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Evidence for Addiction-like Behavior in the Rat

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Although the voluntary intake of drugs of abuse is a behavior largely preserved throughout phylogeny, it is currently unclear whether pathological drug use ("addiction") can be observed in species other than humans. Here, we report that behaviors that resemble three of the essential diagnostic criteria for addiction appear over time in rats trained to self-administer cocaine. As in humans, this addiction-like behavior is present only in a small proportion of subjects using cocaine and is highly predictive of relapse after withdrawal. These findings provide a new basis for developing a true understanding and treatment of addiction.

The voluntary intake of drugs of abuse is a behavior largely conserved throughout phylogeny. Preferences for drug-associated environments or drug-reinforced learning of tasks have been found in several species (*1*–*6*). The possibility of studying these behaviors in animals has helped us to understand the neurobiological basis of drug taking (*7*–*10*) and, more generally, the brain systems for reward (*11*).

As important as the comprehension of drug taking and reward is, however, the major goal of drug abuse research is to uncover the mechanisms of addiction. Addiction is not just the taking of drugs but compulsive drug use maintained despite adverse consequences for the user (*12*). This pathological behavior appears only in a small proportion (15 to 17%) of those using drugs (*13*) and has the characteristics of a chronic disease (*12*). Indeed, even after a prolonged period of withdrawal, 90% of addicted individuals relapse to drug taking (*14*). Unfortunately, our knowledge of the biological basis of addiction lags behind our knowledge of the mechanisms of drug taking, probably because convincing evidence of addiction in animals is lacking.

We thus investigated whether addiction-like behaviors can be observed in rodents. Our experiments used intravenous self-administration (SA), the most common procedure for the study of voluntary drug intake in laboratory animals. Freely moving rats learned to obtain intravenous infusions of cocaine by poking their noses into a hole. To allow for addiction-like behavior to appear, we studied SA over a time frame of about 3 months, much longer than is typical in SA experiments (i.e., between 10 and 30 days). During this prolonged SA period, we repeatedly evaluated the intensity of three behaviors resembling those currently considered the hallmarks of substance dependence in the DSM-IV (*12*):

(i) The subject has difficulty stopping drug use or limiting drug intake. We measured the persistence of cocaine seeking during a period of signaled nonavailability of cocaine. The daily SA session included three 40-min "drug periods" that were separated by two 15-min "no-drug periods." During the drug periods, a standard FR5 reinforcement schedule was in effect: Five nose-pokes resulted in an infusion of 0.8 mg of cocaine per kilogram of body weight (mg/kg). During the no-drug periods, nose-pokes had no effect. The two different periods of drug availability were signaled by a change in the illumination of the SA chamber (*15*).

(ii) The subject has an extremely high motivation to take the drug, with activities focused on its procurement and consumption. We used a progressive-ratio schedule: The number of responses required to receive one infusion of cocaine (i.e., the ratio of responding to reward) was increased progressively within the SA session. The maximal amount of work that the animal will perform before cessation of responding, referred to as the breaking point, is considered a reliable index of the motivation for the drug (*16*).

(iii) Substance use is continued despite its harmful consequences. We measured the persistence of the animals' responding for the drug when drug delivery was associated with a punishment. During these sessions, nose-pokes on the standard FR5 schedule resulted in the delivery of both the drug and an electric shock. This shock punishment was signaled by a new cue light that was turned on at the time of the first nose-poke and off after the delivery of the shock (*15*).

To provide further validity to the addiction-like behaviors studied here, we analyzed their development as a function of the propensity of an individual to relapse to drug seeking. This approach was chosen because, as mentioned above, in humans the most predictable outcome of a first diagnosis of addiction is a 90% chance of relapse to drug use even after long periods of withdrawal (*14*). To study the propensity to relapse, we used the "reinstatement" procedure (*17*). After a 5- or 30-day period of withdrawal that followed the 3 months of SA, rats were exposed to stimuli known to induce relapse in humans, such as small amounts of the abused drug or a conditioned stimulus associated with drug taking. These challenges induce high levels of responding (reinstatement) on the device previously associated with drug delivery. The rate of responding during the test for reinstatement is considered a measure of the propensity to relapse.

In a first experiment, rats ($n = 17$) were assigned to two groups on the basis of their behavior on the test for reinstatement, induced here by the infusion of small quantities of cocaine given after 5 days of withdrawal that followed 76 days of testing for SA (*15*). The two groups ($n = 7$ each) contained the rats with the 40% highest (HRein) and 40% lowest (LRein) cocaine-induced reinstatement of responding (Fig. 1D) (*15*). HRein and LRein differed profoundly on the occurrence of addiction-like behaviors (Fig. 1, A to C) (*15*). HRein rats progressively increased their drug-seeking behavior during the no-drug periods ($F_{2,12} = 3.54$, $P < 0.05$) and after punishment ($F_{1,6} = 8.14$, $P < 0.05$) and also had higher breaking points on the progressive-ratio schedule ($F_{1,12} = 22.07$, $P < 0.0005$). In contrast, none of these behaviors increased over time in LRein rats, and in fact they tended to decrease. Finally, correlation analyses revealed that each addiction-like behavior strongly predicts the propensity to reinstatement (persistence in drug seeking, $r = 0.96$; resistance to punishment, $r = 0.67$; motivation for the drug, $r = 0.79$; $P < 0.001$ in all cases). A regression analysis including the three addiction-like behaviors as independent variables showed a multiple R equal to 0.82 ($P < 0.001$).

In a second experiment ($n = 15$), we assessed whether addiction-like behaviors could also be related to the propensity to reinstatement after a longer period of withdrawal (30 days). This time, reinstatement of responding induced by both cocaine and a cocaine-associated conditioned stimulus (CS) was studied (*15*). HRein rats ($n = 6$) showed higher levels of reinstatement responding induced by cocaine ($F_{3,30} = 4.07$, $P < 0.01$) and by the CS ($F_{1,10} = 4.62$, $P < 0.05$) than did LRein rats ($n = 6$) (Fig. 2, D and E) (*15*). Again (Fig. 2, A to C) (*15*), HRein rats displayed higher levels of addiction-like behaviors than did LRein rats (group effect for each behavior,

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$F_{1,10} = 7.09$ to 13.73, $P < 0.05$ to 0.005).

In humans, the diagnosis of addiction is performed by counting the number of diagnostic criteria that are met by an individual subject; a positive diagnosis is made when a preestablished number of criteria are found (*12*). We used a similar approach in rats by scoring them for each of the three addiction-like behaviors. For this analysis we added rats from a third experiment ($n = 26$) to increase the total number of subjects ($n = 58$) that completed the SA procedure. An individual was considered positive for an addiction-like criterion when its score for one of the three addiction-like behaviors was in the 66th to 99th percentile of the distribution (*15*). This allowed us to separate our sample of rats into four groups according to the number of positive criteria met (zero to three). The intensity of the three addiction-like behaviors was proportional to the number of criteria met by the subject (criteria effect for each behavior, $F_{3,54} = 16.99$ to 30.7, $P < 0.0001$) (Fig. 3, A to C) (*15*). Strikingly, the group that met all three positive criteria represented 17% of the entire sample (Fig. 3D), a percentage similar to that of human cocaine users diagnosed as addicts (*13*). Finally, despite this profound difference in addiction-like behavior scores, rats showing zero or three addiction-like behaviors did not differ on intake of cocaine during the entire SA period (Fig. 3E) or on sensitivity to the unconditioned effects of the drug, as measured by locomotion during SA (Fig. 3F) (*15*).

A factor analysis was then performed to determine whether the three addiction-like behaviors and the level of responding during extinction (*15*) were indices of two different underlying constructs. Extinction conditions allow for the measurement of persistence of responding for the drug when it is no longer available. Continued responding under these conditions is considered a measure of impulsivity/disinhibition (*18*), a general factor that could influence addiction-like behaviors (*19*, *20*). Remarkably, the factor analysis showed that the three addiction-like behaviors loaded equally on one factor ($r = 0.70$ to 0.88) and extinction loaded on a second independent factor ($r = 0.94$), with minimal cross-loading (Fig. 4A) (tables S1 and S2) (*15*). These findings indicate that the three addiction-like behaviors are measures of a single factor that may reflect compulsive drug use.

Finally, complementary behavioral tests were performed in rats from a fourth experiment ($n = 44$). These studies (*15*) confirmed that other dimensions previously related to vulnerability to drugs (*19–24*) do not explain individual differences in addiction-like behaviors. For example, rats with zero or three positive criteria did not differ (Fig. 4, B and C) (*15*) with respect to spontaneous motor activity (*19–22*) and anxiety-like behaviors (*23*, *24*). Similarly, a higher sensitivity to the unconditioned effects of the drug did not seem to be involved, because drug seeking persisted in a drug-free state ($F_{1,23} = 8.74$, $P < 0.005$) (Fig. 4D) (*15*). In contrast, as predicted by DSM-IV criteria, addiction-like behaviors were associated with difficulty in limiting drug intake when access to the drug was prolonged ($F_{1,23} = 4.4$, $P < 0.05$) (Fig. 4E).

These experiments show that after a prolonged period of SA, addiction-like behaviors can be found in rats. Although it is always difficult to translate findings from rats to humans, our data show striking similarities between the two species. Some rats develop behaviors similar to the diagnostic criteria for addiction described in the DSM-IV. Addiction-like behaviors are not present after a short period of SA but develop, as does addiction in humans, only after a prolonged exposure to the drug. Furthermore, as do human addicts, rats showing an addiction-like behavior have a

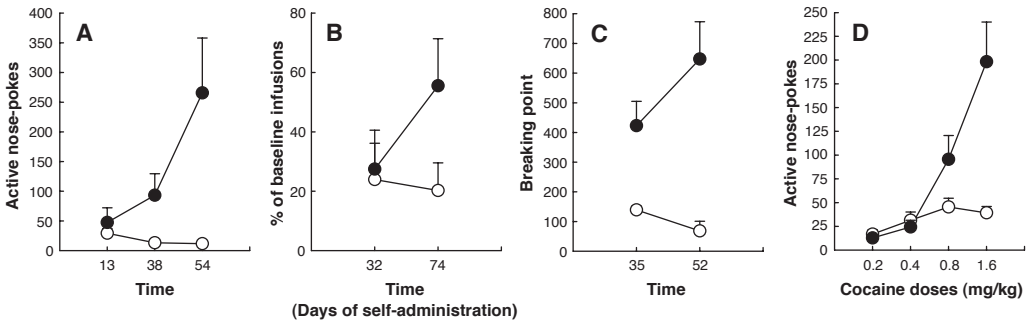

Fig. 1. Development of addiction-like behaviors over subsequent cocaine SA sessions in rats showing high (●, HRein) or low (○, LRein) cocaine-induced reinstatement after 5 days of withdrawal. (**A**) Persistence in drug seeking, as measured by number of nose-pokes in the cocaine-associated device during the no-drug period. (**B**) Resistance to punishment, as measured by change in the number of cocaine self-infusions (expressed as percentage of baseline SA) when cocaine delivery was associated with an electric shock. (**C**) Motivation for the drug, as measured by the breaking point during a progressive-ratio schedule. (**D**) Drug-induced reinstatement, as measured by number of nose-pokes in the drug-associated device as a function of the priming dose of cocaine. LRein and HRein contained the rats ($n = 7$ per group) with the lowest and highest reinstatement, respectively, induced by cocaine infusion at 1.6 mg/kg.

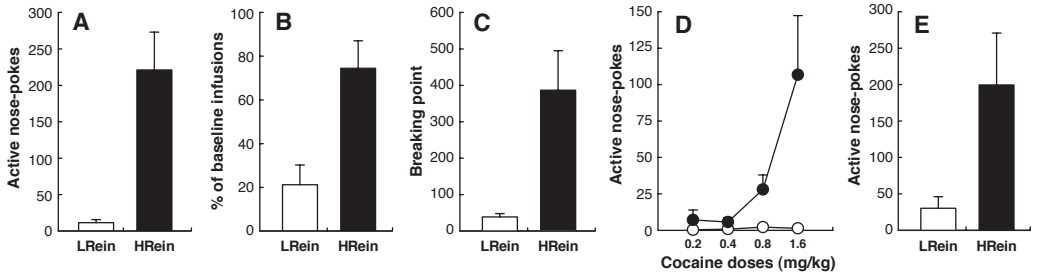

Fig. 2. Development of addiction-like behaviors over subsequent cocaine SA sessions in rats showing high (HRein) or low (LRein) cocaine-induced reinstatement after a 30-day withdrawal period. (**A**) Persistence in drug seeking, as measured by number of nose-pokes in the cocaine-associated device during the no-drug period of the 54th SA session. (**B**) Resistance to punishment, as measured by change in the number of cocaine self-infusions (expressed as percentage of baseline SA) when cocaine delivery was associated with an electric shock during the 72nd SA session. (**C**) Motivation for the drug, as measured by the breaking point during the progressive-ratio schedule conducted during the 60th SA session. (**D**) Drug-induced reinstatement, as measured by number of nose-pokes in the drug-associated device as a function of the priming dose of cocaine. (**E**) Reinstatement induced by a conditioned stimulus (CS), as measured by the number of nose-pokes in the drug-associated device when responding was associated with the contingent presentation of the CS. LRein and HRein contained the rats ($n = 6$ per group) with the lowest and highest reinstatement, respectively, induced by cocaine infusion at 1.6 mg/kg. Tests for cocaine- and CS-induced reinstatements were performed after 30 and 32 days of withdrawal, respectively, using a latin square design.

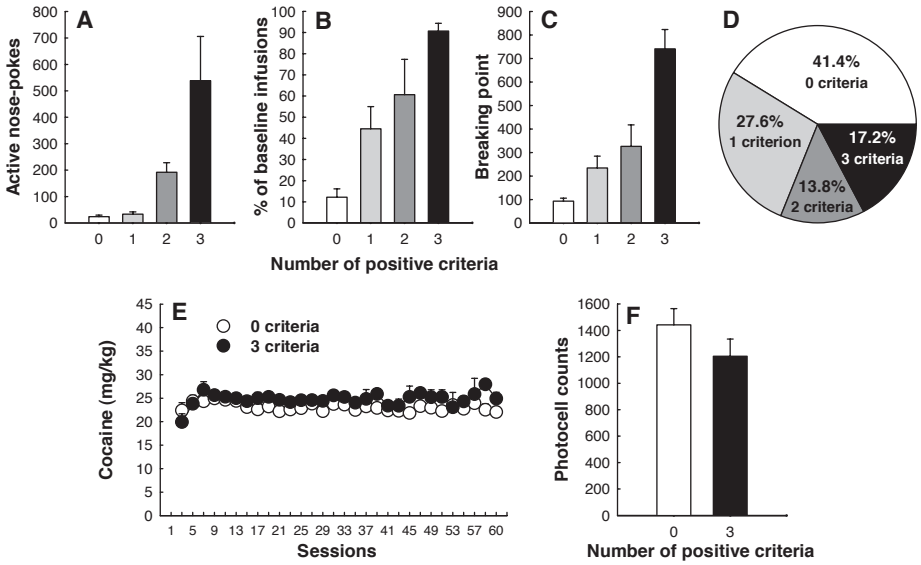

Fig. 3. (**A** to **D**) Addiction-like behaviors in rats positive for the presence of zero, one, two, or three addiction-like criteria. An individual was considered positive for an addiction-like criterion when its score for one of the three addiction-like behaviors was in the 66th to 99th percentile of the distribution. (A) Persistence in drug seeking, as measured by number of nose-pokes in the cocaine-associated device during the no-drug period of the 54th SA session. (B) Resistance to punishment, as measured by change in the number of cocaine self-infusions (expressed as percentage of baseline SA) when cocaine delivery was associated with an electric shock between the 72nd and 74th SA sessions. (C) Motivation for the drug, as measured by the breaking point during a progressive-ratio schedule performed between the 52nd and 60th SA sessions. (D) Percentage of the total population ($n = 58$) of rats positive for zero, one, two, or three addiction-like criteria. (**E** and **F**) Drug intake and motor activity during baseline SA in rats positive for the presence of zero or three addiction-like criteria. (E) Cocaine intake per session during baseline SA sessions (every other session is represented). (F) Horizontal motor activity during SA, as measured by number of photocell beam breaks. Results are expressed as the mean over three baseline SA sessions (between sessions 49 and 59).

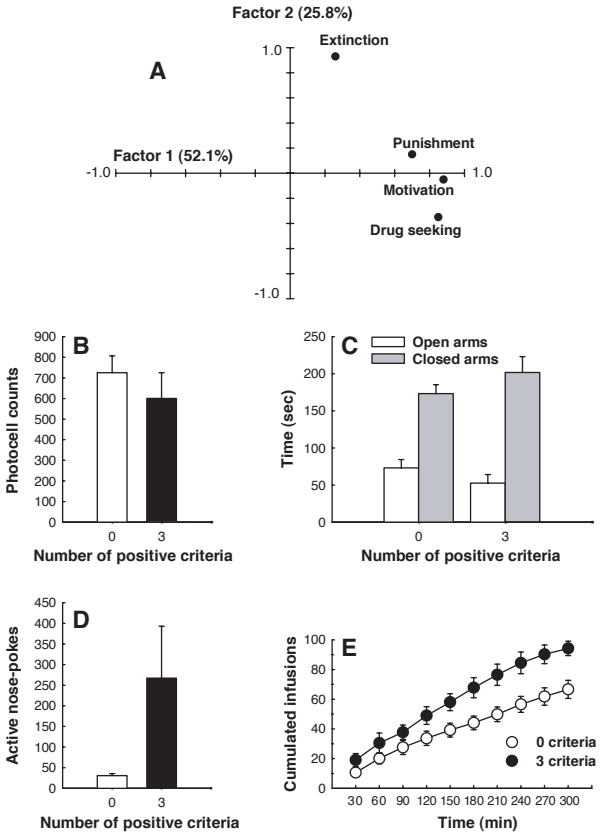

Fig. 4. (**A**) Factor analysis of SA variables. Two factors were extracted; factor 1 is represented by the horizontal axis and factor 2 by the vertical axis. Factor 1 (compulsive drug intake) accounts for 52.1% of the total variance, factor 2 (extinction) for 25.8%. The locations of the variables (●) correspond to the following parameters: Persistence in drug seeking was measured by the number of nose-pokes in the cocaine-associated device during the no-drug period of the 54th SA session. Resistance to punishment was measured by change in the number of cocaine self-infusions (expressed as percentage of baseline SA) when cocaine delivery was associated with an electric shock between the 72nd and 74th SA sessions. Motivation for the drug was measured by the breaking point during a progressive-ratio schedule performed between the 52nd and 60th SA sessions. Extinction was measured by the number of active nose-pokes during a 1-hour extinction session conducted between the 60th and 63rd sessions. (**B** and **C**) Measures of other potentially drug-related behaviors in rats positive for the presence of zero or three addiction-like criteria. (B) Spontaneous horizontal motor activity, as measured by number of photocell beam breaks exhibited during a 2-hour exposure to a novel environment. (C) Anxiety-related behavior, as measured by the comparison of the time spent in the open versus the closed arms during a 5-min exposure to an elevated plus-maze. (**D** and **E**) Measure of drug seeking in a drug-free state and of drug taking during extended access to cocaine in rats positive for the presence of zero or three addiction-like criteria. (D) Persistence in drug seeking in a drug-free state, as measured by the number of nose-pokes in the cocaine-associated device when a no-drug period precedes the SA session (mean of five consecutive tests performed between the 47th and 58th SA sessions). (E) SA during extended access to the drug. Cocaine was continuously accessible for 5 hours, and SA was estimated by the cumulated number of self-infusions over time.

high propensity to relapse even after a long period of withdrawal. Finally, the percentage of rats (17%) that show a high score for all three addiction-like criteria is similar to the percentage (15%) of human cocaine users diagnosed as addicts (*13*).

It could seem surprising that the capacity of drugs of abuse to induce addiction-like behavior exists across species. As already mentioned, however, voluntary intake of drugs abused by humans is present in several species (*1–6*). Drugs of abuse have reinforcing effects by activating endogenous reward systems that are similar in different species. Thus, the mechanisms mediating the neuroadaptations induced by chronic drug exposure and their behavioral consequences (addiction) may be similar in different species. Indeed, preliminary results show similar changes in brain activity between rats showing addiction-like behaviors and human addicts (*15*).

Our results allow us to propose a unified vision of the origin of addiction that integrates the experimental and clinical perspectives. The major hypotheses driving experimental research consider the degree of drug exposure as the key factor leading to addiction (*7–10*, *25*). By contrast, clinical visions of drug abuse have been progressively shifting weight from the role of drug exposure to the role of the higher vulnerability to drugs in certain individuals (*26–30*). Our data indicate that addiction results from the interaction of these two variables: (i) the degree of exposure to drugs (because addiction-like behavior appears only after extended access to cocaine), and (ii) the degree of vulnerability in the exposed individual (because, despite a similar drug intake in all subjects, addiction-

like behavior appears only in a few). It is thus the interaction between a long exposure to drug and a vulnerable phenotype, not one or the other factor in itself, that seems to determine the development of addiction.

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Supporting Online Material

www.sciencemag.org/cgi/content/full/305/5686/1014/DC1
Materials and Methods
SOM Text
Tables S1 and S2

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Drug Seeking Becomes Compulsive After Prolonged Cocaine Self-Administration

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Compulsive drug use in the face of adverse consequences is a hallmark feature of addiction, yet there is little preclinical evidence demonstrating the actual progression from casual to compulsive drug use. Presentation of an aversive conditioned stimulus suppressed drug seeking in rats with limited cocaine self-administration experience, but no longer did so after an extended cocaine-taking history. In contrast, after equivalent extended sucrose experience, sucrose seeking was still suppressed by an aversive conditioned stimulus. Persistent cocaine seeking in the presence of signals of environmental adversity after a prolonged cocaine-taking history was not due to impaired fear conditioning, nor to an increase in the incentive value of cocaine, and may reflect the establishment of compulsive behavior.

Compulsive drug seeking and drug taking distinguishes drug addicts from casual drug users. Addicts display drug-dominated, inflexible behavior and are unable to shift their thoughts and behavior away from drugs and drug-related activities. Even with awareness of the deleterious consequences of this drug-centered behavior, addicts have enormous difficulty in abstaining from drug seeking and use (*1*, *2*). Several hypotheses try to explain the occurrence of compulsive drug use; it may reflect the establishment of an automatic stimulus-response habit (*3*, *4*), drug-induced loss of impulse control (*5*), sensitization of an incentive ("wanting") system (*6*), or disruption of hedonic homeostasis (*7*). Remarkably, there is little evidence from animal studies demonstrating the actual progression from casual to compulsive drug use, although drug intake in rats escalates after weeks of prolonged drug self-administration (*8*). Modeling compulsive drug seeking in animals would clarify our understanding of the neuropsychology of drug addiction and may also lead to the development of novel treatments.

Here, we tested the hypothesis that an extended drug-taking history renders drug seeking impervious to environmental adversity (such as signals of punishment), capturing one element of its compulsive nature (*1*). Appetitive behavior for natural and drug rewards is readily suppressed by aversive environmental stimuli or outcomes, a phenomenon termed conditioned suppression (*9*–*11*). We investigated whether the ability of a footshock-paired conditioned stimulus (CS) to suppress cocaine-seeking behavior diminishes after a prolonged cocaine-taking history and whether this reduced susceptibility to conditioned suppression also followed a similarly prolonged history of seeking sucrose, a high-incentive natural reinforcer.

In experiment 1, 21 rats were trained to self-administer cocaine under a heterogeneous seeking-taking chain schedule (*12*), in which drug seeking and taking are separate acts (*13*). Thus, meeting a response requirement on one lever (the seeking lever) in an operant chamber never resulted in drug, but instead gave access to a second lever (the taking lever), responding on which resulted in an intravenous infusion of cocaine. Immediately after the rats reached training criterion on this schedule—that is, after a limited cocaine-taking history—12 rats received tone-footshock pairings (the CS-shock group), whereas the other nine rats received presentations of the same tone not paired with footshock (the control group). Several days later, conditioned suppression of drug seeking was assessed in a session in which the rats had access to the seeking lever only and the footshock CS was presented for three 2-min periods interspersed with three 2-min periods when no CS was presented (*13*). The CS-shock group showed a profound conditioned suppression of drug seeking during presentation of the CS [$F(\mathrm{CS}) = 5.32$, $P < 0.05$; $F(\mathrm{CS} \times \mathrm{group}) = 25.65$, $P < 0.001$] (Fig. 1A). There was also a marked increase in the time taken to make the first seeking response (seeking latency) in the CS-shock group [$F(\mathrm{group}) = 7.43$, $P < 0.01$] (Fig. 1B). Thus, in rats with limited cocaine self-administration experience, drug seeking was greatly suppressed by presentation of an aversive CS, showing that it was sensitive to an adverse outcome.

Next, we tested whether cocaine seeking would become less susceptible to an aversive CS after prolonged cocaine self-administration

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