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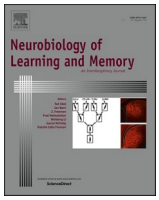

The multiple faces of footshock punishment in animal research on addiction

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A B S T R A C T

Continued drug use despite negative consequences is a hallmark of addiction commonly modelled in rodents using punished drug intake. Over the years, addiction research highlighted two subpopulations of punishment sensitive and resistant animals. While helpful to interrogate the neurobiology of drug-related behaviors, these procedures carry some weaknesses that need to be recognized and eventually defused. Mainly focusing on footshock-related work, we will first discuss the criteria used to define punishment-resistant animals and how their relative arbitrariness may impact our findings. With the overarching goal of improving our interpretation of the punishment-resistant phenotype, we will evaluate how tailored punishment protocols may better apprehend resistance to punishment, and how testing the robustness of punishment resistance could yield new results and strengthen interpretations. Second, we will question whether and to what extent punishment sensitivity, as currently defined, is reflective of abstinence and suggest that punishment resistance is, in fact, a prerequisite to model abstinence from addiction. Again, we will examine how challenging the robustness of the punishment-sensitive phenotype may help to better characterize it. Finally, we will evaluate whether diminished relapse-like behavior after repeated punishment-induced abstinence could not only contribute to better understand the mechanisms of abstinence, but also uniquely model progressive recovery (i.e., after repeated failed attempts at recovery) which is the norm in people with addiction. Altogether, by questioning the strengths and weaknesses of our models, we would like to open discussions on the different ways we interpret punishment sensitivity and resistance and the aspects that remain to be explored.

1. Introduction

Continued drug use despite negative consequences is a hallmark of substance use disorder (SUD). Practically, one of its most prominent expressions involves direct harm such as continued drug use despite negative effects on physical and mental health, or despite the risk of encountering dangerous situations (e.g., dangerous environment, illegal activities) (American-Psychiatric-Association, 2013). Progressive recovery of harmless, drug-free behaviors is, of course, the primary goal of every therapy but also a sign that a given therapy is effective. This is partly why continued drug intake despite negative consequences is a key feature that preclinical addiction studies try to model. Indeed, having animals taking drug despite aversive outcomes would mimic addiction-like behavior and reversing this behavior would indicate potential therapeutic avenues. In rodents, negative consequences are modeled using punishment of drug intake. There are two types of punishment: negative punishment consists of removing a rewarding event or outcome contingent on performing a behavior while positive punishment consists of delivering an aversive event or outcome contingent on performing it (Jean-Richard-Dit-Bressel, Killcross, and McNally, 2018). Though both types of punishment are sometimes used, positive punishment is, by far, the most frequently used type of punishment in addiction research on animals. This state of affairs is presumably mainly because this type of punishment is generally thought to more closely simulate addiction-relevant adverse events in humans. A variety of aversive events has been used as positive punishers of drug intake, including lithium chloride, histamine, quinine or capsaicin adulteration, air puffs, electric footshock, but the latter has become over the years the model of choice. Indeed, contrary to chemical punishers, footshock can be applied with a finer degree of control to test specific contingencies and/or allow testing different levels of punishment severity. Moreover, footshock is easily implemented for various types of drugs, especially in intravenous self-administration paradigms compared to quinine adulteration, for example, that is restricted to oral intake. For these reasons, the following text will focus mainly on findings obtained with footshock punishment.

The discovery that some individuals overcome the unpleasant experience induced by a low-to-mild footshock intensity to continue taking drugs has been used to interrogate the neurobiological substrates of compulsive drug use in animals (Blackwood, McCoy, Ladenheim, and Cadet, 2019; Cadet, Patel, and Jayanthi, 2019; Chen, Yau, Hatch, Kusumoto-Yoshida, Cho, Hopf, and Bonci, 2013; Kasanetz, Deroche-Gamonet, Berson, Balado, Lafourcade, Manzoni, and Piazza, 2010; Krasnova, Gerra, Walther, Jayanthi, Ladenheim, McCoy, Brannock, and Cadet, 2017; Lesscher and Vanderschuren, 2012; Pascoli, Hiver, Li, Harada, Esmaeili, and Luscher, 2023; Subu, Jayanthi, and Cadet, 2020; Torres, Jayanthi, McCoy, and Cadet, 2018; Vendruscolo, Barbier,

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Schlosburg, Misra, Whitfield, Logrip, Rivier, Repunte-Canonigo, Zorrilla, Sanna, Heilig, and Koob, 2012) (for a recent discussion, see: (George, Ahmed, and Gilpin, 2022)). Conversely, animals that stop taking drugs when facing punishment have been studied to explore the neurobiological basis of abstinence (Cadet et al., 2019; Jayanthi, Peesapati, McCoy, Ladenheim, and Cadet, 2022; Krasnova, Marchant, Ladenheim, McCoy, Panlilio, Bossert, Shaham, and Cadet, 2014; Torres et al., 2018).

Here, we propose to discuss the value and limitations of these two faces of punishment in addiction research which will allow us to identify and define a possible third face: diminished relapse-like behavior after repeated punishment-induced abstinence as a model of progressive recovery.

An elusive dividing line between punishment-resistant and nonresistant drug use.

Historically, electric punishment was first studied as a tentative behavioral therapy to suppress or reduce various undesirable behavior, including drug use in people with alcoholism and drug addiction (Rachman, 1964). It is only later that footshock punishment was used in animal research to study drug use in the face of negative consequences (Smith and Davis, 1974). Since then, researchers found conditions that favor the expression or emergence of individual variation to punishment, with punishment sensitive and resistant animals. The comparison of these different individuals has gained popularity for studying multiple drug-related mechanisms, and among them continued drug use despite negative consequences. Briefly, in order to separate these two subpopulations, a relatively medium intensity footshock (usually around 0.3–0.4 mA in rats and 0.15–0.2 mA in mice) is applied by the experimenter (with variations in the punishment schedules). Most of the time, this yields a split of 41 % (±11) of punishment resistant rats across studies (Table 1). While interesting, this relatively high rate raises a question: is taking a drug in face of a punishment that causes about half of the remaining population to stop, a genuine sign of addiction-like behavior? This point, of course, takes us back to the classic issue of the relevance of using a statistical norm to draw a line to separate the pathological from the normal (Ahmed, 2022; Canguilhem, 1978; Wakefield, 1992). But this relatively high rate, at least, questions the significance of the aversive event used in such paradigms to recapitulate the extreme negative consequences of drug use that are crucial in the diagnosis of SUD.

Together, the relatively balanced proportions of punishment sensitive vs. resistant animals suggest that there is something beyond associating a punishment to a behavior, and as formulated by Marchant and colleagues: "*Punishment-resistant drug self-administration is only seen when the parameters are set to observe it*" (Marchant, Campbell, and Kaganovsky, 2018). These observations, however, led to consider wider variations in strength of punishment. For example, a paradigm using daily gradual increases in shock intensities showed that methamphetamine self-administration drops only after reaching a certain punishment threshold. Of note, this study also revealed that in this setting, food self-administration was more resistant to punishment than methamphetamine self-administration was, further prompting careful interpretation of punishment data with regard to the type and nature of the reward ((Krasnova et al., 2014) but see also (Sneddon, Fennell, Bhati, Setters, Schuh, DeMedio, Arnold, Monroe, Quinn, and Radke, 2023)). A follow-up study using alcohol self-administration further confirmed that, contrary to stable punishment which provokes resistant and vulnerable subpopulations, daily gradual increases in shock severity eventually led to virtually complete intake cessation in all individuals (Marchant et al., 2018), further confirming that punishment resistance mostly depends on shock intensity. Accounting for individual variations, exposure to progressively increasing shock intensities was then used to confirm the resistance phenotype and test its associated neurobiological mechanisms (Farrell, Ruiz, Castillo, Faget, Khanbijian, Liu, Schoch, Rojas, Huerta, Hnasko, and Mahler, 2019). Here, resistance was asserted for animals that required shock intensities higher than a predefined threshold to stop responding for the drug. Such approach is interesting as it improves the behavioral characterization of the resistance trait. However, it still depends on a relatively arbitrarily defined shock threshold. To further explore this issue, we determined from the existing research literature on punishment sensitivity vs. resistance as the delimiting feature of addiction-like behavior the contribution of 1) prior drug exposure, 2) shock exposure and 3) shock intensity (Table 1, Fig. 1). Interestingly, while we observed a good correlation between resistance to punishment and shock intensity ($r = -0.48$), we found that no matter how long rats were exposed to drugs or to footshock, this had virtually no influence on the punishment resistant phenotype (Fig. 1). This, of course, confirms the main role of shock intensity, and as previously described (Marchant et al., 2018), when intensity is sufficiently high, all animals eventually stop responding. But while significant, this correlation is not strong and high variability remains both across and within studies. For instance, Jones and colleagues recently assessed punishment resistance vs. sensitivity in 5 cohorts of rats, with the same experimental procedure, and found rates of resistance ranging from 31 to 63 % (Jones, Paladino, Cruz, Spencer, Kahanek, Scarborough, Georges, and Smith, 2024). This, as well as similar findings from other studies (Table 1), indicates that indiscriminately applying the same shock intensity to every rat can yield different outcomes and suggests that the line between taking drugs despite punishment and drug cessation might be blurrier that we often presuppose.

Recently, an interesting attempt to deconvolute this picture used a self-adjusting shock procedure. Here food rewards were associated with progressively increasing footshock strengths within a single session (similar to progressive ratio), allowing animals to titrate the punishment intensity they were willing to endure for a reward (Desmercieres, Lardeux, Longueville, Hanna, Panlilio, Thiriet, and Solinas, 2022). Such tailored protocol could contribute to apply more "meaningful" punishments specific to each animal without the need of arbitrarily choosing a shock intensity threshold. Self-adjusting protocols have yet to be adapted to drug-related behaviors in rodents, but it will be useful to focus on the animals' reaction to an event that is truly aversive for them. Thus, while we may not find sensitive vs. resistant subgroups with such protocols, we may be able to more closely interrogate what a given individual does when it faces a significant negative event. Will it completely stop drug intake? Which settings (e.g., frequency of punished reward, number of punished sessions, etc.) may promote abstinence- vs. relapse-like behaviors? Of note, this does not necessarily mean that self-adjusting protocols should replace the "classical" punishment models. Each answers different questions. Indeed, when comparing different reactions to a similar punishment, classical models potentially allow investigating the underpinnings of interindividual differences in conditions where other parameters (e.g., body weight, drug exposure, pain sensitivity, etc.) are somewhat equal. Conversely, self-adjusting protocols could allow testing the substrates of punished responding to a stimulus known to be aversive to a given individual. Thus, both provide complementary information that could be used in conjunction (after technical consideration) to isolate specific mechanisms.

Together, the different protocols discussed above bring us to consider another key aspect of punishment resistance, namely its robustness over a range of intensity. It is indeed important to be able to appreciate the extent to which a resistance phenotype is robust. For instance, take 3 individual animals whose behavior is punished with a single intensity of 0.3 mA: we may find one animal classified as sensitive and two as resistant to this intensity. Assessing punishment robustness (e.g., testing animals over a range of punishment) may, however, reveal that the maximal intensity that each animal is capable of enduring before stopping drug use is in fact 0.25, 0.35 and 0.6 mA. From a cognitive and neurobiological standpoint, the 0.25 and 0.35 mA individuals may have more in common (although initially classified as sensitive vs. resistant) than the 0.35 and the 0.60 mA individuals (although both initially classified as resistant). Measuring robustness

Table 1
Shock sensitivity vs. resistance in rats: Studies were included when the sensitivity vs. resistance to punishment phenotype was the defining feature (i.e., when response to punishment was directly used to segregate two rat subpopulations, not as a complementary trait). Shock resistant animals are reported as % of the experimental population. On average studies report 41 % (SD ± 11) of shock resistant rats (independently of the drug). Data are reported for males unless specified with ♀.

Drug	Intake schedule	Drug exposure	Shock exposure	Shock intensity (mA); Duration	Punished trials	Separation method (resistance)	Shock resistant animals (% per group)	Reference
					Rat			
Oxycodone	LgA, FR1	22 days	6 days	0.18 to 0.36 (0.06 increments); 0.5 s	50 %	Intake suppression < 20 %	55 %	(Blackwood, McCoy, Ladenheim, and Cadet, 2019)
	LgA, FR1	20 days	10 days	0.18 to 0.36 (0.06 increments); 0.5 s	50 %	Intake suppression < 20 %	50 %	(Cadet, Krasnova, Walther, Brannock, Ladenheim, McCoy, Collector, Torres, Terry, and Jayanthi, 2016)
	LgA, FR1	22 days	13 days	0.18 to 0.42 (0.06 increments); 0.5 s	50 %	Intake suppression < 30 %	44 %	(Torres, Jayanthi, Ladenheim, McCoy, Krasnova, and Cadet, 2017; Torres, Jayanthi, McCoy, and Cadet, 2018)
	LgA, FR1	20 days	5 days	0.18 to 0.30 (0.06 increments); 0.5 s	50 %	k-mean clustering	39 %	(Duan, Tsai, Salmeron, Hu, Gu, Lu, Cadet, Stein, and Yang, 2022; Hu, Salmeron, Krasnova, Gu, Lu, Bonci, Cadet, Stein, and Yang, 2019)
Meth.	LgA, FR1	21 days	8 days	0.18 to 0.36 (0.06 increments); 0.5 s	50 %	Intake suppression < 20 %	47 %	(Jayanthi, Peesapati, McCoy, Ladenheim, and Cadet, 2022; Subu, Jayanthi, and Cadet, 2020)
	LgA, FR1	21 days	8 days	0.18 to 0.36 (0.06 increments); 0.5 s	50 %	Intake suppression < 20 %	53 %	(Munoz, Jayanthi, Ladenheim, and Cadet, 2022)
	LgA, FR1	22 days	8 days	0.18 to 0.36 (0.06 increments); 0.5 s	50 %	Intake suppression < 40 %	46 %	(Daiwile, McCoy, Ladenheim, Subramaniam, and Cadet, 2024)
	S – T *FR1 (RI120s) – FR1*	48–52 days	8 days	0.55; 0.5 s	50 %, #	Significantly higher suppression ratio	31 %	(Pelloux, Everitt, and Dickinson, 2007)
	LgA, S – T *FR1(RI60s) – FR1*	34–36 days	8 days	0.55; 0.5 s	50 %, #	≥ lowest unpunished, baseline level	21 %	(Pelloux, Dilleen, Economidou, Theobald, and Everitt, 2012)
	S – T *FR1(RI60s) – FR1*	34–38 days	4 days	0.4; 0.5 s	30 %	≥10 injections	30 %	(Chen, Yau, Hatch, Kusumoto-Yoshida, Cho, Hopf, and Bonci, 2013)
	S – T *FR60 (RI30s) – FR1*	69 days	4 days	0.4; 0.5 s	50 %	≥400 seeking response and ≥10 injections	45 %	(Zhou, Zhang, Yu, Zhang, Shi, and Shen, 2019)
Cocaine	VI30	14 days	6–7 days	0.60–0.75; 0.5 s	50 %	High suppression ratio + require higher intensities for abstinence	21 %	(Farrell, Ruiz, Castillo, Faget, Khanbijian, Liu, Schoch, Rojas, Huerta, Hnasko, and Mahler, 2019)
	FR1	12 days	3 days	0.25; 0.5 s	100 %	Unsupervised clustering analysis	34 %	(Chen, Wang, Zhang, Han, Zhang, Xu, Meng, Lu, Xue, and Shi, 2022)
	S – T *RR20 or FR1 (RI60s) – FR1*	≥26 days	4 days	0.4; 0.3 s	33 %	Completion of ≥ 65 % of unpunished, baseline trials	35 % 63 % 31 % 43 % 40 % ♀	(Jones, Paladino, Cruz, Spencer, Kahanek, Scarborough, Georges, and Smith, 2024)
	VI30*	24 days	3 days	0.3; 0.5 s	50 %	Suppression ratio > 0.25	58 %	(Marchant, Campbell, and Kaganovsky, 2018)
	S – T * *FR1(RI60s) – FR1*	28 days	10 days	0.25 to 0.45 (0.05 increments); 0.5 s	30 %, #	k-mean clustering	34 %	(Giuliano, Pena-Oliver, Goodlett, Cardinal, Robbins, Bullmore, Belin, and Everitt, 2018)
Alcohol	S – T * *FR1(RI60s) – FR1*	28 days	10 days	0.25 to 0.45 (0.05 increments); 0.5 s	30 %, #	k-mean clustering	38 %	(Giuliano, Belin, and Everitt, 2019)
	FR2	15 days	14 days	0.2; 0.5 s	100 %	Unimodality test: resistance score > 0.45	38 %	(Domi, Xu, Toivainen, Nordeman, Gobbo, Venniro, Shaham, Messing, Visser, van den Oever, Holm, Barbier, Augier, and Heilig, 2021)

(*continued on next page*)

Table 1 (*continued*)

Drug	Intake schedule	Drug exposure	Shock exposure	Shock intensity (mA); Duration	Punished trials	Separation method (resistance)	Shock resistant animals (% per group)	Reference
	FR2	≥40 days	14 days	0.2; 0.5 s	100 %	Unimodality test: resistance score > 0.45	41 %	(Domi, Xu, Toivainen, Wiskerke, Coppola, Holm, Augier, Petrella, and Heilig, 2023)
	FR3	59 days	6 days	0.25; 0.5 s	33 %	Responses ≥ 70 % of the baseline performances	42 %	(Goutaudier, Joly, Mallet, Bartolomucci, Guicherd, Carcenac, Vossier, Dufourd, Boulet, Deransart, Chovelon, and Carnicella, 2023)
					Mouse			
	FR3	16 days	4 days	0.2; 0.5 s	33 %	Unbiased clustering analysis (4 behavioral parameters	12 %	(Li, Simmler, Van Zessen, Flakowski, Wan, Deng, Li, Nautiyal, Pascoli, and Luscher, 2021)
Cocaine	FR3	13 days	1 day	0.2; 0.5 s	100 %	Perseverance rate: punished infusion / baseline infusion	23 %	(Pascoli, Hiver, Li, Harada, Esmaeili, and Luscher, 2023)

Meth. = Methamphetamine; LgA = Long Access; FR = Fixed Ratio; S – T = Seeking-Taking (italics detail the seeking – taking schedules; only the seeking lever is paired with footshock); VI = Variable Interval; # denotes that rewards were omitted during punished trials; * denotes Alcohol preferring rat strain.

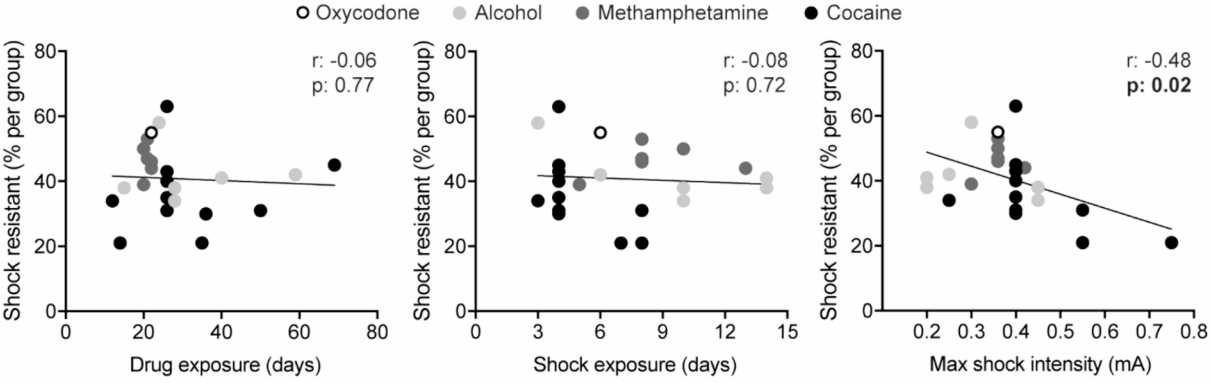

Fig. 1. Resistance to punishment is correlated with shock intensity: the proportion of shock resistant rats is neither correlated to the duration of drug exposure (left panel) nor to the duration of exposure to punishment (middle panel). However, maximum shock intensity significantly correlates with resistance to punishment (right panel). This is consistent with studies showing a progressive shift to complete cessation with increasing shock intensities. Given the limited number of studies for each drug, data from all drug regiments were pooled. Each point represents a group of rats from a study. Because of the differences in shock intensities used in mouse studies, data are only taken from rat studies (displayed in Table 1). Please note that the criteria used to segregate resistant and sensitive rats vary between studies (see Table 1).

over a range of shocks may thus highlight individual characteristics otherwise overshadowed in classical punishment protocols. Of note, since such approach requires to expose individuals to a range of punishment intensity, this may lead them to learn several characteristics of punishment that could alter the way they respond to it. While this could represent a potential limitation, we may also envisage that such learning might reproduce some aspects of the human clinic (i.e., facing multiple negative events of various magnitude) that could further improve the quality of our models. Moreover, another important aspect to consider regarding robustness of punishment-resistance is its intra-individual stability over time. Indeed, when facing punished drug delivery, some animals may show the same robustness initially but may part from one another after prolonged punishment. For instance, a prolonged experience with punished drug use may progressively alter the value of drug reward in some individuals, thereby causing them to stop taking the drug and become abstinent. Thus, assessing the stability of individual punishment robustness over time could constitute another valuable metric. Finally, the generalizability of punishment resistance across different types of punishers is another factor to consider. Indeed, animals are often tested with a single punishment modality, and it is plausible that rats tested with one type of punishment may, in fact, show greater sensitivity to another type of punisher. For instance, while crossed high-alcohol-preferring (cHAP) mice display strong resistance to quinine adulteration, they show unaltered sensitivity to footshocks (Sneddon, Schuh, Fennell, Grahame, and Radke, 2022). A given event has not necessarily the same aversive character in every individual. Testing a set of aversive stimuli could contribute to better characterize a punishment resistant trait. Moreover, testing generalizability of punishment resistance across sexes will further contribute to improve this characterization, as sexual dimorphism are reported in resistance to punishment (Toivainen, Xu, Gobbo, Della Valle, Coppola, Heilig, and Domi, 2024). Although there is some work on the generalizability of punishment resistance (Augier, Barbier, Dulman, Licheri, Augier, Domi, Barchiesi, Farris, Natt, Mayfield, Adermark, and Heilig, 2018; Domi, Xu, Toivainen, Nordeman, Gobbo, Venniro, Shaham, Messing, Visser, van den Oever, Holm, Barbier, Augier, and Heilig, 2021; Terris and Barnes, 1969), this remains an underexplored area of research.

In summary, every negative consequence is not necessarily the “one too many” that has the power of leading people with SUD to abstinence. Using more “personalized punishments” and interrogating punishment resistance robustness may improve our ability to understand the mechanisms underlying continued drug use despite negative consequences, notably whether and to what extent it reflects loss of control or compulsion. This issue has already been discussed elsewhere, but, briefly, while compulsion could represent one facet, there are other plausible alternative explanations to punishment resistance. For example, if a punishment is immediate and certain, continuous responding could arise from preexisting interindividual differences in

nociception, hypoalgesic effects of the drug, footshock-induced anti-nociception, etc. (George et al., 2022). In contrast if punishment is delayed and/or uncertain, a remarkable body of work both in rats and humans recently showed that punishment resistance comes from difficulty, for some individuals, to learn the instrumental contingencies between their action and punishment (Jean-Richard-Dit-Bressel, Lee, Liew, Weidemann, Lovibond, and McNally, 2021; 2023; Jean-Richard-Dit-Bressel, Ma, Bradfield, Killcross, and McNally, 2019). Importantly, among people who were initially resistant to punishment, most became sensitive when provided with explicit verbal information about the punishment contingency while few remained resistant to punishment as if they behaved compulsively (i.e., they continued to respond despite correct knowledge of punishment) (Jean-Richard-Dit-Bressel et al., 2023). At present, it is not clear whether a similar heterogeneity could also be uncovered among animals that are resistant to punishment since they cannot be given explicit/declarative instructions or provide explicit feedback (Jean-Richard-Dit-Bressel, Gaetani, Zeng, Weidemann, and McNally, 2024). Finally, basal levels of stress and anxiety could affect both types of punished responding, although studies report contrasting results and suggest a main influence of sex (Campbell, Maddern, and Lawrence, 2021; Toivainen et al., 2024). In summary, individual variation in the way punishment is integrated and processed certainly contributes to variation in resistance to punishment responding. Whether this reflects genuine compulsion is, however, difficult to establish since, in humans, compulsion is strongly associated with a subjective inner conflict between wanting to stop a given behavior and the urge to perform it (Heinz, Gutwinski, Bahr, Spanagel, and Di Chiara, 2024; Luigjes, Lorenzetti, de Haan, Youssef, Murawski, Sjoerds, van den Brink, Denys, Fontenelle, and Yucel, 2019; Smith, 2022). So far, no preclinical model has managed to reproduce this key aspect which is the reason why caution is warranted in interpreting data on punished drug use in terms of compulsion (George et al., 2022).

Altogether, although sensitive vs. resistant subgroups are getting more used to study the mechanisms of SUD, it appears that the way punishments are applied, and subpopulations are separated should receive more weight in our analysis and interpretation. Considering more tailored protocols, assessing the robustness of the phenotypes we uncover, ruling out alternative explanations beforehand will be useful to improve the relevance of our findings for understanding the mechanisms of SUD.

The precariousness of punishment-induced abstinence.

People with SUD frequently face different levels of adverse events. Yet, they continue to take drugs. However, sometimes a specific negative event happens. For a portion of them, this event makes them feel like they “hit rock bottom”, thereby causing them to quit drug use and become abstinent, at least for some time. There are different reasons for an event to become sufficiently meaningful to precipitate abstinence. It can be related to degradations in interactions with significant others, losing a job or a place to live, health-related issues, etc. (Bischof, Rumpf, Hapke, Meyer, and John, 2001). Some of these aspects are obviously more difficult to access in rodents. There has been some attempt to model this feature in the punishment sensitive vs. resistant paradigm where sensitive individuals that stop drug use are considered as becoming abstinent (Cadet et al., 2019; Jayanthi et al., 2022; Krasnova et al., 2014; Marchant et al., 2018; Seif, Chang, Simms, Gibb, Dadgar, Chen, Harvey, Ron, Messing, Bonci, and Hopf, 2013; Torres et al., 2018). While this approach clearly has merit, as the neurobiological mechanisms of abstinence remain largely unknown, it mostly depends on our interpretation of punishment resistance. As explained above, if punishment resistance reflects an addiction state, then animals which stop taking drug with no or little initial resistance to punishment may not be considered to become abstinent from a prior state of addiction. This is a likely possibility because stopping drug use rapidly after encountering the first adverse situation or event is not consistent with the corresponding criteria used to define SUD. In this regard, the behavior of so-called punishment sensitive animals may reflect earlier, pre-addictive stages of drug use. Thus, paradoxically, evidence for initial sign of individual resistance to punishment seems to be a precondition to study abstinence from addiction in animals.

A complementary approach for studying abstinence may consist in using a high intensity punishment to try to mimic a “hit rock bottom” experience in animals. For instance, we recently showed that after experiencing a high intensity footshock punishment during cocaine self-administration (i.e., 0.7 mA), rats became sensitive to previously inoffensive punishment (i.e., 0.1 mA), causing them to stop using cocaine regardless of punishment intensity (Durand, Girardeau, Freese, and Ahmed, 2022). This supports the idea that distinctly strong events can induce behavioral changes capable of modifying resistance to subsequent negative events. For example, someone who experienced a heart-attack following cocaine intake might become more sensitive to simple increases in heart rate during subsequent experiences with drug, eventually leading them to initiate abstinence. Thus, this approach could be useful to study the neurobiological substrates underlying such drastic changes in behavior. However, after repeated testing without punishment, animals ultimately recovered their initial levels of cocaine intake (Durand et al., 2022). While return to pre-punishment level of drug intake shows that the effects of intense punishment are not permanent, at least initially, this phenomenon may represent a unique window to study post-abstinence relapse in animals. For instance, individual comparison in relapse rate may reveal that some animals relapse faster than others and that this may be related to the robustness of punishment resistance. Moreover, it may be useful to question whether and how interindividual differences in relapse rate are related to the shock intensity used to induce abstinence. For example, are there differences in relapse speed, intensity or persistence between an animal needing 0.7 mA and one needing 0.3 mA to stop responding? Indeed, one can imagine that an individual more resistant to punishment, and requiring higher intensities to trigger abstinence, might also have higher propensity to relapse. Including such measures could contribute to propose additional criteria usable to segregate animal subpopulations. Furthermore, this post-punishment relapse phenomenon highlights elements that might be important to consider in regard to the human clinic. Specifically, what are the odds for individuals who entered abstinence following an intense negative event to remain abstinent if they stay in or return to the drug-associated environment with the drug available. A common (although nonessential) condition to successful recovery is when abstinence is associated with an important change in daily life or situation. Moving to another city, finding a new job, the birth of a child, for instance (Cunningham, Blomqvist, Koski-Jännes, and Cordingley, 2005; Sobell, Sobell, Toneatto, and Leo, 1993). As animals are typically returned to the same drug intake environment after punishment (Crombag and Shaham, 2002; Marchant, Campbell, Pelloux, Bossert, and Shaham, 2019), one should expect that they will eventually relapse to drug intake. Thus, one way to sustain abstinence after punishment would be to place animals in a novel environment that contains alternative rewards. Experiments on the resurgence phenomenon may exemplify this approach. After cocaine self-administration has stabilized, drug intake is associated with footshock while an alternative food reward is made available. Unsurprisingly, rats stop taking the drug and turn to the alternative reward. However, when all consequences are removed (both food and drug rewards as well as punishment), rats rapidly increase their behavior toward the drug lever (Nall and Shahan, 2020). Additionally, post-punishment relapse to drug intake may also depend on the punishment parameters. For instance, if the initial punishment is intense but relatively uncertain, it should take longer time for the animals to relapse post-punishment.

Together, while negative events can act as powerful starting points for modifying drug-oriented behavior, their enduring consequences alone may be limited. This is an important point that must be considered when studying punishment-induced abstinence and subsequent relapse. Notably, this raises the question of whether and to what extent it is

possible to punish drug use in animals to induce abstinence and prevent relapse permanently.

Relapse again, abstain again, abstain better.

Questioning the different models of continued drug use despite aversive events led us to consider the robustness of both the resistant and the sensitive phenotype. Doing so, we found individuals can evolve from one trait to another through repeated punishment exposure. This encouraged us to further examine the role of learning and memory dynamics in the progression of drug intake, and especially regarding relapse. Indeed, an important factor to consider in the maintenance of punishment-induced abstinence from drug use is the passage of time between the initial event that triggered abstinence and the present. As time passes during abstinence, negative events could lose their punishing efficacy and contribute to relapse. For instance, drug memories may strengthen through mechanisms, like incubation of craving (Grimm, Hope, Wise, and Shaham, 2001), to become more influential in controlling behavior than memories of aversive events. Recent work showed that, contrary to nondrug memories that are progressively forgotten, memories of cocaine-related cue undergo consolidation processes, involving the prelimbic cortex and the basolateral amygdala, that enhance their stability and intensity (Liu, Lu, Chen, Huang, Zheng, Zhang, Meng, Yan, Shi, Bao, Xue, Shi, Yuan, Han, and Lu, 2024). Accordingly, experiments in rats report higher drug seeking when tested several weeks after punishment compared to short term abstinence (Krasnova et al., 2017; Krasnova et al., 2014), although differences in protocols yield contrasting results (Barnea-Ygael, Yadid, Yaka, Ben-Shahar, and Zangen, 2012). Similarly, punished methamphetamine intake emerged in a subgroup of previously shock-sensitive rats following abstinence (Daiwile, McCoy, Ladenheim, Subramaniam, and Cadet, 2024), further stressing the importance of incubation of craving mechanisms even in the presence of negative events. However, it is also important to mention that, like drug memories, aversive memories can undergo incubation. Early work showed the expression of conditioned aversive taste memory was stronger when tested after longer intervals (Kraemer and Roberts, 1984). Later studies confirmed these observations by showing incubation of conditioned fear memory has time-dependent effects with stronger aversion associated to longer incubation and longer shock exposure (Pickens, Golden, Adams-Deutsch, Nair, and Shaham, 2009). Interestingly, more recent work showed that rats with high drinking levels display lower incubation of fear (Pajser, Limoges, Long, and Pickens, 2019), further suggesting that, depending on certain factors, incubation of rewarding and aversive memory might compete to shape subsequent behaviors. Although future studies will need to further clarify these competitive mechanisms, finding ways to weaken the consolidation of drug-related memories might be useful for maintaining abstinence.

Repeated (i.e., failed) attempts to quit drug use is part of the diagnosis of SUD (American-Psychiatric-Association, 2013) and repeated relapse is often presented as evidence of SUD being a chronic disease in which "*drugs rob the brain of the capacity to exercise free will*" (see (Heyman, 2017)). But overall, is relapse a failure from the ultimate goal of remission? Frequently people with SUD experience multiple cycles of abstinence and relapse. But this does not necessarily keep them away from recovery. Some people simply need more time than others (Heyman, 2013). And, as suggested above, maybe this is a way by which memories of negative events are strengthened. In fact, many people go into remission of SUD by learning from previous relapse experiences. And it is by knowing how hard remaining abstinent is that some people progressively recover (Burman, 1997). This suggests that each relapse episode incorporates important information for future attempts. Knowing what to expect (withdrawal symptoms, abstinence-related stress, etc.) seems indeed crucial in building successful recovery. As the context in which the aversive events (punishments) happened plays a significant role in reducing drug intake (Bouton and Schepers, 2015), repeatedly experiencing them in various context may help to generalize the learning of key components. While such aspects might be difficult to model in animals, they can be approached in protocols that allow episodes of abstinence to cycle with episodes of relapse (Schepers and Bouton, 2015) see also (Shahan, Browning, and Nall, 2020). This is also consistent with previous reports depicting increased response to punishment after a second cycle of punishment-induced abstinence (Durand et al., 2022; Pelloux, Hoots, Cifani, Adhikary, Martin, Minier-Toribio, Bossert, and Shaham, 2018). Additionally, such repeated abstinence-relapse cycles may be suitable to interrogate the associated neurobiological substrates of both abstinence and relapse. Notably, this may also reveal unexplored individual variation in propensity to repeated post-punishment relapse.

2. Conclusion

It is, of course, difficult to take into account every factor mentioned above within a single experiment, and it is often necessary to use well defined criteria to differentiate subpopulations based on their response to punishment. Specific time points or binary behaviors are sometimes required to measure precise neurobiological mechanisms. However, what comes out from this reflection is that resistance to punishment is not always as straightforward as we may think. The line between sensitivity and resistance may sometimes be arbitrary and thus difficult to draw. And although an individual may show resistance at first, repeated exposure to punishment and competition between incubation mechanisms may come into play to build abstinence. These aspects are important to consider when designing our experiments and analyzing our data. To investigate abstinence more realistically, resistance is in fact a prerequisite. Indeed, there cannot be genuine recovery if there is no addiction first. Finally, it might be worth mentioning that although we almost exclusively discussed positive punishment, negative consequences of substance use in humans are arguably more comparable to negative punishment. Losing a job, a place to live, a partner essentially corresponds to removing positive aspects of life. Although we are unsure of how this type of punishment could be effectively modeled in animals, more future research effort toward this goal could further the comprehensiveness of preclinical models of addiction. Then, finding the parameters influencing behaviors toward abstinence and evaluating their mechanisms might provide fruitful paths to propose more effective therapies.

CRediT authorship contribution statement

Michel Engeln: Writing – original draft, Data curation, Conceptualization. **Serge H. Ahmed:** Writing – review & editing, Data curation, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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