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Short report

The discriminative stimulus effects of nicotine & ethanol with two distinct olfactory contexts in male and female rats

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ABSTRACT

Odor cues and interoceptive cues can combine in promoting drug seeking behavior. Drug discrimination methodology was combined with odor-context conditioning in 8 male and 8 female rats. One drug (nicotine or EtOH) plus odorant (peppermint or anise) compound functioned as setting the occasion for sessions of food-reinforced nose poke responses (i.e., the S^D) that were maintained on a variable interval 30 s schedule (VI-30), whereas the opposite drug (EtOH or nicotine) plus odorant (anise or peppermint) compound predicted intermixed sessions of non-reinforcement of nose poking (i.e., the S^Δ). During brief non-reinforcement tests conducted with each condition there was significantly greater responding under the S^D drug plus odor compound compared to the S^Δ drug plus odor compound. Discriminative control was evident and there was a sex by stimulus role interaction with greater S^Δ responding in females. The odor contexts and drug contexts alone also sustained strong stimulus control but to a lesser extent compared to the full drug-odor compounds. These data suggest configural learning among drug and odor cues.

1. Introduction

Drug states in animals promote interoceptive changes in the nervous system that can function in directing behavior that is motivated by biologically relevant outcomes (e.g., food, water, shock-escape, and sexual copulation, drug reward) (e.g., Troisi and Akins, 2004). The operant drug discrimination procedure has been a staple behavioral assay in this regard for evaluating "subjective" experience (i.e., interoception) (Troisi, 2013a, b). Previously, this laboratory reported several associative phenomena evident with the discriminative stimulus effects of drugs including: Pavlovian-instrumental transfer (Troisi, 2006), feature positive and negative learning (Troisi and Akins, 2004), context renewal (Troisi, 2003b; Troisi and Craig, 2015), configural learning with drug mixtures (Troisi et al., 2013); transfer across operants (Troisi et al., 2010), extinction and spontaneous recovery (Troisi, 2003a,b; Troisi, 2011), reinforcer devaluation (Troisi et al., 2012), and modulation of complex operant chains (Troisi et al., 2013). Of course, exteroceptive contextual stimuli (lights and tones) also function as discriminative stimuli that facilitate voluntary responding (i.e., S^D) and/or inhibit responding (i.e., S^Δ) in directing behavior-outcome relations noted above (e.g., Troisi, 2013a, b). S^D predicts that behavior will lead to reward, whereas S^Δ predicts that behavior will not lead to reward.

Exteroceptive and interoceptive stimuli combine to *set the occasion* for specific response-reinforcer (or non-reinforcer) outcomes (e.g., Troisi, 2013a,b,c). Previously, our laboratory (Troisi and Craig, 2015) used two different exteroceptive contexts with two distinct interoceptive drug states (nicotine and EtOH) that functioned as S^D and S^Δ response modulators. Within subjects, one distinct exteroceptive context (e.g., strobe light and tone) was compounded with administration of nicotine and functioned as an S^D in occasioning reinforcement sessions (VI-30 s), whereas, a second exteroceptive context (dim lighting and white noise) was compounded with ethanol administration and functioned as S^Δ occasioning non-reinforcement sessions. The drugs and exteroceptive contexts were fully counterbalanced across rats. The context plus drug compounds promoted robust stimulus control with significantly greater responding in the S^D condition compared to S^Δ condition during multiple nonreinforcement tests. Discrimination indices averaged 98% responding in the S^D condition. The interoceptive drug states alone (administered with bright room without noise, strobe, or tone) promoted 80% responding under the S^D conditions, whereas the exteroceptive contexts alone (i.e., saline administration) promoted only 73% S^D responding. Thus, the full interoceptive-exteroceptive compound gestalt promoted greater stimulus control than the interoceptive and exteroceptive contexts alone. The present investigation continued this line of research with two distinct olfactory contexts (peppermint or anise) that were compounded with either nicotine or EtOH interoceptive S^D and S^Δ. As in our prior investigation, the two

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drugs and two olfactory contexts were fully counterbalanced across animals for their S^D and S^Δ roles. An added feature of this investigation was the potential sex differences as olfactory sensitivity and hormonal differences have been reported (e.g Kunkheyn et al., 2018; Pietras and Moulton, 1974). Moreover, the reinforcing and subjective effects of several drugs of abuse vary across the estrous cycle (Lynch et al., 2002). It should be noted here, that estrous phase was not an independent variable in the present investigation. Invariably, multiple interoceptive and exteroceptive stimuli combine to guide drug-maintained behavior (Troisi et al., 2013). The present investigation evaluated the combined effects of drug interoceptive states with exteroceptive olfactory contexts. Stimulus control among the full drug-odor gestalts was tested along with just the two drugs and odors alone. Based on our previous work, it was predicted that the full drug-odor compounds would promote stronger stimulus control than either the drugs or odors alone.

2. Materials and methods

2.1. Animals

16 experimentally 90 day old naïve Sprague Dawley rats (8 male and 8 female) (Envigo Breeders, Frederick, MD) were maintained at 80% of their free-feeding weights (females 250–275; males 300–330 g m). 15 g was added every week for growth. Rats were housed individually in hanging cages in the vivarium with ad-lib access to water and were maintained on 12 h light-dark cycle (7:00 am to 7:00 pm – light phase) but received daily socialization in environmental enrichment. Daily temperature averaged approximately 21C.; relative humidity averaged 60%. Animals were used in accord the ethical guidelines of the Saint Anselm College Institutional Animal Care and Use Committee, Psychology Department, and the PHS Guide for the Care and Use of Laboratory Animals.

2.2. Apparatus

Sessions took place in eight operant chambers (Med-Associates ENV-01; L 28 x W 21 x H 21 cm), equipped a food magazine centrally located on the front panel of the chamber measuring (H 5 x W 5 x D 3 cm), which delivered 45 mg standard grain-based food pellets (BioServe, Frenchtown, NJ). Levers were removed, but a nose-poke response device (Med Associates, St. Albans, VT model ENV 114 BM) was installed in each chamber and was located 2 cm above the gridded floor mounted in the rear end of the clear acrylic wall left of the food magazine. The chambers were placed two - three feet apart and located about the perimeter of the sound and light attenuated experimental room (L 16.5 x W 9 feet) designed for undergraduate Psychology courses related to behavioral biology and animal learning and motivation. Two 25 W red lights illuminated the room during session-time and were terminated at the end of each session by overhead track-light room-lighting. A white noise source was delivered by an antenna-less and cable-free television, which was turned on at the start of each session and co-terminated with illumination by the overhead lighting, which was also turned on and off manually. Experimental events were programmed via Med-PC Software (Version 2.08) and by a DIG interface (Med-Associates, St. Albans, VT) to an IBM 386 in an adjacent monitoring room.

2.3. Drugs & drug administration

13.2 ml of ethanol (95% stock) was diluted in 100 ml solution of 10% 10-X phosphate buffered saline to sustain a pH of 7.0. The solution was delivered in a volume of 10 ml/Kg, delivering a dose of 1.0 g/Kg. (-)-nicotine hydrogentartrite (Sigma) (0.3 mg/Kg; base) was dissolved in saline and administered in the same volume as EtOH. These doses (and preparations) were selected based on past work in this lab with these doses that show equi-salience (Troisi et al., 2013; Troisi and Craig, 2015; Troisi et al., 2013). Approximately ten minutes prior to the 20-min discrimination training session, rats received intraperitoneal injections of either nicotine or ethanol.

Table 1
Drug and odor condition assignments for males (n = 8) (top) and females (n = 8) (bottom). N is nicotine, E is ethanol, P is peppermint, and A is anise. Plus and minus signs refer to the S^D and S^Δ conditions, respectively.

Condition Assignments			
male (n = 2)	NP+ EA-	male (n = 2)	NP- EA+
male (n = 2)	NA+ EP-	male (n = 2)	NA- EP+
fem (n = 2)	NP+ EA-	fem (n = 2)	NP- EA+
fem (n = 2)	NA+ EP-	fem (n = 2)	NA- EP+

2.4. Procedure

Magazine training took place on the first day, with the nose-poke devices covered with stainless steel plates. On the second day, nose-poking was established with little training; it was initially maintained on an FR-1, but was abruptly switched and maintained on a VI-30 s schedule of food reinforcement for 5 sessions. Drug discrimination training took place over the next 24 sessions. 2 ml McKormick's peppermint or anise extract was poured in a 20 ml scintillation vial cap that was located under the grid floor in the middle of the chamber. Only one odor was presented on each day, but half the rats received nicotine (n = 8) and the other half (n = 8) received EtOH on a given session. Table 1 outlines the drug-odor and stimulus role assignments for all rats.

For 4 rats in the nicotine session nose-pokes were reinforced on a VI-30 schedule, but for the remaining four rats nose-poking was without consequence. For those same animals, the EtOH and the odor roles were reversed. Thus, drug-odor compound conditions and reinforcement/non-reinforcement sessions were counterbalanced across rats. Daily sessions were 20-min. 24 sessions alternated with no more than two consecutive presentations of one condition and there were 12 sessions of each condition. Full drug plus odor compound test sessions were 3-min, and were conducted just prior to each of the last four 20-min training sessions: two with nicotine with its associated context and two with ethanol in the opposite odor context. During those 3-min test probes, food was not dispensed but nose-poking was recorded under both conditions. Two additional training sessions followed, one with the S^D drug plus odor compound and one with the opposite drug plus odor compound S^Δ. The S^D and S^Δ odors alone were then tested for stimulus control with two counterbalanced 3-min non-reinforcement tests conducted over two days, one with peppermint and the other with anise. On these days, saline was administered 10 min prior to the test session. Two additional training sessions followed. The final two tests evaluated just the drug states without the odor background, one with nicotine and one with ethanol; these sessions were conducted without odors present.

3. Results

3.1. Drug plus odor compound tests

After the 24 training sessions (data not displayed) a 2 (sex; between group) X 2 (S^D and S^Δ, within group conditions) repeated measures ANOVA was conducted on the test data. Data were averaged across S^D and S^Δ conditions for odors-drugs for males and females and revealed compelling stimulus control by the 2 full odor-drug compound conditions with significantly greater response rates in the S^D compound compared to the S^Δ compound [$F(1,14) = 111.97$; $p \leq .001$; $\eta_p = .94$]. There was no significant sex difference; however, there was sex by drug (S^D vs. S^Δ) interaction [$F(1,14) = 6.57$; $p = .023$; $\eta_p = .57$]