# Habitual Alcohol Seeking: Time Course and the Contribution of Subregions of the Dorsal Striatum

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**Background:** Addictions are defined by a loss of flexible control over behavior. The development of response habits might reflect early changes in behavioral control. The following experiments examined the flexibility of alcohol-seeking after different durations of self-administration training and tested the role of the dorsal striatum in the control of flexible and habitual alcohol self-administration.

**Methods:** Rats were trained to lever-press to earn unsweetened ethanol (EtOH) (10%). The sensitivity of the lever-press response to devaluation was assessed by prefeeding the rats either EtOH or sucrose before an extinction test after different amounts of training (1, 2, 4, and 8 weeks). We subsequently tested the role of the dorsomedial striatum (DMS) and dorsolateral striatum (DLS) in controlling alcohol seeking with reversible inactivation techniques (baclofen/muscimol: 1.0/.1 mmol/L, .3 μL/side).

**Results:** We find that operant responding for EtOH early in training is goal-directed and reduced by devaluation, but after 8 weeks of daily operant training, control has shifted to a habit-based system no longer sensitive to devaluation. Furthermore, after relatively limited training, when responding is sensitive to devaluation, inactivation of the DMS greatly attenuates the alcohol-seeking response, whereas inactivation of the DLS is without effect. In contrast, responding that is insensitive to devaluation after 8 weeks of training becomes sensitive to devaluation after inactivation of the DLS but is unaffected by inactivation of the DMS.

**Conclusions:** These experiments demonstrate that extended alcohol self-administration produces habit-like responding and that response control shifts from the DMS to the DLS across the course of training.

**Key Words:** Devaluation, dorsolateral striatum, dorsomedial striatum, ethanol, goal-directed, habit learning

Addiction is characterized by the loss of flexible control over drug use despite negative consequences (1). This might reflect the development of habitual drug seeking (2–5); however, few studies have examined whether self-administration of drugs of abuse, including alcohol, is in fact habitual. Several studies have shown that prolonged exposure to alcohol renders consumption insensitive to quinine adulteration (6–8), consistent with inflexible intake, yet changes in the flexibility of responses performed to gain access to alcohol have not been explicitly examined. Furthermore, because most recreational drug use presumably starts as a flexible behavior, it is unclear at what point control shifts to a habit-based system. Within the animal learning field, specific tests have been developed wherein flexible versus habitual control over responding can be assessed, and these tests can be employed to address this question.

Flexible performance relies on an expectancy related to the outcome of a particular action. Thus, responding tracks the current value of that outcome and is normally reduced when outcome value is decreased (9). In contrast, automatic or habitual responding is elicited by antecedent stimuli and not directly controlled by outcome expectancy. When responding is habitual, therefore, changes in the value of the rewarding outcome have no immediate effect on performance of that response (10,11). By specifically manipulating outcome value and observing consequent effects on performance, revaluation tests (9,12,13) have become the preferred diagnostic for identifying goal-directed versus habitual responses (reliant on response-outcome [R-O] vs. stimulus-response [S-R] associative architectures, respectively).

Previous studies have employed devaluation to examine control of responding for alcohol (14); however, several limitations—including the presence of a nonspecific devaluation, affecting responding for both alcohol and a nonalcohol reward, and the use of a sucrose substitution procedure to induce responding for alcohol, thereby promoting associations of the lever with both sucrose and alcohol—make these results difficult to interpret. Therefore, the aim of Experiment 1 was to test the prediction that after relatively limited training responding for alcohol is flexible, but after more extensive practice, responding shifts to habitual control.

A role for the basal ganglia, especially the dorsal striatum (DS) in habit or S-R learning has been demonstrated in humans (15,16) and other animals (17–21). Rats with lesions or inactivation of the dorsolateral striatum (DLS) remain sensitive to outcome devaluation under conditions in which control subjects have lost this sensitivity (22,23), indicating that the DLS supports habitual instrumental performance. Flexible performance, therefore, must be controlled by a neural circuit that does not include the DLS. Indeed, pharmacological inactivation or *N*-methyl-D-aspartate (NMDA) antagonist infusion into medial regions of the dorsal striatum (DMS) before instrumental training (24,25) or devaluation testing (26) renders responding insensitive to outcome devaluation, suggesting that the DMS mediates performance on the basis of the R-O relationship. Hence functionally distinct circuits contribute to instrumental responding, with the DLS mediating habit/S-R learning and the DMS mediating R-O learning (13,27).

On the basis of its role in habit learning, the dorsal striatal system might contribute to the development of a drinking habit. Recent studies found that alcohol self-administration enhances activity at NR2B-containing NMDA receptors in the DMS and is decreased by DMS infusion of the NMDA receptor antagonist ifenprodil (28). Furthermore, alcohol self-administration is decreased by brain-derived neurotrophic factor infusion into the DLS and increased by local reductions in brain-derived neurotrophic factor expression in

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the same region (29). These and other studies (30–34) support a critical role of the DS in controlling alcohol self-administration. To explore the nature of that role, Experiment 2 tested the hypothesis that flexible responding for alcohol relies on the DMS, whereas responding for alcohol that is habitual—after extended training—relies on the DLS.

## Methods and Materials

### Experiment 1a: Sensitivity to Outcome Devaluation Across Extended Training: Repeated Testing of Subjects After 1, 2, 4, and 8 Weeks of Training

**Subjects and Apparatus.** Nineteen male Long-Evans rats (approximately 300 g; Harlan, Indianapolis, Indiana) were singly housed with free access to food and water. All procedures were approved by the Institutional Animal Care and Use Committee of the Ernest Gallo Clinic and Research Center at the University of California, San Francisco. Training and testing took place in Med Associates (East Fairfield, Vermont) operant chambers housed within sound-attenuating shells. Each chamber was equipped with a pump fitted with a syringe that delivered a fixed volume of solution into a recessed magazine in the chamber when activated. The chambers contained retractable levers to the left and right of the magazine. A houselight mounted on the top-center of the opposite wall provided illumination.

**Alcohol Acclimation in the Home Cage.** Rats initially were given, to familiarize them with alcohol, free access to 10% ethanol (EtOH) (10E) (vol/vol) in filtered water in the home cage, for 24 hours/day for 14 days, followed by 14 days of 1-hour access to 10E at the time that training would subsequently occur. Water was always available in a separate bottle fixed to the home cage. Rats were weighed daily, and EtOH consumption was recorded.

**Instrumental Training.** Rats underwent a single 30-min magazine training session, wherein 10E was delivered under a random time-60s schedule. Rats were next trained to make a lever-press response to deliver small aliquots (.1 mL) of 10E in 60-min sessions. The first 2 days of training were under a continuous reinforcement schedule; reinforcement was then shifted to a random ratio-2 schedule for 3 days, followed by a random ratio-3 schedule. Animals failing to respond at levels sufficient to achieve alcohol intake of at least .3 g/kg for 5/7 days/week were excluded from the study (2 animals excluded according to this criterion, leaving 17 in this group). The reward receptacle was examined at the end of each session to ensure that the earned rewards were consumed; this was always the case. Training data are shown in Figure S1 in Supplement 1.

**Devaluation Testing.** For each test, rats were divided into two groups, devalued and nondevalued. For the devalued condition, rats were given 45 min of free access to 10E in the home cage. For the nondevalued condition, rats were given 45 min free access to 1% sucrose (wt/vol; this concentration was chosen, because it produces consumption volumes similar to those found with 10E) (Figure S2 in Supplement 1). A consumption criterion of 3 mL was required for the data of an animal to be included. Immediately after home-cage pre-feeding, rats were tested for lever-press responding in a 10-min extinction test. After this first test, rats received 2 days of retraining and were tested again such that rats that had received the devaluation treatment now received the nondevalued treatment and vice versa. Tests were conducted after 1, 2, 4, and 8 weeks of training; after each pair of tests, rats underwent daily EtOH training sessions as in the preceding text.

### Experiment 1b: Sensitivity to Outcome Devaluation After Extended Training: Comparison of Separate Groups Trained for 2 or 8 Weeks

**Subjects and Apparatus.** Rats were assigned to a 2-week ($n$ = 11) or 8-week ($n$ = 10) group. Home cage EtOH exposure was identical to that described in the preceding text.

**Instrumental Training and Devaluation Testing.** Rats were trained to lever-press for 10E as described in the preceding text. The 2-week group underwent 14 daily sessions, and the 8-week group underwent 56 daily sessions before the first devaluation test, conducted as described in the preceding text, with each rat tested in the devalued and nondevalued conditions (order counterbalanced).

### Experiment 1c: Sensitivity of a Sucrose-Seeking Response to Outcome Devaluation After 2 or 8 Weeks of Training

**Subjects and Apparatus.** Rats were assigned to a 2-week ($n$ = 9) or 8-week ($n$ = 9) group or an 8-week plus EtOH group (SucEth) ($n$ = 13). Rats had 48 hours of free access to a 2% sucrose solution (2S) (wt/vol in filtered water) in the home cage before training. The total volume of 2S made available was equivalent to the average total volume of 10E consumed by rats in the aforementioned preexposure phase of Experiment 1b. The 2S solution was chosen in an attempt to produce similar response rates as 10E (Figure S3 in Supplement 1).

**Instrumental Training and Devaluation Testing.** Animals were trained to lever-press for .1 mL aliquots of 2S as in Experiment 1a, with 14 (2-week group) or 56 daily sessions (8-week group) before the first devaluation test. To address whether noncontingent exposure to EtOH accelerates habit formation, a SucEth group was given 4 weeks of home cage 10E, followed by training to lever-press for sucrose. This group received 30 min EtOH access in the home cage 4 hours after each of 56 daily sucrose self-administration sessions. Devaluation followed the test procedures described in the preceding text except that for the devalued condition rats were given 45 min of free access to 2S, whereas for the nondevalued condition rats were given access to a 5% polycose solution that produced similar consumption levels (Figure S3 in Supplement 1). Each rat underwent two tests, one in the devalued condition and one in the nondevalued condition (order counterbalanced).

### Experiment 2: The Role of the DMS and DLS After Limited or Extended Training

**Subjects and Apparatus.** Subjects were 46 rats, with housing conditions, testing apparatus, and initial acclimation to 10E identical to Experiment 1a.

**Instrumental Training.** Rats were trained to lever-press for 10E as described in the preceding text. Rats were divided into a 2-week (14 daily sessions) and an 8-week (56 daily sessions) group (see Figure S4 in Supplement 1 for training data).

**Surgery.** Rats in the 2-week and 8-week groups were further divided into lateral or medial groups after attempting to equate baseline instrumental response rates ($n$ = 11–12/group). Surgery was performed after approximately 1 week of training for the 2-week group and after approximately 7 weeks of training for the 8-week group to allow 1 week of post-surgery responding before testing. Stereotaxic surgery was conducted under isoflurane anesthesia to implant 26 gauge guide cannulae (Plastics One, Roanoke, Virginia) targeted at either the DLS (anterior-posterior: +1.2 mm, medial-lateral: ± 3.4 mm, dorsal-ventral: −1.0 mm) or DMS (anterior-posterior: +1.2 mm, medial-lateral: ± 1.5 mm, dorsal-ventral: −1.4 mm; coordinates relative to bregma). Guide cannulae tips were positioned 3 mm dorsal to the intended infusion site; thus,