VI) schedules of reinforcement, and responses to an inactive alternative had no programmed effect. Experiment 2 explored the effects of METH on choice between the VRF and a water reinforcer (H₂ORF) using concurrent VI schedules in male rats. In Experiment 1, response-contingent onset of the VRF produced an increase in both the relative frequency and absolute rate of active responding. The rate of both active and inactive responding declined across the 40-min test sessions. METH did not differentially enhance active responding for the VRF. Instead, METH nondifferentially increased the rate of responding and attenuated the within-session decline of responding. In Experiment 2, METH differentially increased the rate of responding for the VRF relative to the H₂ORF. The results of these exploratory experiments indicate that the reinforcing effects of the VRF were weak and transient. In addition, METH treatment increased responding, and the specificity of the enhancement of METH was dependent upon the testing conditions. Potential explanations of these differences, such as novelty and reinforcer type, are discussed.

Keywords

novelty; drug abuse; operant conditioning; rats; learning

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There is a large older literature that describes research into the primary reinforcing effects of sensory stimuli, such as visual cues, which are not usually thought of as primary reinforcers (Kish, 1966; Tapp, 1969). An example of a sensory reinforcer that does not affect homeostatic balance is response-contingent onset, offset, and incremental changes in illumination, which have all been shown to increase the frequency of responding (for reviews, see Berlyne, 1969; Eisenberger, 1972; Kish, 1966; and Tapp, 1969). The intrinsic reinforcing properties of sensory stimuli may be overlooked because they are very weak reinforcers when compared with other primary reinforcers such as food and water (H₂O). Further, when used in association with more powerful primary reinforcers, the conditioned discriminative and reinforcing effects of these stimuli are considered to be more important determinants of behavior than the intrinsic “weak” primary reinforcing effects of sensory reinforcers. However, in the case of drugs of abuse, the primary reinforcing effects of sensory stimuli may play a more important role.

There is evidence that stimulant drugs increase the reinforcing efficacy of sensory reinforcers and that sensory reinforcers may play a role in the acquisition and maintenance of drug-reinforced responding. Systemic injections of both amphetamine (Glow & Russell, 1973a, Glow & Russell, 1973b, Glow & Russell, 1974; Gomer & Jakubczak, 1974; Winterbauer & Balleine, 2007) and nicotine (NIC; Palmatier et al., 2007; Raiff & Dallery, 2009) increase the rate of responding for visual stimuli. According to these studies, the reinforcing effects of sensory reinforcers may be amplified by stimulant drugs. In a recent study, we reported that operant responding for a response-contingent visual reinforcer (VRF) is related to locomotor activity in a novel environment and that both of these measures predict acquisition of methamphetamine (METH) self-administration (Gancarz, San George, Ashrafioun, & Richards, 2011). Caggiula et al. (2002) have completed a series of self-administration (SA) studies in rats indicating that nicotine and visual reinforcers, when presented together, have synergistic effects such that the reinforcing value of the combination is greater than the sum of the two when presented alone. They hypothesized that nicotine increases the reinforcing value of other reinforcers and that the effectiveness of nicotine as a reinforcer is due, in part, to its ability to increase the value of other reinforcers (for reviews, see Caggiula et al., 2002, and Chaudhri et al., 2006).

As was noted above, the reinforcing effects of sensory reinforcers such as visual stimuli are weak. However, weak sensory reinforcers are ubiquitous in the natural environment. Because they are so widespread, the importance of the role of sensory reinforcers in guiding behavior may be underappreciated. Recently, Redgrave and colleagues (Redgrave & Gurney, 2006; Redgrave, Gurney, & Reynolds, 2008) have proposed that phasic firing of dopamine (DA) neurons observed after the presentation of novel sensory stimuli (e.g., light onset) enables organisms to learn about “action–outcome routines under circumstances in which the outcome has no immediate benefit” (Redgrave & Gurney, 2006, p. 971). According to this approach, the phasic firing of DA neurons immediately following the unexpected occurrence of novel sensory stimuli is an important component of a neural system that allows organisms to learn about casual relationships between stimuli and the responses that produced them. This action–outcome learning does not depend upon the occurrence of biologically important reinforcers such as food or water. It is possible that the DA mediated action–outcome system described by Redgrave et al. (Redgrave & Gurney, 2006; Redgrave, Gurney, & Reynolds, 2008) is a component of the neural basis of sensory reinforcement. Since the action–outcome learning system described by Redgrave and colleagues (Redgrave & Gurney, 2006; Redgrave, Gurney, & Reynolds, 2008) is DA-mediated, it would be expected to be sensitive to the effects of stimulants drugs such as METH that increase dopaminergic neurotransmission. Such a system may also underlie the synergistic interaction between nicotine and sensory reinforcers reported by Caggiula and colleagues (Caggiula et al., 2002; Chaudhri et al., 2006).

The two studies reported here examined the within- and between-sessions patterns of responding maintained by a response-contingent onset of a light and the disruption of these response patterns by METH. In these studies, METH was administered noncontingently and the sensory reinforcer was the onset of light presented on variable interval (VI) schedules of reinforcement in an otherwise dark operant test chamber.

Experiment 1: Responding for a Visual Reinforcer—Effects of METH

Experiment 1 examined the acquisition of responding for a VRF and also tested the effects of various doses of systemically administered METH on responding maintained by the VRF. In this experiment, we determined if treatment with METH would differentially increase responding for the active response that produced the VRF relative to the inactive alternative response that had no programmed effect. In addition, we examined the within-session pattern of responding and the effects of METH on this pattern of responding.

Rats were preexposed to a dark test chamber with two snout poke apertures. Following preexposure, responding to the active snout poke alternative caused a 5-s illumination of the chamber, while responding to the inactive alternative had no programmed consequence. From a previous experiment (Gancarz et al., 2011), we knew that this visual stimulus, used under these conditions, would be a reinforcer. The effects of the response-contingent VRF and the effects of METH on active and inactive snout poking were examined.

Method

Subjects—Sixteen naïve Holtzman Sprague-Dawley (Harlan) male rats, weighing between 400 and 450g at the time of testing, were used. The rats were housed in pairs in plastic cages in a colony room on a 12-hr light–dark cycle. Testing took place once per day during the light cycle, 7 days a week. The rats were water-restricted but had constant access to food. Thirty-min access to water was given in the home cage at the end of each test session. The study was conducted in accordance with the guidelines set up by the Institutional Animal Care and Use Committee of the State University of New York at Buffalo.

Apparatus—Sixteen experimental chambers, previously been described in detail (Richards, Mitchell, de Wit, & Seiden, 1997), were used for the experiment. These chambers have stainless steel grid floors, aluminum front and back panels, and Plexiglas sides and tops. Two snout poke apertures, which can also be used as H₂O dispensers, are located on either side of the test panel. The test chambers were located inside of sound and light-attenuating boxes with wall-mounted fans that provided ventilation and masking noise. The VRF used in the experiment was the onset of two lights: (a) one of the lights was located above and midway between the two snout poke apertures, and (b) the other was located in the middle of the back wall of the test chamber. Onset of VRF produced a total of 68-lux light, as measured in the center of the test chamber. Snout pokes were monitored with infrared photo sensors located in snout poke apertures. The chambers were connected to a computer using a MED Associates interface. MED PC[®] programming language was used for programming of the experimental contingencies.

Drug—Sterile 0.9% saline was used to dissolve (+) methamphetamine hydrochloride (Sigma, St. Louis, Missouri). A constant injection volume of 1.0 ml/kg was used. METH doses were calculated as salts. Saline and doses of the drug (0.125 mg/kg, 0.25 mg/kg, 0.5 mg/kg, and 1.0 mg/kg) were injected intraperitoneally (IP) 30 min prior to the start of each session.

Procedure

Preexposure (Sessions 1–10)—During preexposure, rats were placed in the dark testing chambers for 10 daily 40-min sessions. Responses to both snout poke apertures were recorded, but there were no programmed consequences associated with either aperture.

Concurrent (Conc) VI 2- or 12-min VRF/Extinction (Ext) (Sessions 11–20)—The length of the test sessions was increased to 50 min. The rats were placed into the testing chambers, and responses to the active snout poke alternative produced a VRF according to either a VI 2-min ($n = 8$) or a VI 12-min ($n = 8$) schedule of reinforcement. The VI schedules were reproduced from a list of 20 intervals generated using Fleshler-Hoffman progressions (Fleshler & Hoffman, 1962). During the test session, the computer selected intervals from this list without replacement. The first response after the interval elapsed resulted in presentation of the visual stimulus (VS) and another VI value was then selected from the list. The response-contingent VRF was 5-s illumination of the test chamber. Additional responses to the active lever during the 5-s stimulus presentation did not have any effect, and the VI timer was paused until the end of the stimulus presentation. Responding to the inactive alternative did not produce any programmed consequence, but responses were recorded (Ext). The active alternative was counterbalanced so that half of the rats received the VRF presentation on the left side of the test panel and the other half received the VRF presentation on the right side of the test panel.

Conc VRF/Ext and METH (Sessions 21–30)—Responding to either of the two alternatives produced the same consequences as in the previous concurrent VRF/Ext phase. An A-B-C design was employed such that the pattern of injections across sessions was as follows: (a) saline injection, (b) METH injection, and (c) no injection. This pattern of injections resulted in a METH injection every third test session. On METH-injection days, the rats were injected with ascending doses of METH (0.125, 0.25, 0.5, and 1.0 mg/kg).

Data analysis—The dependent variables were active responding, inactive responding, and the relative frequency of active responding (i.e., $\text{Active}/[\text{Active} + \text{Inactive}]$ or preference for the active alternative). In order to achieve equal variances between groups, active and inactive responding was transformed to log form. There were no between-group differences in responding in the two VI schedules during any of the phases. As a result, data from the two VI schedules were combined for all further statistical analyses. Data from preexposure and response-contingent VRF phases of the experiment were analyzed in terms of 2-day session blocks. Two-day session blocks were calculated as the average of consecutive sessions (e.g., Sessions 1 and 2, 3 and 4, etc.). In the METH administration phase, data for saline are the overall average of each of the saline injection sessions. Least significant difference tests were used for post hoc analysis.

Results

Preexposure

During the preexposure phase, snout poke responding showed a between-session decline (Figure 1a). Responding during the 10-day preexposure phase was analyzed using a two-factor within-subject analysis of variance (ANOVA), with response alternative (active and inactive) and session (2-day session blocks) as the factors (the active alternative during the preexposure phase was the side designated as active during the response-contingent VRF phase). Snout poking to both the active and inactive alternatives decreased across the five 2-day session blocks, $F(4, 60) = 19.142$, $p < .001$. There was no significant interaction between response alternative and session.

In contrast to the between-session declines in absolute response rate, the relative frequency of responding to the active side remained at approximately 50% throughout the 10 days of preexposure (Figure 1b). The relative frequency of active responding during preexposure was analyzed using a one-way ANOVA, with the five 2-day session blocks as the within-subject factor. There was no significant effect of session.

As indicated above, responding decreased between sessions as the animals were repeatedly exposed to the test chamber. Similarly, responding also decreased within sessions. Figure 2a shows the within-session pattern of responding during the 40-min preexposure sessions in 10-min epochs. There was a clear decline in responding from the beginning to the end of the test sessions. The within-session pattern of responding was analyzed with a two-factor 2×4 repeated measures ANOVA with response (active or inactive) and epoch (four 10-min session epochs) as the factors. This analysis produced a significant effect of epoch, $F(3, 39) = 17.31$, $p < .000$. There was no main effect for response or interaction between response and epoch. Taken together with the results shown in Figure 1a, these results indicate that the rats showed both between- and within-session declines in the snout poke response during the preexposure phase.

Concurrent (Conc) VI 2- or 12-Min VRF/Ext

The response-contingent VRF increased active responding but had no effect on the Ext alternative (Figure 1a). VRF and Ext responding was averaged across the 10 days of Conc VRF/Ext. These averages were compared to the average VRF and Ext responding during the last 2 days of preexposure using a two-factor within-subject ANOVA, with response alternative (active and inactive) and sessions (preexposure and response-contingent VRF) as the factors. There was a significant interaction between response alternative and session, $F(1, 15) = 55.16$, $p < .001$. Post hoc tests indicated that VRF responding was significantly increased ($p < .001$), while Ext responding remained unchanged.

The relative frequency of VRF responding peaked at a constant value of approximately 0.7, indicating a preference for the VRF alternative (Figure 1b). The relative frequency of VRF responding was averaged across the 10 days of Conc VRF/Ext. This average was compared to the average relative frequency of VRF responding during the last 2 days of preexposure using a t test. The relative frequency of VRF responding was significantly increased by the response-contingent VRF ($p < .001$).

As was observed in the preexposure phase, responding decreased within sessions during the Conc VRF/Ext phase. Figure 2b indicates that there was a within-session decline in responding to both the VRF and Ext alternatives. The within-session pattern of responding was analyzed with two-factor repeated measures ANOVA, with response type (VRF or Ext) as the independent variable and epoch (five 10-min session blocks) as the repeated measure. This analysis produced a significant effect of epoch, $F(4, 60) = 40.53$, $p < .001$, and response type, $F(3, 39) = 8.19.31$, $p < .001$, with no significant interaction. Figure 2 indicates that VRF and Ext responding declined across the 10 epochs in a parallel fashion; however, the animals responded at a higher frequency to the VRF alternative compared with the Ext alternative.

Conc VRF/Ext & Dose Response of METH

METH dose dependently increased responding from baseline to both the VRF, $F(4, 60) = 10.936$, $p < .001$, and the Ext alternatives, $F(1, 60) = 7.078$, $p < .001$ (Figure 3a). Post hoc tests indicated that VRF and VRF responding were significantly increased from baseline at the 0.25-, 0.5-, and 1.0-mg/kg ($p < .01$) doses of METH but not at the 0.125 mg/kg dose. The relative rate of responding to the VRF alternative remained unaffected across doses

(Figure 3b), indicating that METH increased the rate of responding to both alternatives in a proportional fashion.

A detailed examination of the within-session pattern of VRF and Ext responding was performed for the saline and the 0.25- and 1.0-mg/kg doses of METH (see Figure 4). The within-session pattern of responding was analyzed at these doses using two-factor repeated measures ANOVA, with response type (VRF or Ext) as the independent variable and epoch (5 10-min session blocks) as the repeated measure. All three doses produce significant effects of response type (saline, $F(1, 60) = 11.684$, $p < .000$; 0.25 METH, $F(1, 60) = 25.590$, $p < .00$; 1.0 METH, $F(1, 60) = 10.079$, $p < .00$) and epoch (saline, $F(4, 60) = 28.27$, $p < .00$; 0.25 METH, $F(4, 60) = 5.95$, $p < .00$; 1.0 METH, $F(4, 60) = 3.57$, $p < .01$), with no significant interactions between response type and epoch across the three doses. Figure 4 shows clear decreases in both VRF and Ext responding following saline and METH injections; however, it appeared that within-session decreases in responding across the session following METH injections may have occurred less rapidly than decreases following saline injections.

In order to determine if VRF and Ext responding declined less rapidly after METH injections the VRF and Ext responding data for saline, 0.25- and 1.0-mg/kg-treated animals were plotted as the proportion of total responses that occurred in each of the five 10-min epochs in Figure 5. This transformation to proportion allows comparisons to be made between saline and drug that are independent of the rate increasing effects of amphetamine. Since the proportions must sum to 1.0, this analysis describes how the animals distributed their responding across the test session independently of the absolute rate of responding.

VRF and Ext responding at the 0.25 and 1.0 METH doses were then compared to saline responding using a two-factor repeated measures ANOVA, with METH dose (saline VRF, 0.25 mg/kg, or saline VRF, 1.0 mg/kg) as the independent variable and epoch (five 10-min session blocks) as the repeated measure. This analysis produced significant interactions between saline and METH for both VRF (0.25 METH, $F(4, 60) = 8.36$, $p < .001$; 1.0 METH, $F(4, 60) = 9.38$, $p < .001$) and Ext (0.25 METH, $F(4, 60) = 18.50$, $p < .001$; 1.0 METH, $F(4, 60) = 19.40$, $p < .001$) responding. Post hoc tests indicated that METH decreased the proportion of responses that occurred in the first 10 min of the session and increased the proportion of responses that occurred during minutes 20 to 39 of the session. This analysis clearly indicated that both doses of METH disrupted the within-session decrease in both VRF and Ext responding.

Discussion

In summary, these results demonstrate that response-contingent onset of a light for 5 s on a VI schedule of reinforcement increased the rate of VRF responding and that the VRF did act as a primary reinforcer. However, the reinforcing effects of the VRF were weak. Responding was increased from about 20 responses (rs)/40 min at the end the preexposure phase to approximately 50 rs/50 min during Sessions 7 and 8 of the Conc VRF/Ext phase. Furthermore, the reinforcing efficacy of the light rapidly decreased both between and within test sessions. There was a clear decline in responding between test sessions. After achieving a peak of approximately 50 rs/50 min, the rate decreased between sessions to an average of approximately 35 rs/50 min during the drug testing (no injection and saline data). In contrast, the relative frequency of VRF responding did not decrease after reaching a peak about 0.7 on Sessions 5 and 6 of the response-contingent phase, indicating that the VRF maintained its relative strength as a reinforcer. There were also marked within-session declines in both VRF and Ext responding. As is indicated in Figure 2b, VRF responding declined from approximately 20 responses (in the first 10 min of the test session) to

approximately five responses (in the last 10 min of the test sessions). Similarly, Ext responding declined from approximately 10 responses in the first 10 min of the test session to approximately three responses during the last 10 min of the session. The low rates of responding obtained and the between- and within-session declines in responding indicate that the effects of the VRF were weak and transient.

METH dose dependently increased the rate of VRF and Ext responding in a proportional fashion, so that the relative frequency remained unchanged. This result indicates that METH did not differentially increase responding for the VRF. Rather, METH effects can be best described as nonselectively amplifying both VRF and Ext responding. Interestingly, METH decreased the within-session decline in both VRF and Ext responding.

Experiment 2: Choice Between Visual and Water Reinforcers—Effects of METH

In Experiment 1, we found that the VRF was a weak transient reinforcer that showed both within- and between-session decreases in reinforcing strength. Furthermore, we found that METH increased the rate of both active and inactive responding but did not differentially increase the rate of responding for the VRF. A parsimonious interpretation of this result would be that METH induced a general increase in motor output. An alternative interpretation would be that snout poking into both the active and inactive holes was maintained by sensory reinforcers. For example, the tactile stimulation (including the vibrissae contact) produced by the snout poking was reinforcing. The active snout poke hole was more reinforcing because it produced the additional sensory stimulation provided by the VRF. If this were the case, then the results of Experiment 1 could be explained by postulating a METH-induced increase in the reinforcing strength of the sensory reinforcers in general. However, this cannot be differentiated from the more parsimonious general increase in motor output explanation.

Experiment 2 was designed to further characterize the reinforcing strength of the VRF by giving the animals a choice between a VRF and a qualitatively different water reinforcer (H₂ORF) using concurrent VI schedules of reinforcement, thus giving the animal a choice between a sensory reinforcer and a biologically important reinforcer that alters homeostatic balance. A similar concurrent VI procedure was used by Reed, Mitchell, and Nokes (1996) to reveal the intrinsic reinforcing properties of light onset. The objective of the current experiment was to determine the reinforcing efficacy of a VRF relative to a H₂ORF and to determine if METH had differential effects on H₂O and visual reinforcers.

Method

Subjects and apparatus—Thirty naïve Holtzman Sprague-Dawley (Harlan) male rats with the same characteristics as those described in the first experiment were used for Experiment 2. The apparatus and the availability of food and water were the same as described in the first experiment.

Drug—The drug, preparation, and route of administration remained the same as described in the first experiment.

Procedure

Concurrent (Conc) VI 12-min H₂O/Ext (Sessions 1–16)—Responding to one of two available snout poke holes was reinforced by 25 µl H₂O available on a VI 12-min schedule of reinforcement, while responding to the other snout poke hole had no programmed consequences (Ext). All 30 of the rats were trained on this procedure for 16 50-min test

sessions. The active alternative was counterbalanced so that half of the rats received H₂O on the left side and the other half received H₂O on the right side of the test panel.

Conc VI 12 min H₂O/VI 1-min VRF (Sessions 17–26)—During this phase, test sessions were reduced to 40 min. Responding to the H₂O alternative remained the same as described in the previous phase of the experiment. The animals were divided into three groups ($n = 10$). For two of these groups, a VRF was available according to a VI 1-min schedule of reinforcement for responding to the previous Ext alternative. The VRF was the same as the VRF used in Experiment 1. In addition, one of these VRF groups (H₂O & VRF METH) received IP injections of 0.5 mg/kg METH 30 min prior to each test session. The other VRF group (H₂O & VRF METH) received saline. The third group remained on the Conc VI 12-min H₂O Ext schedule and was injected with 0.5 mg/kg METH (H₂O & Ext METH).

Data analysis—The dependent variables were frequency of responding to the two separate response alternatives and the relative frequency of responses to the non-H₂O alternative. Thus, for the H₂O & VRF condition, the relative frequency was calculated as $VRF/(VRF + H_2O)$, and for the H₂O & Ext condition, the relative frequency was calculated as $Ext/(Ext + H_2O)$. In order to achieve equal variances between groups, response frequencies were transformed to log 10 form. Data from all 26 test sessions of the experiment were analyzed in terms of 2-day session blocks, as described in Experiment 1. Least significant difference tests were used for post hoc analysis.

Results

Conc VI 12-Min H₂O Ext

In all three plots shown in Figure 6, the portion of the plots to the left of the vertical dashed line show responding on the Conc VI 12-min H₂O Ext schedule of reinforcement for 16 sessions. The portion of the plots to the right of the dashed line show responding after introduction of METH, saline, and/or the VRF.

Separate two-way mixed ANOVAs, with group as the between-subjects factor and session as the within-session factor, were conducted on the relative frequency of VRF or Ext responses (Left portion of Figure 6a), VRFs or Ext responses/40 min (left portion of Figure 6b), and H₂ORF responses/40 min (left portion of Figure 6c) during Conc VI 12-min H₂O Ext phase. All three ANOVAs produced significant main effects of session for the relative frequency of VRF or Ext responses (left portion of Figure 6a), $F(7, 189) = 20.898$, $p < .001$, VRFs or Ext responses/40 min (left portion of Figure 6b), $F(7, 189) = 30.887$, $p < .001$, and H₂ORF responses/40 min (left portion of Figure 6c), $F(7, 189) = 20.898$, $p < .001$, but no significant effects of group or interaction effects. This analysis indicates that the relative frequency (or proportion) of responses to the Ext alternative (Figure 6a) decreased during the Conc VI 12-min H₂O Ext phase. This change in relative frequency occurred as a function of a small decrease in the rate of responding to the Ext alternative (Figure 6b) coupled with a larger increase in responding to H₂O alternative (Figure 6c).

Conc VI 12-Min H₂O VI 1-Min VRF

In all three plots shown in Figure 6, the portion of the plots to the right of the vertical dashed line show responding after introduction of the VRF and/or METH and saline. For the data shown in Figure 6a, the relative frequency of responding of all three groups was averaged across the 10 days of the Conc H₂O & VRF phase and compared to the last 2-day block of the previous Conc H₂O Ext phase using a two-way mixed ANOVA, with group and session as factors. This analysis produced a significant interaction between group and session, $F(2,$

27) = 18.843, $p < .001$. Post hoc analysis revealed a significant within-group increase in relative frequency compared to the last 2-day block of the H₂O-alone phase only in the H₂O & VRF METH group ($p < .001$). Between-groups post hoc analysis indicated the relative frequency of the H₂O & VRF METH group was significantly greater than both the H₂O & VRF Saline and H₂O & Ext METH groups ($p < .05$), and that the H₂O & VRF Saline group was not different from the H₂O & Ext METH group. These results indicate that introduction of the combination of VRF and METH injections increased the relative frequency of responding for the VRF in the H₂O & VRF METH group compared with animals in the H₂O & Ext METH and H₂O & VRF Saline groups.

The portion of Figure 6b to the right of the dashed vertical line shows the results for absolute rates of responding to the VRF or Ext alternative. For the data shown in Figure 6b, the rate of responding to the VRF or Ext alternative for all three groups was averaged across the 10 days of the Conc H₂O & VRF or Ext phase and compared to the last 2-day block of the previous Conc H₂O Ext phase using a two-way mixed ANOVA with group and session as factors. This analysis produced a significant interaction, $F(2, 27) = 18.384$, $p < .001$. Post hoc analysis indicated that the source of this interaction was a between-group increase in the absolute rate of responding to the H₂O & VRF METH group compared with animals in the H₂O & Ext METH and H₂O & VRF Saline groups ($p < .001$). There was also a small but significant within-group increase in responding to VRF or Ext alternative in all three groups (Figure 6b).

The portion of Figure 6c to the right of the dashed vertical line shows the results for absolute rates of responding to the H₂O alternative. For the data shown in Figure 6c, the rate of responding to the H₂O alternative for all three groups was averaged across the 10 days of the Conc H₂O & VRF or Ext phase and compared to the last 2-day block of the previous Conc H₂O Ext phase using a two-way mixed ANOVA, with group and session as factors. This analysis produced a significant interaction between group and session, $F(2, 27) = 25.613$, $p < .001$. Post hoc analysis revealed a significant within-group increase in the rate of responding compared to the last 2-day block of the H₂O alone phase only in the H₂O Ext METH group ($p < .001$). Between-groups post hoc analysis failed to find between-group differences in the rate of H₂O responding. This analysis indicated that the source of the significant interaction was an increase in the rate of responding only in the H₂O & Ext METH group. The pattern of responding for the H₂O reinforcer was markedly different from that observed for the relative and absolute rates of responding for the alternative that produced the VRF shown in Figures 6a and 6b. Overall, this pattern of results indicated that METH differentially affected responding for VRF and H₂O reinforcers.

The within-session pattern of responding on the Conc VI 12-min H₂O VI 1-min VRF is shown in Figure 7. The relative frequency of VRF responding indicated the same within-session decline as was observed in Experiment 1 (Figure 7a). A two-factor mixed ANOVA with group and epoch as factors produced a significant interaction between group and epoch, $F(8, 108) = 2.99$, $p < .01$. Post hoc tests comparing the H₂O & VRF METH group with the H₂O Ext METH group at each of the five epochs indicated significantly greater relative frequencies at all five epochs. In contrast, the H₂O & VRF Saline group had a significantly greater relative frequency at only the first epoch (first 8 min) of the test session. An identical analysis of the absolute rate of VRF responding produced similar results (Figure 7b). A significant interaction between group and epoch was found, $F(8, 108) = 4.96$, $p < .001$. Post hoc tests indicated that the H₂O & VRF METH group had significantly greater rates of responding than the H₂O Ext METH at all five epochs but that there were no significant differences between the H₂O & VRF Saline group and the H₂O Ext METH group at any of the five epochs.

The within-session pattern of responding for H₂ORF was very different from the within-session pattern of responding for the VRF (Figure 7c). There was no within-session decrease in the rate of H₂O responding as was observed for the rate of VRF responding. Instead of decreasing, the rate of responding to the H₂ORF alternative increased from the first epoch (Minutes 1–8 of the session) to the epochs 2 and 3 (Minutes 9–24 of the session) of the test session. A two-factor mixed ANOVA with group and epoch as factors produced a significant effect of epoch, $F(4, 108) = 9.70$, $p < .001$, and no significant effect of group or the interaction between group and epoch. Post hoc testing indicated a significant quadratic contrast for the epoch, $F(1, 27) = 39.53$, $p < .001$, indicating that the change in the rate of responding across epochs for the H₂ORF had an inverted “U” shape, which differed markedly from the pattern of within-session declines in response rate observed for the VRF.

Discussion

The most important result of Experiment 2 was that treatment with METH increased choice of the VRF relative to a H₂ORF reinforcer, consistent with a differential increase in the reinforcing efficacy of the VRF. METH-induced increases in choice of the VRF were reflected by increases in both the relative frequency of responding for the VRF and the absolute rate of responding for the VRF. At the same time, the rats treated with saline showed only small increases in responding following presentation of the VRF on concurrent responding for the VRF and H₂ORF. In contrast, depending on the group, METH either did not affect or increased the absolute rate of concurrent responding for the H₂ORF. A rate-dependency explanation, where a low rate responding for the VRF was increased in comparison to the higher rate responding for the H₂ORF, is unlikely because METH had a much greater effect on responding for the VRF alternative in the H₂O & VRF METH group than responding for the EXT alternative in the H₂O & EXT METH group, and baseline rates of responding during the water only phase were equal for these two groups. The reinforcing effects of the VRF were weak in comparison to the water reinforcer, particularly in the saline treated rats, and showed both within- and between-session declines in responding. Within- and between-session declines in responding were not observed in responding for the H₂ORF.

General Discussion

Past research into sensory reinforcement included broad classes of sensory stimuli and behaviors, including visual, auditory, locomotor exploration, and manipulation (Eisenberger, 1972; Kish, 1966). The initial study of operant responding for a visual reinforcer was an effort by a graduate student (John Girdner) to arrange a situation in which an organism could make a precisely measured operant response that would produce novel environmental change. Girdner considered the response measured in this situation as being analogous to locomotor and orienting investigatory responses that expose organisms to novel environmental change (as described by Kish, 1966, p. 111). From this perspective, making an operant response to produce a light can be thought of as a convenient way to precisely measure exploratory behaviors. The within- and between-session habituation of light-reinforced responding observed in the current study is consistent with the hypothesis that light-contingent responding is an investigatory behavior, since a similar pattern of habituation is observed in exploratory activity measured in open fields and various mazes (Eisenberger, 1972). In fact, in support of Girdner's speculation, we have found that locomotor activity in a novel environment predicts acquisition of light-reinforced responding (Gancarz et al., 2011).

Glow (1985) and, more recently, Redgrave and colleagues (Redgrave & Gurney, 2006, Redgrave et al., 2008) have argued that sensory reinforcement provides a way for animals to

learn about their environment in absence of biologically important reinforcers that are important for maintaining homeostasis. Glow (1985) hypothesized that *control* is the essential function of sensory reinforcement. He speculated that sensory reinforcement has biological utility because it allows the organism to develop a schema of the relationship between its behavior and environmental events. According to Glow's (1985) hypothesis, updating this schema is intrinsically rewarding. In a similar vein, Redgrave and colleagues (Redgrave & Gurney, 2006; Redgrave et al., 2008) have recently hypothesized that sensory reinforcement allows organisms to learn about unpredicted sensory events for which the organism is responsible, and to discover what new responses are required to make these events happen. The observation that the VRF used in this study was weak and transient is consistent with the hypothesis that the purpose of sensory reinforcement is to enable organisms to learn about unpredicted sensory events. After all, once an animal has learned that a particular response produces a stimulus, there is no longer any utility in repeating the response. In contrast, there is much utility in maintaining responding for reinforcers such as water that are important for maintaining homeostatic balance. The weak and transient nature of sensory reinforcers is not indicative of the functional importance of sensory reinforcers for enabling organisms to successfully interact with their environment.

The within- and between-session declines in responding for the VRFs conform to several of the important characteristic of habituation described by Rankin et al. (2009). The within-session decreases in responding are consistent with habituation due to the repeated presentation of the VRF. Additionally, the increase in responding observed at the start of each new test session is consistent with spontaneous recovery of the previously habituated VRF, due to its absence. (The same can be said for patterns of responding observed during the preexposure phase of Experiment 1, where the animals appear to be habituating to the test chambers.) The process of habituation was originally used to describe reflexes; however, more recently, it has also been used to describe operant responding. McSweeney and Murphy (2009) have argued that within-session declines in operant responding observed with food and water reinforcers can be best understood in terms of habituation to the sensory properties of these reinforcers. Epstein, Temple, Roemmich, and Bouton (2009) have argued that habituation to the sensory effects of consumable stimuli is an important determinate of meal size. Both of these authors have argued that the effects of sensory stimuli on operant responding and consumption of palatable reinforcers cannot be explained in terms of a simple satiation effect. In the case of the VRF studied in this paper, satiation due to energy intake is not a possible explanation of the rapid within-session declines in responding. An important implication of a role for habituation to the sensory effects of stimuli in determining the rate of operant responding and meal size is that the reinforcing effectiveness of biologically important homeostatic reinforcers such as food and water may be partially determined by sensory reinforcement.

Effects of Methamphetamine on the Reinforcing Strength of the Visual Reinforcer

Redgrave and colleagues provide a specific account of the nervous systems role in sensory reinforcement (Redgrave & Gurney, 2006; Redgrave et al., 2008). According to these authors, sensory-driven dopaminergic responses provide reinforcement signals for the learning of action-outcome associations. They argue that the phasic DA responses evoked by novel stimuli provide a signal independent of normal goal-directed reward systems (food, drink, temperature, sex, etc.) that reinforces acquisition of the behavioral "building blocks" necessary for novel sequences of autonomous goal-directed action to be generated. This hypothesis suggests that understanding the interaction between sensory reinforcement and stimulant drugs that enhance dopamine neurotransmission may be important for understanding the effects of these drugs on behavior.

Overall, the results indicate that METH differentially increased the reinforcing efficacy of the VRF in Experiment 2 but not in Experiment 1. There are several possible explanations for the difference in results between Experiment 1 and Experiment 2. First, METH may have increased the strength of both the programmed visual sensory reinforcer available for active responding and the unprogrammed sensory reinforcer(s) that were available for both active and inactive responding. Second, METH may have differential effects on sensory and biologically important reinforcers such as water so that METH increased the strength of the VRF more than the H₂ORF. Third, METH may have differential effects on novel and familiar reinforcers. These possibilities are discussed.

Our finding that METH had a much greater effect on responding for the VRF alternative in the H₂O & VRF METH group than responding for the EXT alternative in the H₂O & EXT METH group (Experiment 2) indicates that rate dependency does not provide a good explanation of the results, since baseline rates of responding during the water-only phase were equal for these two groups. This same differential effect of METH also suggests that a simple motor-increasing effect of METH does not explain the results of Experiment 2. Although small METH-induced increases in responding to both the EXT and H₂O alternatives were observed, these effects were not of the same magnitude as those observed for responding to the VRF alternative in the H₂O & VRF METH group. The differential effect of METH on the VRF alternative is particularly striking when the relative frequency of responding is examined. In contrast, there is no evidence of a differential effect of METH in the H₂O & EXT METH group when measured as a relative frequency.

The absence of a METH-induced selective increase in responding in Experiment 1 may be explained as a general stimulant-induced motor activation. However, this interpretation is incompatible with the differential effects of METH on responding for the VRF in Experiment 2. An alternative interpretation is that snout poking into both the active and inactive holes was maintained by sensory reinforcers, and that METH treatment increased responding for both active and inactive responding in a proportional fashion. According to this interpretation, the active snout poke hole was more reinforcing only because it produced the additional sensory stimulation provided by the VRF. There was some indirect evidence that snout poking was reinforced by the sensory feedback that it generated (which was observed during the preexposure phase of Experiment 1). The operant level (snout poking without any programmed consequences) showed the same between- and within-session declines as was observed for the responding for VRF. Further support for this interpretation is provided by studies that have shown that kinesthetic feedback of lever-pressing can be reinforcing. For example, insertion of a lever into a test cage led to lever depressions despite lack of a programmed consequence (Schoenfeld, Antonitis, & Bersh, 1950). In another study, rats made more contact with a bar that was movable than one that was rigid, leading to the conclusion that the kinesthetic consequences of bar pressing alone are reinforcing (Kish, 1966). Similarly, snout-poking into a hole without a programmed consequence may be reinforcing because of the stimulation resulting from contact with the hole. METH-induced increases in responding may therefore be due to a general amplifying of the reinforcing effects of sensory reinforcers associated with both the active and inactive alternatives (Experiment 1). However, postulating a general stimulant-induced increase in the reinforcing effects of sensory stimuli is not distinguishable at the behavioral level from postulating a general stimulant-induced motor activation.

It is important to identify the conditions in Experiment 2 that allowed for a selective increase in the reinforcing strength of the VRF. There is insufficient evidence to make strong inferences about the interesting possibility of differential effects of METH on the strength of sensory and biologically important reinforcers such as water. In general, it has been found that stimulant drugs such as d-amphetamines decrease operant responding for food at doses

that increase locomotor activation (Cole, 1978). Although these studies generally emphasize the anorexic effects of amphetamines, the increase in locomotion is consistent with an amphetamine-induced increase in sensory reinforcement. Corwin and Schuster (1993) compared the effects of d-amphetamines on choice between a visual reinforcer and food in rhesus monkeys. The sensory reinforcer was visual access to the laboratory in which the monkeys were housed. Using a discrete trials procedure, the monkeys made 100 choices between food and visual access. They found that lower doses of d-amphetamine increased responding for the visual reinforcer and decreased food intake. The authors interpreted these results as indicating amphetamines had anorexic effects. However, it is also possible to explain this pattern of results by hypothesizing an amphetamine-induced increase in the reinforcing strength of the sensory reinforcer. In the present experiment, where water was used as the reinforcer, METH increased responding for water in rats that had a choice between water and extinction. In the group that had a choice between the water and the visual stimulus, responding for water was unchanged. This pattern of results is not consistent with the interpretation that METH decreased the reinforcing strength of water. Rather, the results are consistent with the interpretation that METH increased the reinforcing strength of the visual stimulus. Further research that takes into account the possible confounds, such as novelty, in the present experiment is needed.

Novelty may have been an important or determining factor in the differential effects of METH on the reinforcing strength of the VRF in Experiment 2. In Experiment 1, the VRF was familiar at the time of drug testing, whereas, in Experiment 2, the VRF was novel and the H₂ORF was familiar at the time of drug testing. There is evidence that novelty plays an important role in determining an organism's behavioral response to psychomotor stimulants such as METH (Badiani et al., 1998; Caprioli et al., 2007). Administration of d-amphetamine in a novel environment (in comparison to a familiar environment) results in differential activation of the cortex, caudate, and nucleus accumbens (NAC; Badiani et al., 1998). There are a number of reports indicating that novel visual stimuli activate dopamine neurons in the ventral tegmental area (VTA) and dopamine release in the NAC (Ungless, 2004; Young, Moran, & Joseph, 2005). There is also evidence that psychomotor stimulants retard the normal habituation of DA neurons that occurs as novel stimuli become familiar. Di Chiara (2002) has hypothesized that DA release caused by drug reinforcers, such as METH, prevent the NAC shell from habituating to drug-associated stimuli. Perhaps the combination of a novel VRF and METH has a synergistic effect on DA transmission in the NAC, leading to an enhancement of the reinforcing efficacy of the novel visual reinforcer. In comparison, familiar visual reinforcers would not be expected to cause DA release in the NAC shell. As a result, the amplifying effects of METH on DA may be greater for novel VRFs than for familiar VRFs, resulting in a selective facilitation of responding for a novel VRFs. For example, in Experiment 2, the VRF was novel in the H₂O & VRF METH group, whereas the stimuli available to the H₂O & EXT METH group were familiar. It is possible that METH differentially affected responding for the novel VRF, which caused larger increases in the absolute and relative rates of responding for the novel VRF.

The within- and between-session decreases in responding for the VRF observed in this study may represent habituation to the effects of VRF on DA as the VRF became more familiar. However, it is clear that the reinforcing effects of VRFs are not entirely due to novelty. There is evidence indicating that visual reinforcers maintain reinforcing efficacy, although reduced, after they became familiar. In the current studies, we presented the VRF for only 10 to 20 test sessions, but other studies have maintained responding with visual reinforcers for much longer periods of time (Glow, 1985; Raiff & Dallery, 2009; Stewart & Hurwitz, 1958). It is likely that sensory reinforcers have guiding effects on behavior for indefinite periods of time.

Comparison of the Effects of Methamphetamine and Nicotine on Responding for VRFs

It is of interest to compare and contrast the results of current experiments with recent studies that have examined the effects of nicotine on responding for visual reinforcers (Caggiula et al., 2002; Chaudhri et al., 2006). There are many differences that make comparisons difficult. Differences include (a) the current experiment used METH instead of nicotine, (b) many of the nicotine studies (although see Palmatier et al., 2007, and Raiff & Dallery, 2009) administer nicotine intravenously rather than with experimenter delivered systemic injections, and (c) large differences in procedure. The studies with nicotine used bar pressing while the current experiments used snout poking. In general, the studies with nicotine initially trained animals to bar press using food rewards, followed by extended training for the VRF (without food) over many weeks and months with a fixed interval (FI) 1-min fixed-ratio (FR) 5 schedule of reinforcement (Palmatier et al., 2007). In contrast, the experiments described in this article did not use food reinforcers during initial training, used a snout poke response, were of shorter duration, and used VI schedules of reinforcement. The current studies used procedures such as habituation to the test chamber prior to introduction of the VRF, and VI schedules of reinforcement, which may have accentuated the novelty of the VRF. In the nicotine studies, the animals were undergoing extinction of the food-reinforced response when the VRF was introduced, confounding any effect there may have been of novelty.

Despite these procedural differences, there are several comparisons that are of interest. Based on their results, Palmatier et al. (2007) hypothesized that the nicotine would enhance the reinforcing efficacy of strong reinforcers more than weak reinforcers. In Experiment 2, this hypothesis was tested (for METH) by allowing the rats to choose between a visual stimulus of weak reinforcing value and a H₂ORF of greater reinforcing value. Under these conditions, METH increased the reinforcing efficacy of the weak visual reinforcer while leaving the reinforcing efficacy of the H₂ORF unchanged. This result is a direct contradiction of the Palmatier (2007) hypothesis, although nicotine and METH potentially use different mechanisms to enhance reinforcing efficacy.

A second possible difference is that we observed within-session declines in responding that were partly reversed by METH. Within-session decreases in responding for visual reinforcers have not been reported in the nicotine studies. The within-session decline in responding for visual reinforcers (perhaps indicating habituation) is important because it may be an important clue in understanding the effects of stimulants on responding for visual reinforcers.

Finally, in Experiment 1, we found that METH increased the absolute rate of active responding but did not change the relative rate of active responding. Frenk and Dar (2004) speculated that the effects of nicotine on the reinforcing efficacy of visual stimuli are due to the general activating effects of nicotine on response output rather than a specific increase in the reinforcing value of the VRF. An increase in the relative rate of active responding for the VRF is an important indicator of a selective effect of drug on the reinforcing efficacy of the VRF. For example, an animal with a baseline of 100 active and 10 inactive responses prior to drug injection may increase to 200 active and 20 inactive responses by the drug injection, a substantial increase in the absolute rate of active responding. However, the relative rate of responding (active/[active + inactive]) is .91 in both cases, indicating that there was no selective effect of the drug on active responding. Rather, the drug amplified both active and inactive responding equally. Examination of papers reporting the effects of nicotine on active and inactive responding for a VRF suggest that although the effects of nicotine on the rate of active responding are much greater, small increases in inactive responding are often observed. Because of the low rates of inactive responding, the effects of drugs on inactive responding may be proportionally equivalent. For these reasons, it is important to analyze

relative frequency, as well as absolute rates of responding, particularly since (as is pointed out by Frenk & Dar, 2004), in many studies, the rats are pretrained with food to respond on the active alternative. Such training may have long-lasting effects that are proportionally enhanced by the activating effects of nicotine.

Conclusions

The reinforcing effects of sensory stimuli, although apparently weak compared to more biologically important reinforcers, may be important determinants of behavior because they are ubiquitous and have fundamentally important effects on the ability of organisms to successfully interact with their environment. If stimulant drugs alter the reinforcing efficacy of sensory stimuli, the control exerted by these stimuli over behavior would be increased, making them an even more powerful determinant of behavior. Increasing evidence suggests that drugs of abuse may have the ability to increase the reinforcing properties of sensory reinforcers. Increases in the reinforcing efficacy of sensory stimuli induced by drugs of abuse may be an important component of drug addiction. Further research is needed in order to understand the interaction between sensory reinforcement and drug abuse.

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Figure 1.

Performance during light reinforcement testing. Closed squares indicate responses to the response alternative that resulted in VRF (light onset in an otherwise dark test chamber). Open circles indicate responses to the Ext alternative (no programmed consequences). (a) VRF and Ext responding declined during the 10-day preexposure period, and introduction of the response-contingent light increased VRF but not Ext responding. (b) During the 10-day preexposure period, the relative frequency of VRF responding (VRF Rs/[active Rs + Ext Rs]) was approximately 0.5. Introduction of the response-contingent light increased the relative frequency of VRF responding. For both a and b, data are the means ($\pm$ SEM) of 2-

day session blocks. AVG represents the mean of the 10-response-contingent test session. * Significantly different from the final 2-day session block of preexposure ($p < .05$).

Figure 2.

Within-session responding during light reinforcement testing. Closed squares indicate responses to the response alternative that resulted in VRF (light onset in an otherwise dark test chamber). Open circles indicate responses to the Ext alternative (no programmed consequences). Data are within-session VRF and Ext responding in 10-min epochs. (a) Data are the mean ($\pm$ SEM) VRF and Ext ($\pm$ SEM) responses (Rs) from the final 2-day session block of the Preexposure phase. (b) Data are the mean ($\pm$ SEM) VRF and Ext responses during the 10 test sessions of Conc VRF/Ext phase.

Figure 3.

Effects of systemic METH injections on responding for a light reinforcer. Closed squares indicate responses to the alternative that resulted in VRF (light onset in an otherwise dark test chamber). Open circles indicate responses to the Ext alternative (no programmed consequences). (a) Both VRF and Ext responding were dose-dependently increased by METH. (b) There was no effect of METH on the relative frequency of VRF responding. For both a and b, data are the means ($\pm$ SEM). NI is the average of three sessions in which no injection was given. Saline is the average of the four sessions in which saline was given. *Significantly different from NI ($p < .05$).

Figure 4.

Effects of METH on within-session responding during light reinforcement testing. Closed squares indicate responses to the alternative that resulted in VRF (light onset in an otherwise dark test chamber). Open circles indicate responses to the Ext alternative (no programmed consequences). (a) Data for rats injected with saline. (b) Data for rats treated with 0.25 mg/kg METH. (c) Data for rats treated with 1.0 mg/kg METH. Data are the means ($\pm$ SEM) of VRF and Ext responding in 10-min epochs of the 50-min test sessions.

Figure 5.

Effects of METH on within-session responding during light reinforcement testing. The left panels illustrate within-session proportion of responses to the VRF alternative. The right panels illustrate within-session proportion of responses to the Ext alternative. (a) Within-session performance between saline and 0.25 mg/kg METH-treated rats. Closed squares indicate rats injected with saline; open squares indicate rats injected with 0.25 mg/kg METH. (b) Within-session performance between saline and 1.0 mg/kg METH-treated rats. Closed squares indicate rats injected with saline; open squares indicate rats injected with 1.0 mg/kg METH. In all plots, the data are the means ($\pm$ SEM) of the proportion of the responses in each 10-min epoch. * Significant difference in the proportion of responses between saline and METH-treated rats.

Figure 6.

Effects of METH injections on responding for concurrent H₂O and VRF/Ext. The dashed line indicates the point in testing at which the VRF and METH were introduced. Closed squares illustrate rats preinjected with METH when tested for performance on Conc H₂O & VRF. Open circles indicate rats preinjected with saline when tested for performance on H₂O & VRF. Closed triangles illustrates rats preinjected with METH when tested for performance on Conc H₂O & Ext. (a) These data illustrate the relative frequency (proportion) of responding for VRF. The relative frequency of VRF responding was significantly increased only in the H₂O & VRF METH group. (b) These data illustrate the absolute rate of responding for the VRF. VRF responding was increased only in the H₂O & VRF METH Group C. These data illustrate the absolute rate of responding for the H₂ORF. H₂ORF responding was increased only in the H₂O & Ext METH group. In all plots, the data are the means ($\pm$ SEM). AVG is the mean of the 10 days of testing during the Conc H₂O & VRF phase. *Significant within-group difference between the last 2-day block of testing on the Concurrent (Conc) VI 12 min Ext schedule of reinforcement and AVG. **Significant between group difference of AVG.

Figure 7.

Effects of systemic METH injections on within-session responding for concurrent H₂O and VRF/Ext. Closed squares illustrates rats preinjected with METH when tested for performance on Conc H₂O & VRF. Open circles illustrate rats preinjected with saline when tested for performance on H₂O & VRF. Closed triangles illustrate rats preinjected with METH when tested for performance on Conc H₂O & Ext. (a) Top panel shows relative frequency of VRF responses. (b) Middle panel shows VRF responses across the session. (c) Bottom panel shows H₂ORF responses across the session. METH-treated rats (H₂O & VRF METH) showed increases in both the relative frequency (a) and absolute rates of responding (b) compared to saline-treated rats (H₂O & VRF Saline) and rats treated with METH that were not exposed to the VRF (H₂O & Ext METH). In saline treated rats (H₂O & VRF

Saline), the VRF affected the relative frequency of responding only during the first 8 min of the 40-min test sessions (a). In all plots, the data are the mean ($\pm$ SEM) within-session active and inactive responding in 8-min epochs averaged over the 10 days of testing during the Conc H2O & VRF phase. *Significant between-group differences.