Carrots and Sticks Fail to Change Behavior in Cocaine Addiction.

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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 impairments in cocaine-addicted patients to act purposefully towards a given goal and the influence that extended training has on their behavior. When behavior was rewarded, prolonged training improved their response rate towards the goal, but it simultaneously rendered them insensitive to the consequences of their actions. By contrast, overtraining of avoidance behavior had no impact on their performance at all. Our findings illustrate the ineffectiveness of punitive approaches, whilst highlighting the potential for interventions that focus on improving goal-directed behavior and implementing more desirable habits to replace habitual drug-taking.

One Sentence Summary

Difficulties in changing cocaine users' behavior may stem from impaired goal-directed learning, leading to habit-prone behavior and failure to avoid aversive consequences.

Why do some people take drugs ‘by hook or by crook’, seemingly irrespective of any concern for the consequences? Actions normally constrained by their outcome become ‘out of control’ in drug-addicted individuals, who fail to stop drug-taking even when aware that continuing their drug use gives them little pleasure, whilst inflicting considerable damage on their lives. Even the prospect of contracting an infectious disease fails to deter them 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 towards 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 thus performed irrespective of any goals (*2*). This proposal is consistent with the notion of behavior being jointly regulated by goal-directed 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 either impairments in goal-directed control, or an enhanced propensity to develop stimulus-driven habits, or their combination. 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 re-evaluation (*7*).

We thus investigated in 125 participants whether a newly learned behavior is under voluntary (goal-directed) or habitual (stimulus-driven) control during either positive or 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) whilst 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 towards a monetary reward (**Fig.1A**) or avoiding an unpleasant electrical shock (**Fig.2A,B**). We then reduced outcome desirability either by discontinuing point allocation for that outcome (**Fig.1B**) or physically disconnecting participants from the electrical stimulator (**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.

Instrumental learning performance in participants with cocaine use disorder (CUD) 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 (**Fig1A** and **Fig2B**). Prolonged training, however, affected behavior in CUD differentially depending on the type of reinforcement. For appetitive behavior, extensive training rendered CUD patients less sensitive to outcome devaluation (**Fig1B**). They persistently responded to stimuli previously associated with reward, irrespective of whether their behavior was actually rewarded or not (**Fig1C**). In fact, the shift towards habitual responding improved their response rate to the valued outcome (**Fig1C**). 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 (**Fig1D**) and included as a covariate in the statistical model.

By contrast, overtraining avoidance behavior had no impact on task performance in CUD. Despite intact fear conditioning (**Fig2B**), 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 following 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 **Fig2D**, CUD responded on par with controls to the CS no longer associated with a shock.

In light of the high prevalence of co-morbid 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 were due to addiction to cocaine specifically, or 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 about 13% of the variance of appetitive habits in the slip-of-action test ($R^2 = 0.13; F_{4,117} = 4.48, p = 0.002$), but factors of even greater weight in the model, accounting for one third of the variance ($R^2 = 0.31; F_{8,113} = 6.32, p < 0.001$), were reduced performance accuracy during training ($\beta = -0.410, p < 0.001$) and higher numbers of stressful life events ($\beta = 0.30, p = 0.015$). Our results thus 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) only accounted for 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 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 cocaine-seeking even in the face of aversive consequences (*14*).

Our data provide compelling evidence for impairments in instrumental learning in CUD, irrespective 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 reports of reduced striatal dopamine function in CUD (*15,16*). Our findings are also in line with evidence suggesting 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 co-morbid sample, this hypothesis should, however, be tested in opiate-addicted patients without such co-morbidity. The performance profile of CUD patients in the appetitive condition

may reflect a trans-diagnostic 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, whilst protecting CUD patients from aversive consequences they may fail to avoid.

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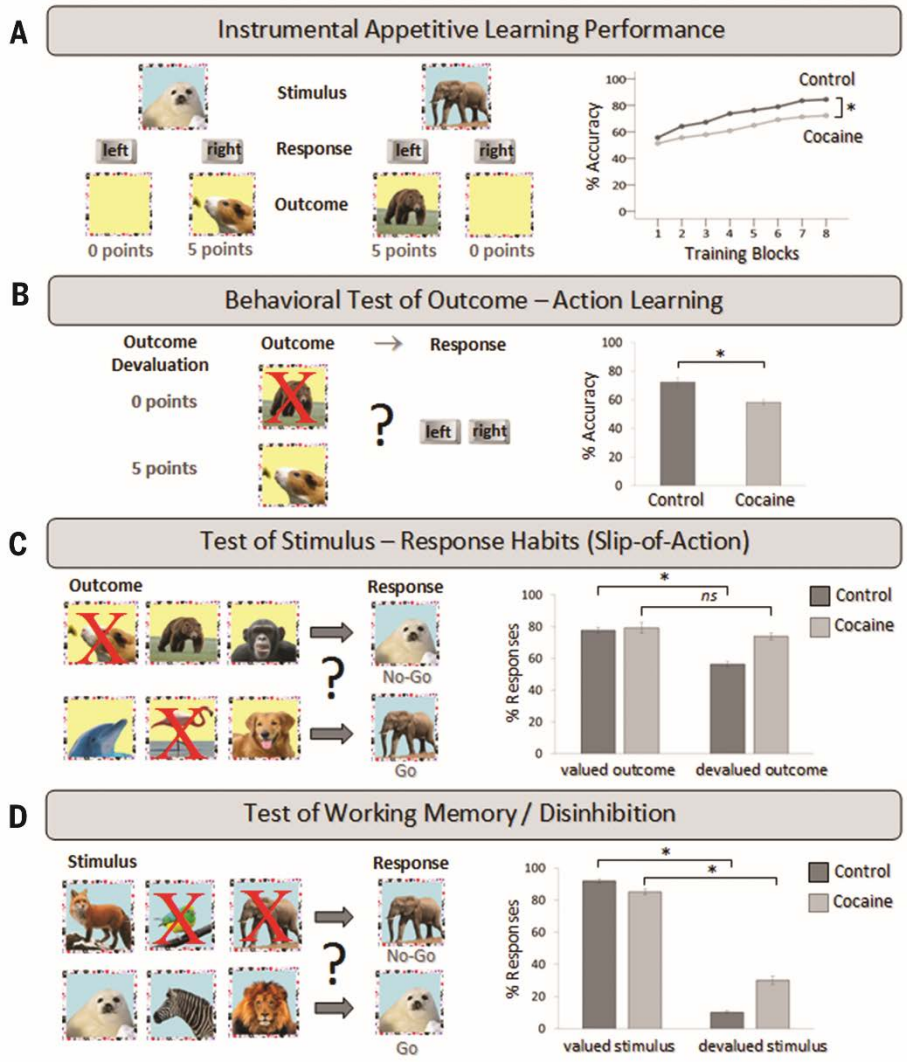

Fig.1: Appetitive Instrumental Learning Task. **A:** Participants learned by trial and error which response associated with an animal picture gained them points. Feedback was provided by a picture of another animal coupled with either a number of points or an empty box with no points. Goal-directed discrimination learning performance improved steadily in all participants over eight training blocks ($F_{6,684}$ = 43.98,p < 0.001), but performance accuracy in CUD was reduced compared with control volunteers ($F_{1,121}$ = 20.19,p < 0.001). **B:** Participants were told that some of the pictures previously gaining points no longer did. 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 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 visualize the correct response). Habitual behavior is reflected by continued responses to devalued outcomes, implying reduced sensitivity to outcome value. CUD showed a highly significant group by outcome-value interaction ($F_{1,121} = 18.24, p < 0.001$). CUD 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 towards 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 solely 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 ($F_{1,121} = 42.10, p < 0.001$). [Error bars denote standard error of the mean, *ns* indicate $p > 0.05$, *indicate $p < 0.05$]. Analysis of co-variance showed that executive impairments in the control task were insufficient to account for the impaired 'slips-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).

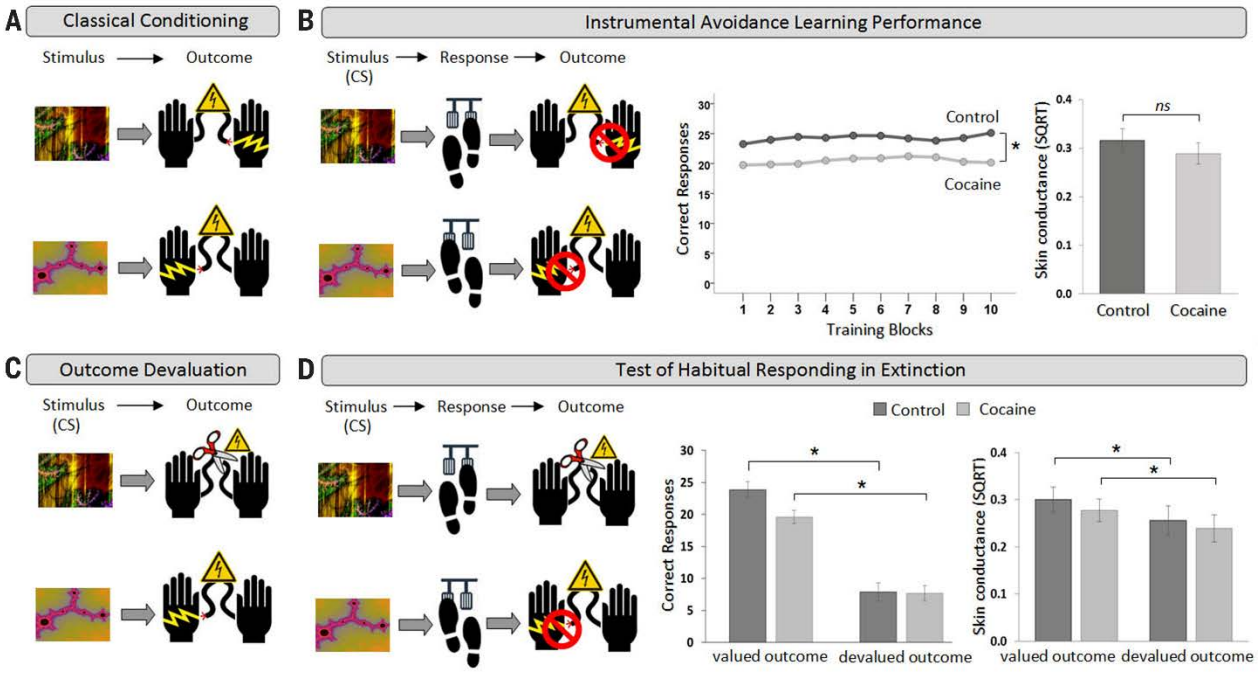

Fig.2: Avoidance Instrumental Learning Task. **A**: Participants were trained to associate distinctive visual stimuli with an electrical shock to one wrist or the other. **B**: Participants were given the goal to avoid receiving shocks by pressing a foot-pedal on the side corresponding to the wrist where they were expecting to receive an electrical shock in response to the appearance of the CS. 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) whilst 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. Stages C and D were conducted twice, once following a short period of training, and again after over-training to promote habit formation. All participants made a greater number of successful avoidance responses to the CS associated with the valued outcome compared to the devalued outcome ($F_{1,121} = 20.05, p < 0.001$); this difference was marginally smaller in CUD compared with controls ($F_{1,121} = 3.23, p = 0.075$). Consistent with their poor performance during the training phases, 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; error bars denote standard error of the mean, SQRT signifies square-root transformation, *ns* indicates $p > 0.05$, and *indicate $p < 0.05$].

Supplementary Materials

Materials and Methods

Supplementary Text

Tables S1 – S2

References (25 – 30)