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Carrots and sticks fail to change behavior in cocaine addiction

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Abstract

Cocaine addiction is a major public health problem that is particularly difficult to treat. Without medically proven pharmacological treatments, interventions to change the maladaptive behavior of addicted individuals mainly rely on psychosocial approaches. Here we report on impairments in cocaine-addicted patients to act purposefully toward a given goal and on the influence of extended training on their behavior. When patients were rewarded for their behavior, prolonged training improved their response rate toward the goal but simultaneously rendered them insensitive to the consequences of their actions. By contrast, overtraining of avoidance behavior had no effect on patient performance. Our findings illustrate the ineffectiveness of punitive approaches and highlight the potential for interventions that focus on improving goal-directed behavior and implementing more desirable habits to replace habitual drug-taking.

Why do some people take drugs by any possible means, seemingly without regard for the consequences? Actions normally constrained by their outcome become “out of control” in drug-addicted individuals, who fail to stop taking drugs despite being aware that continuing drug use provides little pleasure while inflicting considerable damage on their lives. Even the prospect of contracting an infectious disease fails to deter these individuals from sharing drug paraphernalia. Such maladaptive and ill-judged behaviors may be explained in terms of aberrant learning processes (1), where drug-taking is a learned behavior initially directed toward a conscious desire to enjoy a rush or avoid feelings of discomfort. Such goal-directed actions, whether appetitive or avoidant, are modulated by their outcomes. Following extended practice, however, drug-taking may deteriorate into a stimulus-driven habit that is elicited by antecedent stimuli and is thus performed regardless of any goals (2). This proposal is consistent with the notion of behavior being jointly regulated by goal-directed

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and habitual brain systems (3, 4) and the disruption of this balance during the course of addiction (1).

Maladaptive behavior in drug-addicted individuals may thus result from impairments in goal-directed control, an enhanced propensity to develop stimulus-driven habits, or a combination of these factors. Preclinical evidence supports both accounts. Exposure to either cocaine or stress amplifies the transition from goal-directed to stimulus-driven behavior (5, 6). Cocaine administration also diminishes information processing about consequences, leading to failures to adjust behavior during goal reevaluation (7).

We studied 125 participants to determine whether a newly learned behavior is under voluntary (goal-directed) or habitual (stimulus-driven) control using both positive and negative reinforcement. Seventy-two individuals met the DSM-IV-TR criteria for cocaine dependence and were actively using cocaine, as verified by urine screen (8), whereas 53 healthy control volunteers had no history of chronic drug or alcohol abuse (table S1). Participants learned by trial and error that an action was associated with a particular outcome, such as earning points toward a monetary reward (Fig. 1A) or avoiding an unpleasant electrical shock (Fig. 2, A and B). We then reduced the value of previously reinforcing outcomes by discontinuing point allocation for certain outcomes in the appetitive task (Fig. 1B) and physically disconnecting participants from the electrical stimulator in the avoidance task (Fig. 2C). We then tested whether participants made fewer responses to obtain or avoid the (now) devalued outcome, reflecting a goal-directed strategy, or whether they maintained their previously learned behavior despite outcome devaluation, as an index of habit.

In participants with cocaine use disorder (CUD), instrumental learning performance fell significantly short of that of control volunteers, irrespective of whether the goal was to make responses to obtain symbolic rewards or to avoid electrical shocks (Figs. 1A and 2B). However, depending on the type of reinforcement, prolonged training had a differential effect on the behavior of these individuals. For appetitive behavior, extensive training rendered CUD patients less sensitive to outcome devaluation (Fig. 1B). They persistently responded to stimuli previously associated with reward, irrespective of whether their behavior was actually rewarded or not (Fig. 1C). In fact, the shift toward habitual responding improved their response rate to the valued outcome (Fig. 1C). The strong habit bias in the slip-of-action test was not due to executive impairments (9, 10), which were assessed separately in a control task (Fig. 1D) and included as a covariate in the statistical model.

By contrast, overtraining avoidance behavior had no effect on task performance in individuals with CUD. Despite intact fear conditioning (Fig. 2B), CUD patients continued to show attenuated avoidance responses to the conditioned stimulus (CS) associated with a shock, even after extended training (Fig. 2D). Such impairments in the initiation of goal-directed avoidance behavior have previously been reported in animals after dopamine receptor blockade (11) or experimental lesions of dopamine neurons (12). Although CUD patients undervalued the aversive outcome, overtraining did not change their sensitivity to outcome devaluation, either in terms of behavior or skin conductivity. As shown in Fig. 2D,

CUD patients' responses were comparable to controls when the CS was no longer associated with a shock.

In light of the high prevalence of comorbid addictions in CUD, we sought to determine the extent to which the increased formation of appetitive habits and the persistent deficiencies in avoiding aversive outcomes resulted from cocaine addiction specifically or from addiction to other drugs. We also assessed the influence of vulnerability factors such as impulsivity-compulsivity traits, stress, and poor instrumental learning performance (8). Addiction to cocaine, but not to other drugs, explained ~13% of the variance of appetitive habits in the slip-of-action test (coefficient of determination $R^2 = 0.13$; $F_{4,117} = 4.48$, $P = 0.002$). However, reduced performance accuracy during training ($\beta = -0.410$, $P < 0.001$) and higher numbers of stressful life events ($\beta = 0.30$, $P = 0.015$) were factors of even greater weight in the model, accounting for one-third of the variance ($R^2 = 0.31$; $F_{8,113} = 6.32$, $P < 0.001$). Hence, our results suggest that, in individuals with prior exposure to cocaine and stress, impairments in instrumental learning lead to a shift from goal-directed to goal-independent habitual behavior.

We also applied a similar model to examine attenuated avoidance responses to the valued CS in extinction (table S2), revealing that addiction to cocaine (but not to other drugs) accounted for only 9% of the variance ($R^2 = 0.09$; $F_{4,119} = 2.82$, $P = 0.028$). High levels of impulsivity ($\beta = 0.18$, $P = 0.047$) and low avoidance accuracy during overtraining ($\beta = -0.67$, $P < 0.001$)—both associated with reduced striatal dopaminergic neurotransmission (12, 13)—were the strongest predictors in this model, accounting for more than half of the variance of attenuated avoidance ($R^2 = 0.52$; $F_{8,115} = 15.85$, $P < 0.001$). These results are consistent with preclinical evidence for impulsivity predicting compulsive cocaineseeking, even in the face of aversive consequences (14).

Our data provide compelling evidence for impairments in instrumental learning in CUD, regardless of affective valence and whether rewards were primary (shock) or secondary (monetary). In the case of appetitive learning, increased habitual responding may either be an indirect consequence of poor goal-directed action (7) or result from stronger habit learning. Both explanations would be consistent with disruptions of the balance between goal-directed and habitual control hypothesized to underlie compulsive cocaine seeking (1). By contrast, impaired performance for instrumental avoidance in CUD patients occurred in the context of intact fear conditioning and was not accompanied by habit learning. This could be interpreted as a motivational impairment that is consistent with theories of the role of dopamine in motivational processes (11, 12) and with reports of reduced striatal dopamine function in CUD (15, 16). Our findings are also in line with evidence indicating that manipulations of dopamine neurotransmission alter instrumental learning (17) and shift the balance between goal-directed and habitual responding (18, 19).

Although the observed appetitive habit bias was specific to cocaine addiction, the main contributory factors were impaired goal-directed learning and accumulated life stress. We also report evidence of additional executive impairments consistent with previous findings (9); however, these were insufficient to explain the increased goal-to-habit shift in appetitive

behavior. Nonetheless, impulsivity and instrumental learning impairments are critical factors in explaining the reduced propensity to avoid aversive outcomes.

How can these findings be applied to other addictive and compulsive behaviors? Emerging evidence in alcoholism has already shown disruptions in the balance of action control for appetitive behavior (20, 21). Avoidance habits might be more relevant for opiate addiction, given that the avoidance of unpleasant withdrawal symptoms is thought to play an important role in its development. Although we did not find supportive evidence in our comorbid sample, this hypothesis should be tested in opiate-addicted patients without such comorbidity. The performance profile of CUD patients in the appetitive condition may reflect a transdiagnostic risk factor for developing compulsive habits, as was recently shown to explain common deficits seen in obsessive-compulsive disorder (OCD), alcohol addiction, and eating disorders (22, 23). Notably, however, our data show that this pattern may not hold in the context for avoidance behavior, where, for example, OCD patients (unlike our CUD sample) exhibit greater habitual learning (24).

Our findings illustrate the particular difficulty of treating CUD: The persistent deficits in avoiding aversive consequences highlight the ineffectiveness of punitive interventions for cocaine addiction. Moreover, the tendency of patients to perform a rewarded behavior in an automatic fashion, irrespective of its consequences, is unlikely to be affected by cognitive interventions that target the enhancement of alternative outcomes. Treatment of cocaine addiction should thus focus on training desirable habits that replace habitual drug-taking while protecting CUD patients from aversive consequences that they may fail to avoid.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Editor's Summary

Punishment doesn't work in cocaine addicts

Addiction is extremely difficult to treat, particularly cocaine use disorder. Animal experiments have led to the concept of drug addiction as abnormal goal-directed learning and habit formation. Ersche *et al.* found that overtraining with positive reinforcement such as rewards made cocaine-addicted patients less sensitive to the outcome of their actions. In contrast, overtraining on a punishment paradigm had no effect. Thus, habits may determine the behavior of cocaine users.

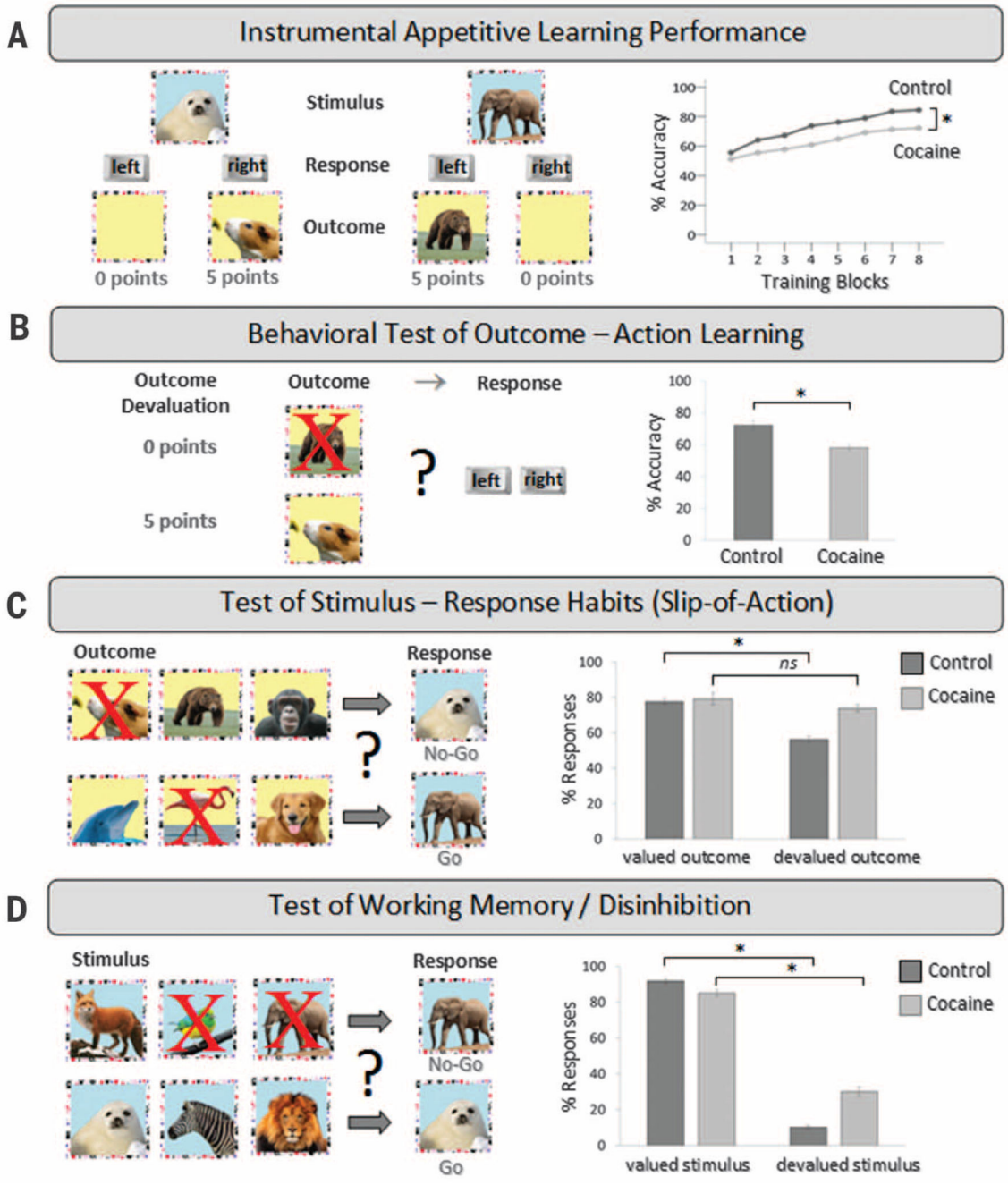

Fig. 1. Appetitive instrumental learning task.

(**A**) Participants learned by trial and error which response associated with an animal picture gained them points. Feedback was provided by a picture of another animal, coupled with a number of points, or an empty box with no points. Goal-directed discrimination learning performance improved steadily in all participants over eight training blocks ($F_{6,684} = 43.98$, $P < 0.001$), but performance accuracy in individuals with CUD was reduced compared with that in control volunteers ($F_{1,121} = 20.19$, $P < 0.001$). (**B**) Participants were instructed that some of the pictures that were previously associated with points would no longer lead to

point increases. Sensitivity to outcome devaluation was tested by simultaneous presentation of two outcome-related pictures and the instruction to select the response leading to a valued outcome without providing performance feedback. CUD patients showed significant impairments when outcome-action knowledge was tested behaviorally ($t_{88.2} = 3.83$, $P < 0.001$). (**C**) Slip-of-action test to determine the balance between goal-directed and habitual responses: Participants were asked to selectively respond to those stimuli still associated with reward and to withhold responding to stimuli that had been devalued. (For demonstration only, we indicated "go" and "no-go" below the pictures to denote the correct response.) Habitual behavior is reflected by continued responses to devalued outcomes, implying reduced sensitivity to outcome value. We observed a highly significant group–by–outcome-value interaction. CUD patients responded significantly more often than controls to the stimuli associated with the devalued outcome ($t_{121} = –4.72$, $P < 0.001$), whereas the level of responding toward valued outcomes did not differ between the groups ($t_{121} = –0.65$, $P = 0.520$). (**D**) Immediately after the slip-of-action test, a control task was introduced: Participants were instructed to respond only to those stimuli still associated with reward and to withhold responding to devalued stimuli. All participants responded more frequently to stimuli associated with the valued rather than the devalued outcome ($F_{1,121} = 111$, $P < 0.001$), but this difference was significantly smaller in CUD patients ($F_{1,121} = 42.10$, $P < 0.001$). (In all panels, error bars denote SEM, *ns* indicates $P > 0.05$, and asterisks indicate $P < 0.05$.) Analysis of covariance showed that executive impairments in the control task were not sufficient to account for the impaired "slip-of-action" performance. The significant group–by–outcome-value interactions in (C) survived statistical correction ($F_{1,120} = 8.79$, $P = 0.004$), indicating enhanced habitual control (see text).

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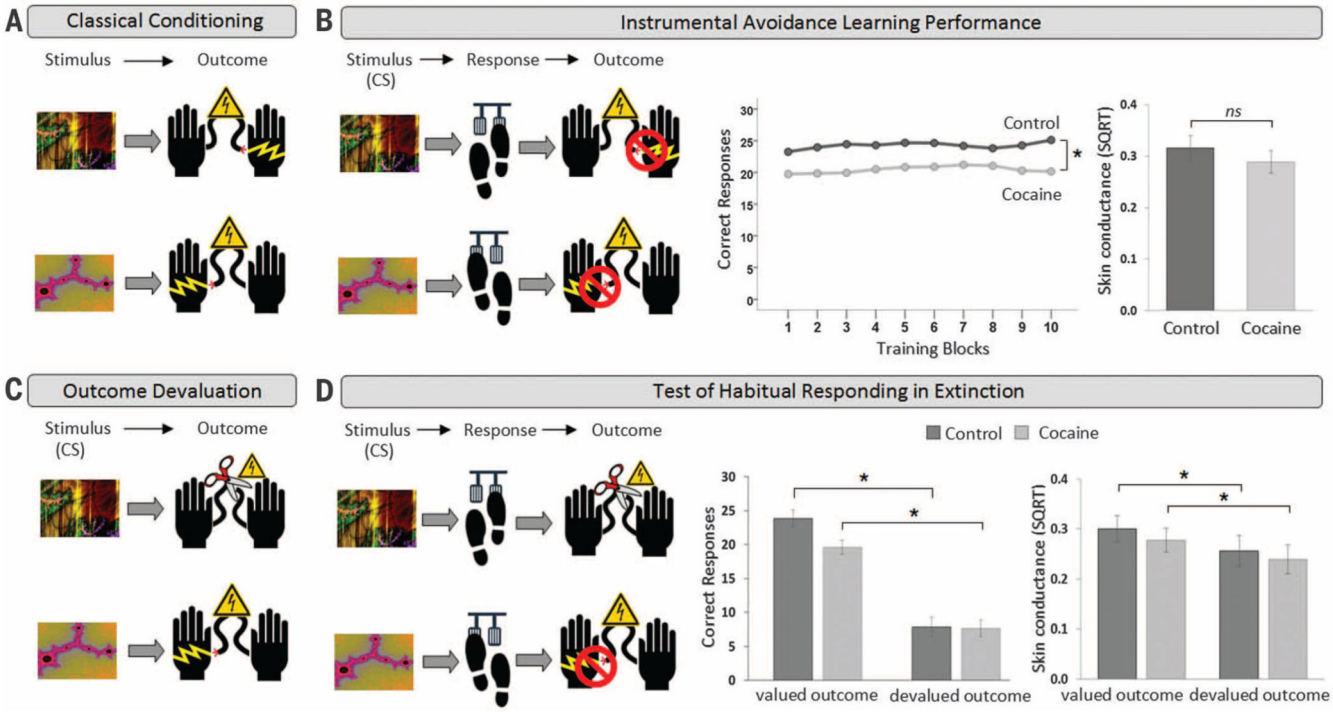

Fig. 2. Avoidance instrumental learning task.

(**A**) Participants were trained to associate distinctive visual stimuli with an electrical shock to one wrist or the other. (**B**) Participants were instructed to avoid receiving shocks by pressing a foot-pedal on the side corresponding to the wrist where they were expecting to receive an electrical shock in response to the appearance of the CS. Individuals with CUD made significantly fewer successful avoidance responses compared with controls ($F_{1,121}$ = 11.28, P = 0.001). No group differences in skin conductance responses to the CS were observed ($F_{1,89}$ = 0.71, P = 0.401). (**C**) In the outcome devaluation procedure, we disconnected one wrist from the electrical stimulator (devalued) while leaving the other wrist connected (valued). Participants were made explicitly aware that one wrist previously associated with an electrical shock was now safe. (**D**) During the extinction procedure, the number of unnecessary foot-pedal presses to avoid shocks from the now disconnected electrical stimulator was measured. The events discussed in (C) and (D) were conducted twice: once after a short period of training and again after overtraining to promote habit formation. All participants made a greater number of successful avoidance responses to the CS associated with the valued outcome compared with the devalued outcome ($F_{1,121}$ = 20.05, P < 0.001). This difference was marginally smaller in CUD patients compared with controls ($F_{1,121}$ = 3.23, P = 0.075). Consistent with their poor performance during the training phases, individuals with CUD remained less successful than controls in avoiding shocks. Skin conductance increased in all participants in response to the CS associated with the valued outcome compared with the devalued outcome ($F_{1,88}$ = 8.23, P = 0.005), but this did not differ between the groups ($F_{1,88}$ = 0.29, P = 0.592). [Results were statistically corrected for group differences in subjective shock intensity. In (B) and (D), error bars

denote SEM, SQRT signifies square-root transformation, *ns* indicates $P > 0.05$, and asterisks denote $P < 0.05$.]

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