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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