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Incubation of ethanol reinstatement depends on test conditions and how ethanol consumption is reduced

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ABSTRACT

In reinstatement studies (a common preclinical procedure for studying relapse), incubation occurs (longer abstinence periods result in more responding). This finding is discordant with the clinical literature. Identifying determinants of incubation could aid in interpreting reinstatement and identifying processes involved in relapse. Reinstated responding was examined in rats trained to respond for ethanol and food under a multiple concurrent schedule (Component 1: ethanol FR5, food FR150; Component 2: ethanol FR5, food FR5–alternating across the 30-min session). Ethanol consumption was then reduced for 1 or 16 sessions either by suspending training (rats remained in home cage) or by providing alternative reinforcement (only Component 2 stimuli and contingencies were presented throughout the session). In the next session, stimuli associated with Component 1 were presented and responses recorded but ethanol and food were never delivered. Two test conditions were studied: fixed-ratio completion either produced ethanol- or food-associated stimuli (signaled) or had no programmed consequence (unsignaled). Incubation of ethanol responding was observed only after suspended training during signaled test sessions. Incubation of food responding was also observed after suspended training. These results are most consistent with incubation resulting from a degradation of feedback functions limiting extinction responding, rather than from increased motivation.

1. Introduction

Recovery from addiction and problematic drinking is threatened by relapse. Pre-clinically, relapse is most often studied using the reinstatement procedure (De Wit and Stewart, 1981; Stretch and Gerber, 1973). In the reinstatement procedure, animals are trained to respond for drug delivery. Once responding is established, animals are placed in extinction or otherwise prevented from responding (e.g. by being removed from the environment where drug was available). Re-exposure to the drug, stimuli associated with drug-delivery, or stressors result in reinstatement of responding (Crombag et al., 2008; Marchant et al., 2013). The amount of responding that occurs is thought to reflect the propensity to relapse, and model craving (Epstein et al., 2006; Marchant et al., 2013). Thus, treatments decreasing reinstated responding are thought to hold promise for preventing relapse (presumably by reducing the motivation to seek a drug) while manipulations increasing responding are thought to increase relapse risk.

Reinstatement has provided a means of studying processes involved in relapse, and for identifying potential treatments to prevent relapse (Marchant et al., 2013). However, reinstatement has been criticized for discrepancies with the clinical phenomenon of relapse (Katz and Higgins, 2003). In particular, longer periods of abstinence often result in increased reinstated responding. This incubation of reinstated responding is discordant with the clinical literature in which longer periods of abstinence generally reduce the risk for relapse (Gilpin et al., 1997; Gossop et al., 1990). Survival curves show a rapid return to substance use early in treatment, but a decreasing likelihood of relapse with increasing lengths of abstinence (e.g. Hunt et al., 1971). Thus, incubation poses a challenge to the interpretation that the amount of reinstated responding reflects the likelihood of relapse.

Incubation has been demonstrated for many drugs including cocaine, heroin, ethanol, and nicotine, as well as for sucrose (Epstein et al., 2006). Despite the broad generality of incubation across many drugs and situations, the behavioral mechanisms responsible for incubation remain poorly understood. Identifying the experimental parameters responsible for incubation could improve our interpretation of it and treatments that affect it.

Conditions present during reinstatement tests might influence the expression of incubation. While drug or food is never deliv-

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ered during the reinstatement test, in some cases responses result in presentation of the stimuli paired with their delivery. In other cases, responses have no programmed consequence. Incubation of cocaine reinstatement has been observed after periods of suspended access in both these situations (Grimm et al., 2001; Lu et al., 2004). However, the generality of these observations remains unclear.

The way responding is reduced prior to reinstatement testing could also affect incubation. Incubation has been demonstrated after suspended training (Abdolahi et al., 2010; Bienkowski et al., 2004; Grimm et al., 2001; Li and Frantz, 2010; Lu et al., 2004; Zhou et al., 2009). In contrast, reducing responding with extinction in the experimental context attenuates incubation of cue-induced cocaine reinstatement (Di Ciano and Everitt, 2002; Kelamangalath and Wagner, 2009). Further, incubation of reinstatement for ethanol or saccharin seeking does not occur when responding is reduced by reinforcing a different response with food delivery (Ginsburg and Lamb, 2013a, 2013b).

Here, we examine whether the expression of incubation depends on the way in which ethanol self-administration is reduced (either by removing the rat from the operant environment or by providing alternative reinforcement within the operant environment). Further, we examine whether presentation of stimuli contingent on fixed-ratio (FR) completion (and previously associated with ethanol delivery) during extinction affects incubation. The results indicate that experimental conditions profoundly affect the expression and extent of incubation of cue-induced reinstatement. Specifically, incubation of reinstated ethanol responding occurs when ethanol self-administration is reduced by suspending training, but not when it is reduced by providing alternative reinforcement, and then, only when FR completion was signaled during the test session.

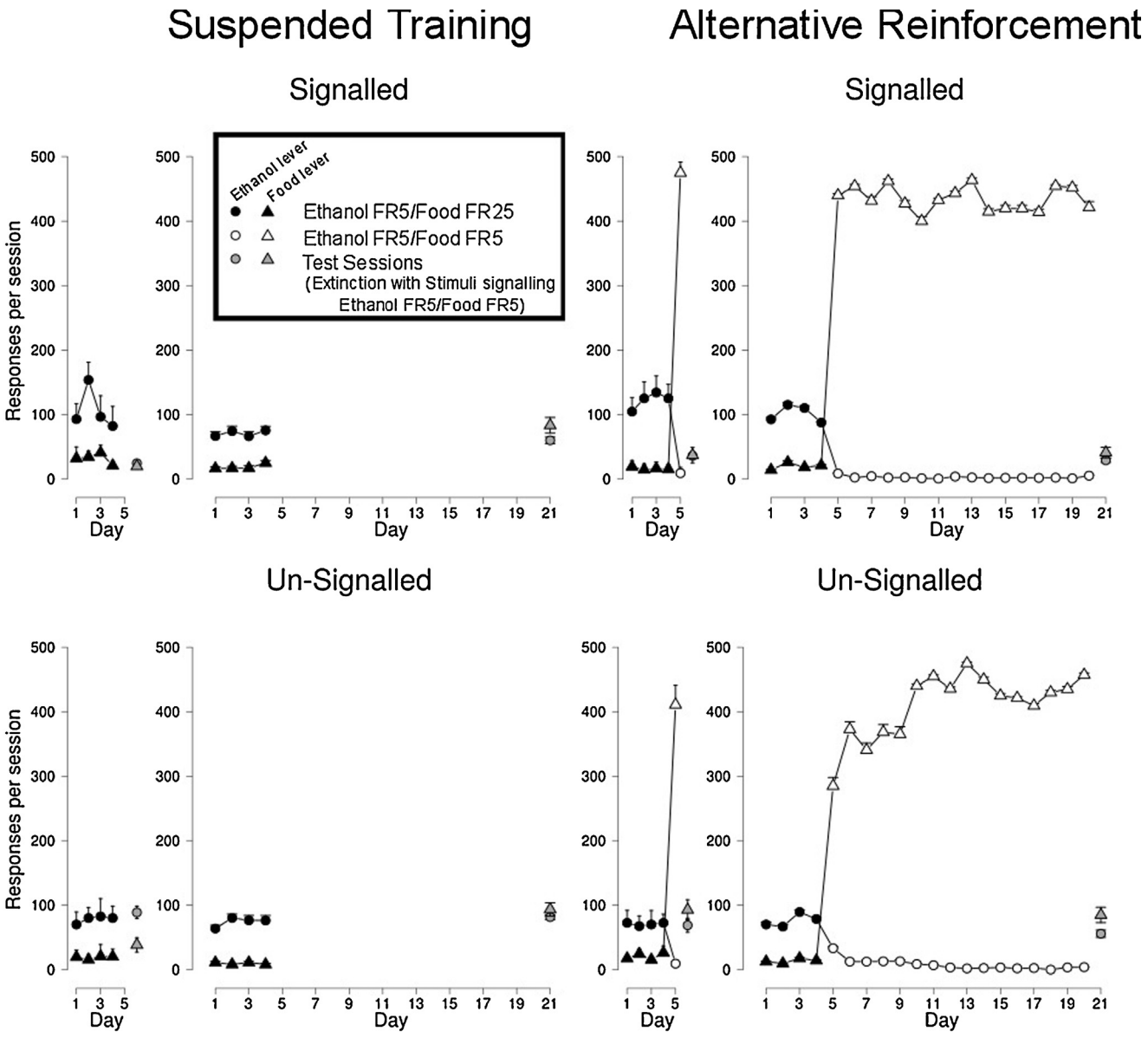

Fig. 1. Responses per session for each condition. Filled symbols represent sessions with ethanol FR5, food FR150, and the stimuli associated with these contingencies. Open symbols represent sessions with ethanol FR5, food FR5, and the stimuli associated with these contingencies. Grey symbols represent test sessions where food or ethanol was not provided. The top row shows data from signaled test sessions where completion of an FR was accompanied by presentation of the appropriate paired stimulus while the bottom row shows unsignaled test sessions. The left column shows data when the intervention was suspended training and the right column shows data when the intervention was alternative reinforcement. Each point represents the mean and standard error. The number of animals represented for each condition can be found in Table 1.