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# Punishment models of addictive behavior

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Substance addiction is a chronic relapsing brain disorder, characterized by loss of control over substance use. In recent years, there has been a lively interest in animal models of loss of control over substance use, using punishment paradigms. We provide an overview of punishment models of addiction, that use quinine, histamine, lithium chloride and footshocks as aversive stimuli, and we discuss the merits and drawbacks of these approaches. Importantly, many studies have demonstrated that under certain conditions, animals are willing to endure punishment during the pursuit of substances of abuse, which captures an essential component of addictive behavior. We conclude that punishment models of addiction represent a valuable contribution to the study of addiction.

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## Introduction

Addiction to substances of abuse remains an enormous global health problem. It has been estimated that 76 million people worldwide are addicted to alcohol [1], 29 million people are addicted to illicit drugs, such as opiates, psychostimulants and cannabis [2] and 1.1 billion people smoke tobacco [3], a substantial proportion of which can be considered addicted. Alongside the suffering inflicted by the addictive behavior itself, substance addiction dramatically increases the risk for a wide range of communicable and non-communicable diseases, including lethal conditions such as cardiovascular problems, liver failure and cancer. Indeed, substance addiction is considered to be one of the leading causes of premature death worldwide [1–3]. Remarkably, only 1 in 6 addicts are estimated to be in treatment [2], and the treatment options available are modest in terms of number and efficacy [4•,5,6]. In order to develop improved treatment strategies for addiction, we think that a profound understanding of the neural underpinnings of addictive behavior is essential.

For more than half a century, animal models have been used to investigate the behavioral and neural mechanisms of addiction. The positive affective, reinforcing properties of substances of abuse have been widely studied using place conditioning [7,8] and intracranial self-stimulation methods [9,10]. Arguably the greatest progress in understanding addictive behavior using animal models has come from oral and intravenous self-administration studies, that derive considerable validity by virtue of the fact that they employ voluntary, active intake of drugs of abuse [11,12]. Moreover, self-administration setups have shown to be a versatile method to investigate addictive behavior, in the sense that variants of this paradigm have been developed to study the incentive motivational properties of substances of abuse [13,14], the role of drug-associated cues in addictive behavior [15,16], and relapse to extinguished drug seeking [17,18].

The most recent development in animal models of addictive behavior constitutes models that explicitly study loss of control over substance seeking and taking. Inspired by the realization that the majority of the diagnostic criteria for addiction in DSM-IV [19] and DSM5 [20] comprise behaviors that signify a lack of control over substance use, researchers have started to develop models that capture these compulsive aspects of addictive behavior. Many of these studies have focused on the DSM criterion of continued substance use despite negative consequences, and have operationalized this as resistance to punishment [21•,22]. In the paradigms that have been used, the pursuit of substances was associated with aversive events or circumstances, and the willingness of animals with a certain predisposition or substance taking history to endure this adversity when access to substance is at stake was assessed. In this overview, we will present punishment models of compulsive substance use, highlight their merits and drawbacks, and discuss challenges for future research.

## Punishment models of addictive behavior

### Quinine

Perhaps the first use of a punishment setup in the context of addiction research is the work of Wolffgramm and

colleagues, who studied alcohol addiction-like behavior in rats [23,24]. The manipulation they used is to render the taste of orally ingested alcohol aversive using the bitter tastant quinine. They observed that the efficacy of quinine to reduce alcohol intake substantially declined after prolonged periods of alcohol drinking, interspaced with periods of forced abstinence. This reduced sensitivity of alcohol intake to quinine was accompanied by a loss of sensitivity to other factors that influence alcohol drinking, such as social rank and social isolation. Comparable findings were later reported for other substances of abuse, including opiates and psychostimulants [24–26]. The finding of reduced sensitivity of alcohol drinking to quinine after prolonged alcohol intake has subsequently been replicated in rats and mice [27,28••,29,30,31•,32,33]. In rats, this relative insensitivity to quinine was observed after prolonged exposure to an intermittent (rather than continuous) pattern of alcohol access [27,28••,32], and sometimes in high alcohol consuming rats only [30]. In these experiments in rats, quinine-containing alcohol was the only source of alcohol during the test. Interestingly, experiments in mice have shown comparable findings, for example, willingness to drink bitter, quinine-containing alcohol if water is the only alternative fluid [29,33]. Moreover, after two months of voluntary alcohol drinking, mice continued to drink quinine-containing alcohol even if non-adulterated alcohol was simultaneously available [29]. Importantly, in these latter experiments, regardless of experience with alcohol drinking, all mice avoided quinine-containing water, indicating that the persistent intake of quinine-containing alcohol was not the result of altered taste perception [29].

### Lithium chloride and histamine

In order to associate substance intake with interoceptive malaise, post-ingestion treatment with lithium chloride has been used. This approach is widely used to evoke conditioned taste aversion, and to assess the ability of animals to use a representation of the value of a reinforcer to direct operant behavior [34]. The first of these studies showed that taste aversion conditioning with lithium chloride profoundly reduced the oral intake of alcohol and cocaine solutions, yet did not alter responding in extinction for alcohol and cocaine [35,36]. These findings suggest that acts distal to substance use (i.e. attempts to obtain the substance) are less sensitive to punishment than the actual substance intake, as long as the taste memory trace provides explicit feedback of the degraded value of alcohol and cocaine after its association with interoceptive malaise. Recently, also the sensitivity of intravenous cocaine self-administration in rats to lithium chloride-induced malaise was investigated [37•]. The findings were comparable to those described above [35,36], inasmuch as that cocaine taking was sensitive to devaluation, whereas responding for a cocaine-associated cue was not. Importantly, the sensitivity to lithium chloride was lost in animals with a history of lengthy cocaine self-administration sessions [37•]. Interoceptive aversion has also been employed using intravenous histamine as a punisher in rats and non-human primates [38–40]. When histamine was added to the solution for intravenous cocaine self-administration, this reduced responding for cocaine, while at the same time increasing responding for concurrently available food or unadulterated cocaine [39,40]. Importantly, the aversive effects of histamine, by intravenous infusion, are direct (as compared to the delayed aversive effects of lithium chloride treatment after self-administration). Indeed, when infusion of histamine was delayed (i.e. for seconds to minutes after cocaine infusion), its ability to reduce responding for cocaine was found to decline [40].

### Footshock

The most widely applied punisher in substance self-administration studies is mild electric shock. Originating from Jenkins' obstruction box studies [41], initial studies in primates showed that response-contingent shocks reduced cocaine self-administration, whereby shocks of higher intensity were more effective, and delayed shocks less effective [42,43]. In the last decade, this setup has been widely used in rats [44–48]. In an influential study, Deroche-Gamonet *et al.* described that response-contingent footshocks suppressed responding for cocaine in rats [45], but that in a subgroup of rats, the sensitivity to footshock profoundly declined after a lengthy cocaine taking history. This latter subgroup of animals was also characterized by high levels of cocaine-induced reinstatement of responding after extinction. Moreover, these rats showed other signs of addictive behavior as well, such as high motivation for cocaine under a progressive ratio of reinforcement and persistence of non-reinforced responding, albeit that these different addiction-like behaviors did not emerge simultaneously [45]. Subsequent experiments showed that this addiction-like behavior could be predicted on the basis of impulsive behavior (i.e. premature responses in the 5-choice serial reaction time task), irregular patterns of cocaine self-administration and a high preference for a novel environment, but not novelty-induced hyperlocomotion [46–48].

In the studies described above, every substance taking episode was punished, and in the studies by Deroche-Gamonet, Belin and colleagues [45–48], the response preceding the one that lead to cocaine infusion was punished as well (i.e., the fourth and fifth response under a fixed-ratio 5 schedule of reinforcement). Since in humans, not every instance of substance taking has inevitable and direct negative consequences, other studies have used somewhat different punishment procedures. For example, footshock punishment was made probabilistic, whereby one in eight responses was punished with a footshock, and one in three responses was reinforced with alcohol [28••]. Thus, even though alcohol taking was punished, delivery of alcohol was more frequent than

punishment. With this approach, a subgroup of rats was shown to become insensitive to footshock punishment. Other studies have moved punishment of responding forward in time, for example, to the acts directed at obtaining cocaine. To achieve this, Pelloux, Everitt and colleagues [49,50,51•] have used a seeking-taking chain schedule of reinforcement, in which rats were trained to respond on one lever ('seeking lever') in order to gain access to a second, 'taking' lever, responding on which produced an intravenous infusion of cocaine. After training, half of the seeking episodes did not lead to presentation of the taking lever, but was punished with a mild electric footshock. Whereas the majority of animals showed profoundly reduced cocaine seeking when the punishment contingency was introduced, a subgroup of animals did not, albeit after a prolonged cocaine taking history [49]. Comparable findings were reported by others, in setups in which seeking, when punished, did [52], or did not allow for subsequent cocaine taking [53••]. Further analysis of this behavior showed that insensitivity to punishment was the result of excessive drug exposure rather than experiencing a large number of cocaine-cue associations [50]. In a subsequent study, punishment of seeking (i.e. footshock after fulfilling the response requirement on the seeking lever) or taking (i.e. footshock after responding on the taking lever) was compared. The data showed that rats were more willing to endure punished taking than seeking [51•], suggesting that punishment of distal substance seeking acts is more effective in reducing addictive behavior than punishment of the actual use of the substance. Importantly, the availability of response-contingent sucrose increased the effectiveness of punishment to reduce cocaine seeking. Threat of adversity has also been used in the context of addictive behavior, as an alternative to immediate and inevitable punishment. To this aim, auditory cues previously associated with mild electric footshocks were used to influence cocaine seeking [54–56]. These experiments revealed that presentation of a footshock-associated cue suppressed cocaine seeking, but after limited drug taking experience only. Thus, after an extended cocaine self-administration history, the effectiveness of the footshock-associated cue to alter cocaine seeking profoundly declined [54,56]. A different threat model has been used in studies on eating disorders, in which rats or mice have to enter an aversive, brightly lit environment in order to get access to a preferred food [57,58]. This approach has as yet not been used in the context of self-administration of substances of abuse.

Punishment of cocaine and heroin self-administration has recently also been performed in studies in which Jenkins' obstruction box [41] was revisited. Thus, in these experiments, rats had to cross an electrified grid to reach the lever, pressing which produced an infusion of the drug [59–62]. For each individual animal, the shock intensity that completely suppressed responding for the drug was determined, after which reinstatement of responding for drug-associated cues was assessed. Interestingly, reinstatement of responding for cocaine was only observed in about half of the rats, whereas in the case of heroin, all rats showed cue-induced reinstatement of responding [60,61]. Last, footshock-induced punishment of alcohol and methamphetamine self-administration has also been used as a method to make rats cease responding for the respective substance, in order to assess context- [63] or cue-induced reinstatement of responding [64].

## Punishment models of addictive behavior: merits and drawbacks

The studies discussed above describe approaches aimed at emulating persistent substance use despite negative consequences. Clearly, these have substantially moved the preclinical addiction field forward by demonstrating that aversive stimuli of different modalities, including gustatory (quinine), interoceptive (lithium chloride, histamine) and tactile (footshock) ones, can inhibit behavior directed at substances of abuse. More importantly, a substantial proportion of these studies also reports that animals with a certain predisposition and/or self-administration history display reduced sensitivity to aversive interference [23,24,27,28••,29,30,35,36,37•,45–50,51•,52,53••,54,56], which resembles the aberrant, unflagging pursuit of substances of abuse in human addicts [19,20]. These contemporary setups of addiction-like behavior hold great promise to increase our understanding of the neural and behavioral structure of substance use disorders. Indeed, recent years have seen explicit progress in the study of the neural underpinnings of addiction using punishment models [28••,31•,52,53••,65–71].

### Quinine and histamine

An issue that needs to be considered with care is which aspect of substance use is being punished in these models. Indeed, gustatory, interoceptive and tactile punishers have all been scrutinized for their validity to study human addictive behavior. The bitter taste of quinine is a gustatory punisher, that is immediately apparent following ingestion of alcohol (as well as other substances of abuse in oral consumption experiments [24–26]). As such, it is an immediate punisher of alcohol drinking, and the sensation of its bad taste actually precedes the perception of the subjective effects of alcohol. It is useful to realize that taste is an important aspect of alcohol ingestion, and that one of the behavioral characteristics of alcohol addiction is the ingestion of unpalatable (cheap, but with high alcohol content) liquors, in order to maximize alcohol intake at minimal financial cost. In extreme cases, alcohol addicts even ingest unsavory alcohol-containing products not intended for human consumption, such as mouthwash and aftershave [72,73], whereby taste has obviously become less important than alcohol content. The willingness of animals to endure the bitter taste of quinine, if this is the only way of obtaining alcohol

[23,24,28••,29,30], reflects the reduced importance of taste in alcohol addiction, which is perhaps even better exemplified by the continued ingestion of quinine-containing alcohol when non-adulterated alcohol is simultaneously available [29]. Comparable to quinine in terms of its immediacy is the interoceptive discomfort induced by intravenous histamine, which has been shown to be an efficient punisher of cocaine self-administration [38–40]. Resistance to histamine punishment has so far not been demonstrated in an animal study, although this may be a matter of histamine dose and/or cocaine self-administration experience rather than histamine being a stronger punisher than quinine, lithium chloride or footshock.

### Lithium chloride

Somewhat different to quinine and histamine, the aversive effects of lithium chloride-induced malaise emerge with a delay after substance taking. This delay stems both from the slower onset (and probably longer duration) of the lithium chloride-induced interoceptive effects compared to the rapid subjective substance effects, but also from the practical point that lithium is passively administered to the animal after drug exposure [35,36,37•]. In this regard, lithium chloride may more closely emulate the visceral discomfort that follows substance taking episodes, such as the gastrointestinal pain that alcohol addicts may suffer from, as well as the physical malaise that characterizes an alcohol hangover or cocaine crash. Remarkably, the studies that have employed lithium chloride to punish addictive behavior have found that it only reduces proximal substance taking acts (i.e. drinking alcohol and cocaine solutions, intravenous cocaine self-administration) but not behaviors distal to substance use, such as responding for cocaine or alcohol in extinction (i.e. without immediate gustatory feedback about the degraded reinforcer) and responding for cocaine cues [35,36,37•]. This indicates that the effectiveness of punishment declines with increasing temporal distance, consistent with the classic observation that the strength of a learning process declines with the delay between action and outcome [74].

### Footshock

As is clear from the studies discussed here, mild electric shocks are the most widely employed punisher in preclinical addiction research [28••,41–50,51•,52,53••,54–64]. This has probably both scientific reasons, as the large number of fear conditioning studies in the literature yields an enormous database of methodological and neural background information, as well as practical reasons. Thus, the intensity, quantity and probability of footshocks can easily be varied, which renders this a very versatile way of interfering with behavior. Comparable to quinine and histamine, footshocks are often used as an immediate punisher of substance use, but the manner in which addictive behavior is punished is likely to be different. That is, the sensation of footshock is immediate, noxious, and brief, and the expectation of footshocks generates a state of conflict and fear. This may emulate the emerging adverse consequences of persistent substance use in humans, in which the user has to weigh the immediate positive experience of substance use against the possible adverse consequences, such as job loss, relationship crisis or disease. Comparable to quinine and lithium chloride, it has also been shown that under certain conditions, animals are willing to endure mild electric footshocks in order to obtain cocaine or alcohol [28••,45–50,51•,52,53••]. From a naturalistic point of view, the validity of footshocks for human addictive behavior may be less than the other punishers discussed here. Thus, the pursuit or use of substances in humans is typically not followed by noxious, physical punishment, whereas, as discussed above, addicts are confronted with bad taste or interoceptive malaise as a result of their substance use. That said, a recent study in humans has shown that cocaine addicts are less proficient in the avoidance of electric shocks, suggesting that reduced sensitivity to physical punishment does play a role in addictive behavior [75••].

#### *The validity of immediate punishment*

A limitation that is often noted for experimental approaches as discussed here is the immediacy of punishment. Although the timing of its consequences remains largely unclear, substance use in humans is usually not punished immediately and inevitably. Rather, the negative consequences of addictive behavior are often delayed, probabilistic and difficult to trace back to single substance use episodes. In fact, the observation that delayed punishment (compared to immediate punishment) is substantially less effective in interfering with cocaine self-administration [40,43] perhaps illustrates the very nature of addiction, in that substance abuse persists despite negative, but often delayed consequences. In order to use footshock punishment in a way that more closely emulates the human situation where the adverse sequelae of substance use can be rather unpredictable, researchers have therefore also used probabilistic shocks [28••,49,50,51•,52]. An alternative approach has used threat of footshock punishment, rather than the shocks themselves [54–56], to model seeking substances in a situation where this entails danger (for example, trying to buy drugs while there is police surveillance on the street). Likewise, these approaches have revealed conditions in which animals endure shock or threat when seeking or taking substances of abuse [28••,49,50,51•,54,56]. One could therefore argue that models using threat of adversity or unpredictable adversity more closely capture the anticipation of adverse consequences at the time of substance use, that probably better reflects the internal conflict that human addicts experience. In any event, understanding the relative timing between substance use and adverse consequences, and how this impacts on use,

is one of the main challenges in the management of addiction, and this knowledge should be incorporated into the design of animal models of addictive behavior.

*Understanding interventions*

The overarching aim of the studies discussed here has been to develop and use animal models to elucidate the neural underpinnings of addictive behavior. Subsequently, these approaches can be used to test the effects neural manipulations on addiction [28••,53••,67,68]. In addition, they can also help understand the effectiveness of behavioral strategies to influence addictive behavior. For example, the findings that behaviors proximal to substance use are more sensitive to punishment than distal ones if substance intake is punished [35,36,37•] is very informative about the structure of addictive behavior. Thus, even if substance *taking* has negative consequences, this may not alter their *procurement*, since the temporal distance between seeking substances and the sensation of punishment after substance intake may be too long [74]. An important study in this regard has been performed by Pelloux and colleagues [51•], who reported that punishing distal behaviors (i.e., cocaine seeking) is more effective than punishing cocaine taking, suggesting that interfering with substance use in an early stage of the chain of substance-directed behaviors may yield better results. Also encouraging is the finding in this study [51•] that the availability of an alternative source of reinforcement (i.e., response-contingent sucrose) further reduces cocaine seeking and taking, suggesting that positive (i.e. an alternative source of reinforcement) and negative incentives (i.e. punishment) can have additive beneficial effects on addictive behavior.

*Other aspects of addictive behavior*

A limitation of punishment studies discussed here is that they only model part of the addictive behavior in humans. Thus, whereas one can argue that 9 out of 11 diagnostic criteria in DSM5 comprise behaviors representing loss of control over substance use [20], punishment setups emulate only two of those (i.e., recurrent use in situations in which it is physically hazardous; continued use despite knowledge of substance-related problems). Therefore, if one aspires to generate an animal model that captures multiple aspects of addiction, other signs of addictive behavior should be incorporated as well [21•]. These include high motivation to work for substances (as a model of devoting a great deal of time to procuring, consuming and recovering from use), responding in extinction (to model persistent desire or unsuccessful attempts to restrict use), reinstatement of substance seeking (as a model of craving), choosing substances over natural reinforcers (to model the neglect of alternative, social and professional, sources of reward), and the effects of social isolation and social rank (as a model of continued use despite persistent social problems caused by use and giving up important social activities in favor of use) [18,45,46,76–80,81•,82,83]. The validity of these models is beyond the scope of this paper, but we do acknowledge the value of these approaches for the study of addictive behavior. On the other hand, we think that employing single-aspect models allows for the investigation of the neurobiological underpinnings of distinct aspects of addiction in isolation. In this regard, it is important to keep in mind that addiction is a multi-faceted disorder, in which different aspects, criteria or behavioral aberrations may play a role, depending on, for example, the substance abused, the history of the individual, or the environmental circumstances. Importantly, neurobiological studies in which different aspects of addictive behavior have been combined have provided evidence that exaggerated motivation, responding in extinction, reinstatement of extinguished responding and resistance to punishment rely on distinct neural mechanisms [84–86].

## Conclusion

The last two decades have seen a remarkable interest in the use of punishment paradigms to model the persistent aspects of substance use disorders. These models have used punishments from different sensory modalities, and methodological variations in these setups allow for the assessment of distinct aspects of loss of control over substance use. Although these punishment setups may arguably still be in development, we expect that their optimization and integration with other models, capturing yet other aspects of addictive behavior such as exaggerated motivation for substances and relapse, will make a valuable contribution to our knowledge about the neural and behavioral structure of addiction. This may ultimately contribute to the development of more effective treatments for this devastating disorder.

## Conflicts of interest

The authors declare that, except for income received from their primary employers, no financial support or compensation has been received from any individual or corporate entity over the past three years for research or professional service and there are no personal financial holdings that could be perceived as constituting a potential conflict of interest.

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