Improving translation of animal models of addiction and relapse by reverse translation

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Abstract | Critical features of human addiction are increasingly being incorporated into complementary animal models, including escalation of drug intake, punished drug seeking and taking, intermittent drug access, choice between drug and non-drug rewards, and assessment of individual differences based on criteria in the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV). Combined with new technologies, these models advanced our understanding of brain mechanisms of drug self-administration and relapse, but these mechanistic gains have not led to improvements in addiction treatment. This problem is not unique to addiction neuroscience, but it is an increasing source of disappointment and calls to regroup. Here we first summarize behavioural and neurobiological results from the animal models mentioned above. We then propose a reverse translational approach, whose goal is to develop models that mimic successful treatments: opioid agonist maintenance, contingency management and the community-reinforcement approach. These reverse-translated 'treatments' may provide an ecologically relevant platform from which to discover new circuits, test new medications and improve translation.

Relapse
Resumption of drug-taking behaviour during self-imposed (voluntary) or forced abstinence in humans and laboratory animals.

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Drug addiction consists of different phases, beginning when non-problematic (recreational) use escalates to compulsive and/or problematic use and then cycles through periods of abstinence (withdrawal), and relapse[1–3] (FIG. 1). The cycle is often exacerbated by societal stigma of people who use drugs[4], social isolation, job loss, incarceration and other losses of the 'social capital' that would otherwise be protective[5–7].

In 1997, US National Institute on Drug Abuse (NIDA) Director Alan Leshner published a commentary in *Science* whose title declared: "Addiction is a brain disease, and it matters"[8]. That commentary, and articles accompanying it[9,10], argued that identification of cellular and circuit mechanisms of addiction would lead to new ways to prevent and treat compulsive drug use, drug craving and relapse. Since then, technological advances have improved our understanding of the brain mechanisms underlying behavioural effects of addictive drugs in classic animal models, including psychomotor sensitization[11], conditioned place preference (CPP)[12], drug withdrawal[13], drug discrimination[14], drug self-administration[15,16], extinction of drug-reinforced responding[17,18], reinstatement of drug seeking after extinction[19] and incubation of drug craving after home-cage forced abstinence[20] (Supplementary Table 1).

However, the combination of these traditional models with modern neuroscience technologies, including optogenetics and chemogenetics, has not changed the options available to people who present for treatment[5,21]. This problem is not unique to addiction[22], but it is an increasing source of disappointment[23], and has led some to question the validity of animal models of addiction[24]. The models described above have obvious limitations because human addiction is characterized by drug use despite immediate or delayed adverse consequences, escalation of drug use over time and choice between drug use and abstinence. In addition, all of these behaviours may be modulated by human-specific cognitive processes[24]. The limitations shared by psychomotor sensitization, CPP and drug discrimination are that drug exposure is non-contingent and low. A limitation of many published studies using drug self-administration and reinstatement is that daily access is temporally restricted (1–3 h per day) and rarely involves choices between drug and non-drug rewards[25]. A limitation of extinction and reinstatement procedures is that human abstinence does not involve operant extinction[26]. A limitation of classic procedures for incubation of craving is that abstinence is forced[27], while in humans abstinence is often chosen, either

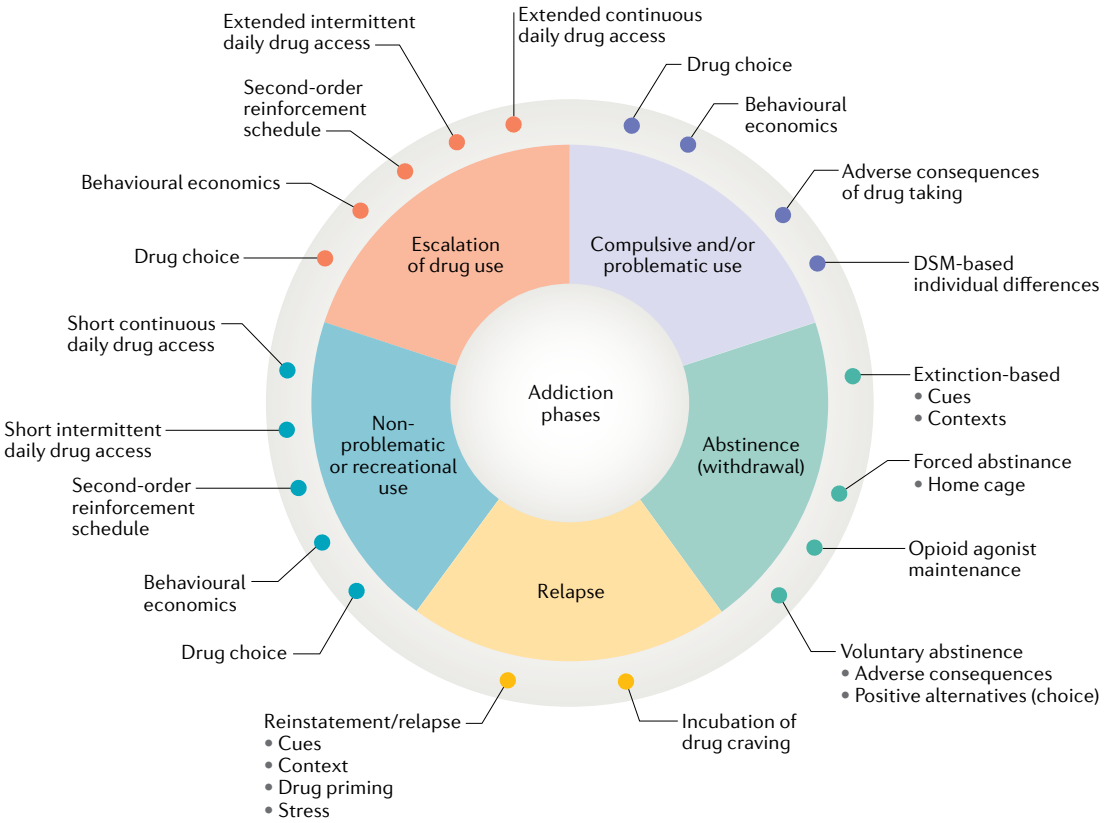

Fig. 1 | **Addiction phase and animal models.** The inner segments of the chart show the different phases of addiction in humans. Outside the external grey circle are listed examples of preclinical research approaches (animal models) that have been used to investigate different behavioural features of human addiction within each phase. DSM, *Diagnostic and Statistical Manual of Mental Disorders*.

Compulsive drug use
Continued use of a drug despite (known) adverse consequences.

Drug craving
An affective state described as an urge for drug; it can be induced in human drug users by exposure to the self-administered drug, drug cues or stress.

Predictive validity
The extent to which laboratory-animal behaviour induced by an experimental manipulation predicts human behaviour induced by a similar event in the modelled condition; it often refers to a model's ability to prospectively identify treatments that are effective in humans.

Postdictive validity
The ability of a laboratory model to retrospectively demonstrate an established human phenomenon.

Forward translation
The process of using mechanistic discoveries from animal models to develop new treatments for the modelled human condition.

Contingency management
A learning-based treatment in which abstinence is maintained by providing non-drug rewards (monetary vouchers, prizes or other incentives, usually tangible/material and given promptly and predictably) in exchange for negative drug test results.

The community-reinforcement approach
A learning-based treatment developed for alcohol addiction in the 1970s, where the goal is to replace drug use with non-drug social rewards (family support and employment) contingent on decrease or cessation of drug use.

to avoid adverse consequences or to retain or obtain alternative rewards[28].

These limitations might help account for shortcomings in predictive validity. As discussed elsewhere, an animal model can have predictive validity without phenomenological similarities to the human condition[29,30]. Additionally, traditional models such as drug self-administration and reinstatement do have some postdictive validity: they 'predict' the effectiveness of already approved treatments such as naltrexone, buprenorphine and methadone[31–33]. However, with the exceptions of the α4β2 nicotinic acetylcholine receptor partial agonist varenicline for nicotine addiction[34] and the preferential μ opioid receptor (MOR) antagonist naltrexone for alcohol addiction[35], years of mechanistic neuropharmacological research using traditional animal models have not resulted in 'forward translation' or 'prospective' predictive validity[5,36] (TABLES 1 and 2). It is important to examine whether this problem can be addressed by focusing on features of the human condition that are clinically important but have not been captured by the commonly used animal models described in Supplementary Table 1.

In this Review, we first describe refinements of traditional models designed to capture critical features of human addiction, including escalation of drug intake[25], adverse consequences of drug use[37], intermittent drug access[38], choice between drug and non-drug rewards[36,39], and individual vulnerability to addiction based on criteria similar to those in the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV)[40] (FIG. 1). We discuss brain mechanisms identified in these models, and their potential predictive validity for identifying new treatments.

We then introduce a reverse translational approach[41] whose goal is to develop models that mimic clinically successful treatments: opioid agonist maintenance[42], contingency management[43] and the community-reinforcement approach[44]. We discuss how this approach could help identify new biomedical treatments and elucidate relapse-related neurocircuits. We conclude with a clinical perspective.

Advances in animal models of addiction

In this section, we describe refinements to existing animal models. For each class of models, we provide a historical perspective and briefly summarize the main results in the realms of behaviour, neuropharmacology and neurocircuitry.

Escalation of drug intake. In 1969, Deneau et al.[45] gave rhesus monkeys unlimited access (24 h per day) to several opioids and psychostimulants. Under this regimen, monkeys rapidly transitioned from stable hourly drug self-administration to binge-like responding that in the case of cocaine (but not morphine)

Binge self-administration
Self-administration characterized by irregular (variable) interinfusion intervals, with alternating periods of high responding and no responding.

Progressive ratio reinforcement schedule
A schedule of reinforcement in which a reinforcer is presented only on the completion of a set number of responses. The number of required responses progressively increases after each presented reinforcement.

Punishment
A consequence that follows an operant response that decreases the likelihood that the response will occur in the future.

caused weight loss and death within several weeks. In 1973, Yokel and Pickens[46], using unlimited access to amphetamine derivates, showed similar emergence of binge-like behaviour in rats, with alternating periods of high drug intake and no drug intake. This was accompanied by weight loss and death within 2 weeks. Subsequent studies in monkeys and rats have replicated the pattern: binge-like self-administration of psychostimulants but not opioids, causing death[47–49]. In 1998, Ahmed and Koob[25] found escalation of cocaine intake in rats given extended access (6 h per day) but not limited access (1 h per day). This seminal study introduced the escalation model, which simulates a critical feature of human addiction, increased drug intake over time. Several other laboratories also developed a variation of the escalation model for oral alcohol intake based on non-contingent prolonged intermittent alcohol vapour exposure[50].

At the behavioural level, the escalation of drug intake model does not look like loss of control, which would be characterized by binge-like infusions at irregular intervals[51]; instead, it is a decrease in the interinfusion interval, which remains relatively stable during the 6-h or 12-h sessions. Escalation of drug intake could reflect an increase in the drug's reinforcing effects or tolerance to its side effects that initially constrain rates of self-administration[52]. Across drug classes, escalation results in an upward shift in the dose–response curve, increased motivation for the drug (assessed by the progressive ratio reinforcement schedule, in which the response requirements increase during the daily sessions until self-administration ceases)[53], decreased punishment sensitivity[54] and increased vulnerability to stress-induced reinstatement[55].

Pharmacological studies using the escalation and alcohol vapour models indicate that escalation of drug intake (unlike limited-access, non-escalated intake) recruits stress-related neurotransmitter systems such as the corticotropin-releasing factor (CRF) and dynorphin/κ opioid systems[56]. For example, CRF receptor 1 (CRFR1) and κ opioid receptor (KOR) antagonists decrease escalated but not non-escalated drug intake[50,56,57]. The effects of CRFR1 and KOR antagonists are mediated through an effect on neurons in the ventral tegmental area (VTA)[58] and nucleus accumbens (NAc) shell[59], respectively. Other studies indicate a role of the central nucleus of the amygdala (CeA) in escalation of cocaine, oxycodone and alcohol self-administration. For instance, CeA injections of CRF antagonists, hypocretin 1 receptor antagonist or the peptide nociceptin decrease alcohol, cocaine and oxycodone intake escalation, respectively[60–62]. Molecular studies show that escalation of cocaine intake is controlled by the short non-coding RNA molecule miR-212 in dorsal striatum via homeostatic interactions with the epigenetic enzyme methyl-CpG-binding protein 2 (MECP2)[63,64]. Escalation of cocaine self-administration is also associated with unique brain neuroadaptations in expression of multiple genes (for example, the genes encoding δ-catenin, microtubule-associated protein 1a, fibroblast growth factor receptor, Homer protein homologue 1b and c, NMDA receptor subunits)[65,66]. Escalation of cocaine intake is associated with tolerance to inhibition of the dopamine transporter by cocaine, resulting in reduced cocaine-induced dopamine overflow (assessed via microdialysis)[67], and also with decreased phasic dopamine release (assessed via voltammetry) in the NAc but not the dorsal striatum[68] (FIG. 2).

Together, studies using the escalation model show that extended-access escalated intake is controlled by neuropharmacological and molecular mechanisms distinct from those controlling limited-access, non-escalated intake. However, the translational utility of the model has yet to be established. For alcohol, the prolonged vapour exposure version of the escalation model shows postdictive validity for effects of the FDA-approved medications naltrexone and acamprosate: each of them decreases dependence-induced increased intake[33]. However, two major receptor targets derived from escalation studies — CRFR1 and KOR — have not yet shown clinical efficacy[69–73]. By contrast, another 'stress-related' target — the glucocorticoid receptor[74–76] — has shown translational promise: its blockade selectively suppressed escalated alcohol self-administration in rats[77], and reduced both

Table 1 | **Forward translation and the traditional (single active lever) cocaine self-administration model**

Potential treatment	Self-administration (rats or monkeys)	Human laboratory study (drug craving, subjective effects or choice)	Clinical study (abstinence rate or drug relapse)	Selected refs
Amphetamine	Decrease	Decrease	Small-to-moderate effect	145,218,219,263
5-HT_{2C} agonist lorcaserin	Decrease	No effect on cocaine choice, increased subjective effects of cocaine	No effect	264–267
Modafinil	Decrease	Decreased subjective effects, inconsistent effect on choice	No effect	268–271
Buspirone	Decrease	No effect on cocaine choice	No effect	117,118,272,273
Cocaine vaccine	Decrease	Moderate effect	No effect	274–276
D1 antagonists	Decrease	Increased cocaine choice, no effect on cocaine craving	Not tested	277–280
Olanzapine	Decrease	Not tested	No effect	281–284
κ agonists	Decrease	Increased cocaine choice	Not tested	285–287
Pioglitazone	Decrease	No effect	Not tested	288–290

Table 2 | **Forward translation and the reinstatement model**

Potential treatment	Reinstatement (rats or monkeys)	Human laboratory study (drug craving, subjective effects or choice)	Clinical study (abstinence rate or drug relapse)	Selected refs
N-Acetylcysteine	Cocaine priming Discrete cue Discriminative cue	Moderate effect	Minimal effect	291,292
Cocaine vaccine	Priming	Moderate effect	Minimal effect	274–276,293
CRFR1 antagonists	Stress	No effect	Not tested	55,72
α_1 antagonist	Stress	Moderate effect	Weak effect	55,294,295
α_2 agonists	Stress Discrete cue	Decrease	Moderate effect as adjunct to opioid maintenance	55,296,297
mGluR2 agonists and positive allosteric modulators	Cocaine priming Discrete cue Context	Not tested	No effect	298,299
Buspirone	Discrete cue	No effect	No effect	118,273,300
5-HT_{2C} agonist lorcaserin	Cocaine priming Discrete cue	No effect on cocaine choice, increased subjective effects	No effect	265–267
Pioglitazone	Stress Discrete cue	No effect	Not tested	289,290,301

CRFR1, corticotropin-releasing factor receptor 1; mGluR2, metabotropic glutamate receptor 2.

cue-induced craving and short-term (1 week) alcohol consumption in a clinical study[76] (TABLE 3).

Intermittent drug access. In 2012, building on work published in 2002 (REF.[78]), Zimmer et al.[79] developed the intermittent-access cocaine self-administration model to simulate the pattern of intake in human cocaine users who tend to self-administer cocaine intermittently within bouts (which are themselves intermittently spaced), resulting in drug brain level spikes[80]. In this model, within a daily session, there are cycles of drug availability (typically 5 min on, 25 min off for 6 h per day), generating peaks and troughs of daily drug exposure[80,81]. This contrasts with the escalation model, in which both drug intake and brain levels are relatively constant during sessions. In both models, drug intake increases over time, punishment sensitivity is reduced and resistance to extinction is increased compared with the limited-access model[25,37,38,82,83]. There are also neurobiological similarities: for cocaine, both intermittent access and escalation result in increased metabotropic glutamate receptor 2/3 (mGluR2/3) function in different brain regions[84,85].

However, there are notable differences between the two models. Behaviourally, the escalation model produces higher daily cocaine intake when response requirements are low[79,81]. Intermittent access produces stronger motivation to seek and take cocaine, as assessed by the progressive ratio reinforcement schedule[79], behavioural economics[86] and incubation of craving[87] procedures. Neurobiologically, the two models have opposite effects on in vivo cocaine-induced extracellular dopamine levels[67,81] and ex vivo cocaine-induced dopamine transporter inhibition[88] in the NAc: tolerance after escalation; sensitization after intermittent access.

More recently, the intermittent-access model was used to identify rats that are highly motivated to self-administer cocaine, methamphetamine and heroin[44,89,90]. Using this approach, James et al.[86] showed a role for lateral hypothalamus orexin in these individual differences (assessed by behavioural economics, progressive ratio reinforcement schedule and reinstatement procedures) (FIG. 2).

Intermittent-access procedures have been productively combined with behavioural economics, the mathematical application of microeconomic principles of consumption of commodities. In behavioural economics, behavioural data from operant self-administration procedures are analysed using three primary measures: Q_0 (the maximum amount of consumption at the lowest price, assessed under a continuous-reinforcement schedule, such that each lever press is reinforced), P_{max} (the price that maintains maximal responding, assessed by the number of lever presses the laboratory animal is willing to perform to obtain the drug amount under Q_0 conditions) and α (an index of price elasticity of demand (demand elasticity), indicating the percent change in intake for a given percent change in 'price'; that is, the response requirement to obtain an infusion)[91]. These measures represent the strength or value of a given reward, and can be directly compared across non-drug and drug rewards[91].

Behavioural economics studies have shown that P_{max} for cocaine (reflecting motivation to self-administer the drug) is higher after intermittent access than after limited or extended access (escalation)[79]. Aston-Jones and colleagues used behavioural economics measures to demonstrate a role of orexin in the lateral hypothalamus and its projection to the ventral pallidum in motivation to self-administer remifentanil[92] and cocaine[86] (FIG. 2). Behavioural economics was also used to examine sex

Q_0
A measure, in behavioural economics, of maximal consumption when the 'price' of a commodity is zero or at the lowest price possible (that is, FR1 reinforcement schedule in self-administration studies).

P_{max}
A measure, in behavioural economics, of the maximum 'price' that maintains maximal responding and represents the inflection point (that is, slope of −1) between inelastic and elastic demand (in other words, the price at which a proportional change in price results in an equal proportional change in consumption of the commodity).

α
A measure, in behavioural economics, of the elasticity of a demand curve or how quickly consumption of a commodity falls with increases in 'price' (response requirement divided by unit drug dose in self-administration studies).

Demand elasticity
In behavioural economics, how quickly demand falls with increases in 'price' (response requirements in self-administration studies).

Second-order reinforcement schedules
Reinforcement schedules in which completion of the response requirements of one schedule (the unit schedule) is treated as a unitary response that is reinforced according to another schedule.

differences in drug self-administration[93] and to evaluate new medications[94].

Together, the findings show that intermittent access robustly increases motivation to seek and take opioids and psychostimulants[38]. There are both similarities and differences in brain responses to intermittent-access versus continuous-access (escalation) cocaine self-administration. Behavioural economics provides a unique tool to study behaviours across models. There are, however, no data on the extent to which these approaches have predictive validity for treatment development, and their postdictive validity has not yet been established.

Second-order reinforcement schedules. In the early 1970s, Goldberg and colleagues showed that non-human primates will maintain high-rate operant responding for morphine-associated, cocaine-associated or amphetamine-associated cues under second-order reinforcement schedules[95,96]. They proposed that these schedules model complex human drug seeking controlled by drug-associated cues[95]. In the 1990s, Everitt and colleagues adapted the procedure to rats and showed that basolateral amygdala (BLA) lesions decrease acquisition of cocaine self-administration under a second-order schedule but not a fixed-ratio schedule[97]. On the basis of these and related data[98], they proposed that circuits of cue-controlled drug seeking (measured by the first phase of a second-order schedule) are partly dissociable from circuits of drug taking (measured by the second phase of the schedule or commonly used low-rate fixed-ratio schedules). Subsequent studies support this premise.

Under commonly used fixed-ratio schedules, cocaine taking increases extracellular dopamine levels in the NAc[99]. In contrast, cocaine given in second-order schedules selectively increases dopamine levels in the dorsal striatum but not the NAc[100,101]. Studies using lesions and site-specific glutamate receptor antagonists show differential roles of NAc subregions in cue-controlled cocaine seeking (NAc core) versus cocaine taking (NAc shell)[102]. Lesions of the NAc core but not the NAc shell also decrease acquisition of heroin self-administration under a second-order schedule[103]. Di Ciano and Everitt[104]

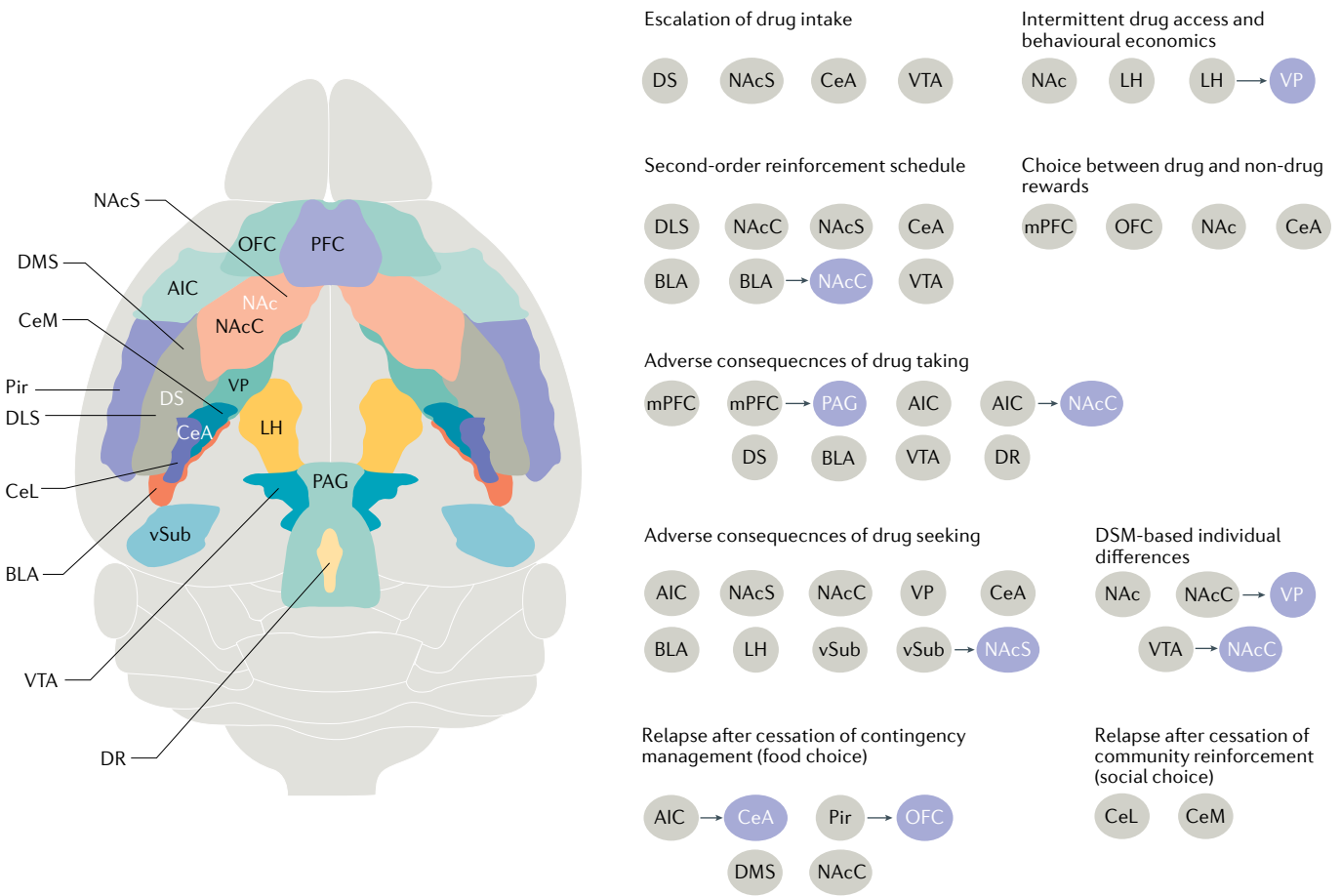

Fig. 2 | **Brain circuits that play a role in drug taking and drug seeking in different animal models.** A horizontal artistic representation of a rodent brain is shown in the left panel. Each brain region and its label are depicted for the left hemisphere. Each brain region and/or projection involved in each animal model is depicted in the right panel. Grey circles represent a brain region critical for drug taking and drug seeking in each animal model. Arrows represent a projection from one brain region (grey circles) to another brain region (violet circles) critical for that animal model. AIC, anterior insular cortex; BLA, basolateral amygdala; CeL, lateral part of the central nucleus of the amygdala; CeM, medial part of the central nucleus of the amygdala; DLS, dorsolateral striatum; DMS, dorsomedial striatum; DR, dorsal raphe; DS, dorsal striatum; DSM, *Diagnostic and Statistical Manual of Mental Disorders*; LH, lateral hypothalamus; mPFC, medial prefrontal cortex; NAc, nucleus accumbens; NAcC, nucleus accumbens core; NAcS, nucleus accumbens shell; OFC, orbitofrontal cortex; PAG, periaqueductal grey; PFC, prefrontal cortex; Pir, piriform cortex; VP, ventral pallidum; vSub, ventral subiculum; VTA, ventral tegmental area.

Table 3 | **Forward translation of the escalation, second-order schedule and choice models (selected examples and citations)**

Potential treatment	Escalation/ extended access	Second-order schedule	Drug choice (rats or monkeys)	Human laboratory study (drug craving, subjective effects or choice)	Clinical study (abstinence rate or relapse)	Selected refs
CRFR1 antagonist	Decrease	Not tested	No effect	No effect	Not tested	56,71–73,302
Glucocorticoid antagonist	Decrease	Not tested	Not tested	Decrease	Decrease	76,77
κ antagonist	Decrease	Not tested	No effect	No effect	Not tested	57,69,302,303
Amphetamine	Decrease	Decrease	Decrease	Moderate decrease	Small-to-moderate effect	133,145,218,219, 263,304,305
5-HT_{2C} agonist lorcaserin	Not tested	Not tested	No effect	No effect on choice, increased subjective effects	No effect	162,163,265,267
α_2 agonists	No effect	Inconsistent effect	Moderate effect	Decrease	Moderate effect as adjunct to opioid maintenance	296,297,306–308
mGluR2/3 agonists	Decrease	No effect	No effect	Not tested	No effect	299,309–311
Cocaine vaccine	Not tested	Not tested	No effect	No effect	No effect	274–276,312
Aripiprazole	Decrease	Not tested	No effect	No effect or increased cocaine choice	No effect	313–317
Buspirone	Not tested	Decrease	Increase	No effect	No effect	117,118,273,318
κ agonists	Not tested	Decrease	Increase	Increased cocaine choice	Not tested	287,319,320
Bupropion	Not tested	No effect	No effect	No effect	No effect	321–325
Modafinil	Not tested	Decrease	Not tested	Decrease cocaine choice	No effect	116,120,268,269
Buprenorphine	Decrease	decrease	Not tested	Decrease cocaine choice	No effect	115,119,326–328
Phendimetrazine	Decrease	Not tested	Decrease	No effect	Not tested	329–331
Lisdexamfetamine	Not tested	Not tested	Decrease	Not tested	No effect	332,333

CRFR1, corticotropin-releasing factor receptor 1; mGluR2/3, metabotropic glutamate receptor 2/3.

used an anatomical disconnection procedure with glutamate receptor antagonists to demonstrate that the BLA to NAc core projection is critical to cocaine seeking but not cocaine taking. Di Ciano and Everitt[105] reported that pharmacological inactivation of the VTA decreases cocaine seeking but not cocaine taking (FIG. 2). The latter results are unexpected because of the known role of mesolimbic dopamine in cocaine self-administration under fixed-ratio schedules[106].

Studies using food rewards have established that extended training under intermittent reinforcement schedules (including second-order schedules) causes habit-like (devaluation-insensitive) responding that depends on the dorsolateral striatum (DLS)[107]. On the basis of this premise, Everitt and colleagues studied the role of the DLS in second-order schedule responding reinforced by cocaine, heroin and alcohol after extended training[108]. Across drug classes, studies using lesions, reversible inactivation and dopamine receptor antagonists demonstrated a role for the DLS (but not the dorsomedial striatum)[109–112]. There is also evidence from anatomical disconnection procedures that transitions from goal-directed acquisition to habitual-like responding involve transfer of control of behaviour from the NAc core to the DLS, and from the BLA to the CeA[113,114] (FIG. 2).

Together, the findings show that second-order schedules can be used to study mechanisms of habit-like drug seeking after prolonged self-administration. The brain mechanisms controlling drug seeking and drug taking are partially dissociable. As with the escalation model, the translational utility of the second-order schedule model has yet to be established. For alcohol, the model has shown postdictive validity: naltrexone decreases alcohol-reinforced responding[111]. However, in rhesus monkeys, the model appeared to generate 'false positives' for buprenorphine, the weak stimulant modafini, and the anxiolytic buspirone (a 5-HT_{1A} agonist), each of which decreased second-order cocaine-reinforced responding[115–117] but were ineffective in multisite clinical studies[118–120] (TABLE 3). Finally, a main pharmacological target that emerged from research using the second-order schedule in rats — D3 dopamine receptor (DRD3) antagonism[121,122] — has not advanced to addiction treatment, despite many years of industry efforts[123] and promising results from other animal models[124–126].

Drug and non-drug rewards. In 1940, Spragg[127] gave chimpanzees choices between intramuscular morphine injections and fruit, and found that preference for morphine over food was increased if the chimpanzees were non-contingently exposed to morphine and experienced withdrawal symptoms (BOX 1). This key finding has been reproduced in monkeys[128,129] and rats[130,131] with intravenous heroin and fentanyl administration. In contrast, withdrawal from prolonged cocaine or methamphetamine administration (for example, short periods after extended-access cocaine or methamphetamine self-administration) had no effect on drug versus food choice in monkeys[132,133] or rats[134,135]. This literature highlights differences between opioids and psychostimulants, with withdrawal having a key role in modulating opioid choice (it is unknown whether withdrawal modulates alcohol or nicotine choice). Differences between these two drug

Disconnection procedure
A procedure in which a role of a neuronal pathway or projection in a given behaviour is inferred when behaviour is disrupted by the contralateral, but not ipsilateral, inactivation of two anatomically connected brain regions.

classes are also evident when rats choose between heroin and cocaine in different environments[49,136]: heroin preference is higher in home environments, while cocaine preference is higher in novel environments[136,137].

From the 1980s onwards, choice studies have led to important insights. At the behavioural level, there have been two key observations. First, drug choice is relatively independent of rates of drug self-administration (for example, number of drug injections per session) in both monkeys[138] and rats[131]. Second, drug choice is sensitive to manipulations that alter the relative cost (that is, response requirement)[139], reward (food or drug) magnitude[134,139], prechoice drug exposure and reward availability[140], and delay of the food reward[44,141,142], and more recently it was unexpectedly observed that identical delay of both cocaine reward and food reward shifts the choice towards cocaine[143]. Overall, concurrent availability of a non-drug reward during a drug self-administration session strongly decreases the drug-rewarding effects[44,131]. These results are consistent with both human laboratory studies of self-administration[144,145] and the clinical efficacy of contingency management[146].

The translational promise of choice models has primarily led to their use in evaluating candidate medications (TABLE 3) and more recently to several studies on neurocircuitry[36]. Guillem and Ahmed[147,148] showed that distinct orbitofrontal cortex (OFC) neurons are activated during choices for food versus cocaine or heroin. These results agree with those from non-choice studies showing that distinct medial prefrontal cortex (mPFC) and NAc neuronal ensembles encode seeking of food versus drugs (cocaine or alcohol)[149–153]. Augier et al.[154] used discrete, mutually exclusive choice between alcohol versus saccharin[142] to identify an alcohol-preferring subpopulation among genetically heterogenous rats. They demonstrated that impaired GABA clearance in the CeA is critical for alcohol choice (FIG. 2).

On the basis of the literature on the inhibitory effects of other non-drug rewards (for example, enriched environment, exercise and social interaction) on drug preference (CPP model), self-administration and reinstatement/relapse[155–160], we recently developed a variation of a choice model[142] to study drug reward (with methamphetamine or heroin) versus rewarding social interaction[44].

Together, drug-choice models are conceptually appealing because they can mimic a cardinal feature of human addiction: preference for drugs over non-drug rewards. At the behavioural level, choice models have prospective predictive validity: drug-choice studies were among the inspirations for contingency management treatment[161]. Choice models also have postdictive validity for treatment: methadone and buprenorphine decrease opioid withdrawal-induced increased heroin preference in rhesus monkeys[36,129] (FIG. 3). In monkeys, choice models can help weed out 'false-positive' potential treatments that appear effective in studies using traditional drug self-administration or reinstatement but fail to affect human choice (for example, the 5-HT_{2C} agonist lorcaserin)[162,163] (TABLE 3). A potential reason for the higher sensitivity of the model is that unlike traditional single-operandum drug self-administration and relapse/reinstatement models, the dependent measure (choice allocation) is rate independent and thus relatively uncompromised by non-specific rate-decreasing effects of test medications. However, for two potential medications (the psychostimulants phendimetrazine and lisdexamfetamine (Vyvanse), prodrugs of phenmetrazine and dextroamphetamine) positive results in the monkey choice model did not predict clinical efficacy (TABLE 3). Finally, the circuits underlying drug choice are largely unknown, because for unknown historical reasons, choice models have rarely been used by addiction neuroscientists. We hope that the recent circuit studies described above[147,148,154] and the translational utility of the choice models will change this state of affairs.

Adverse consequences of drug seeking. Another cardinal feature of human addiction is persistent drug use despite adverse consequences, often referred to as 'compulsivity'[164]. This has been studied in animal models using two main types of punishment: foot shock for intravenous (or oral) drug self-administration, or the bitter taste of quinine for oral drug self-administration[37,165,166]. Other punishments have included intravenous histamine adminstration[167] or presentation of cues previously paired with shock[168]. Punishments have been incorporated into second-order seeking–taking tasks (see above) such that only the seeking response is punished[54], and into choice procedures[169,170]. Relapse to drug seeking has been studied with punishment procedures[171] and with a related electric barrier conflict procedure[172] where rats must cross an electrified grid floor to press a lever for drug infusions[173–176].

In mechanistic studies of punished drug self-administration, investigators typically choose a shock

Box 1 | **The place of non-human primates in addiction research**

Since the 1940s[127], non-human primates have been used to elucidate behavioural and pharmacological mechanisms of drug addiction. This research has improved our understanding of both trait and state variables in addiction and has been invaluable in evaluating candidate therapeutics[36]. There are three specific areas in addiction research where the use of non-human primates may be indispensable.

First, non-human primates develop complex and sex-differentiated social hierarchies that affect both brain function and addiction vulnerability. For example, dominant male monkeys are less prone to cocaine self-administration than subordinate males, and this protective effect is associated with increased striatal D2 dopamine receptor (DRD2)/D3 dopamine receptor (DRD3) availability[335]. In contrast, dominant female monkeys are more prone to cocaine self-administration than subordinate females, and this vulnerability is also associated with increased striatal DRD2/DRD3 availability[336].

Second, the long lifespan of non-human primates affords opportunities to investigate consequences of prolonged drug self-administration and abstinence both within and across multiple life stages (adolescence, adulthood and senescence). For example, in a cohort of 12 rhesus monkeys, baseline availability of striatal DRD2/DRD3 was negatively correlated with cocaine self-administration, and in some of the monkeys, long-term reductions in DRD2/DRD3 availability were present after 1 year of abstinence[337].

Finally, the ongoing opioid crisis has highlighted the need to increase available treatment options and improve matching of treatments to patients[42]. The degree of opioid dependence is a critical factor in treatment selection. To date, the only animal model that addresses this need is a non-human primate heroin-choice model of opioid dependence and withdrawal that has shown sensitivity to opioid agonists versus other clinically used medications (for example, clonidine) that only decrease somatic symptoms of withdrawal[36,302] (FIG. 3). The non-human primate choice model is also uniquely sensitive to identify 'false-negative' potential medications identified in traditional drug self-administration and reinstatement models (TABLES 1,2).

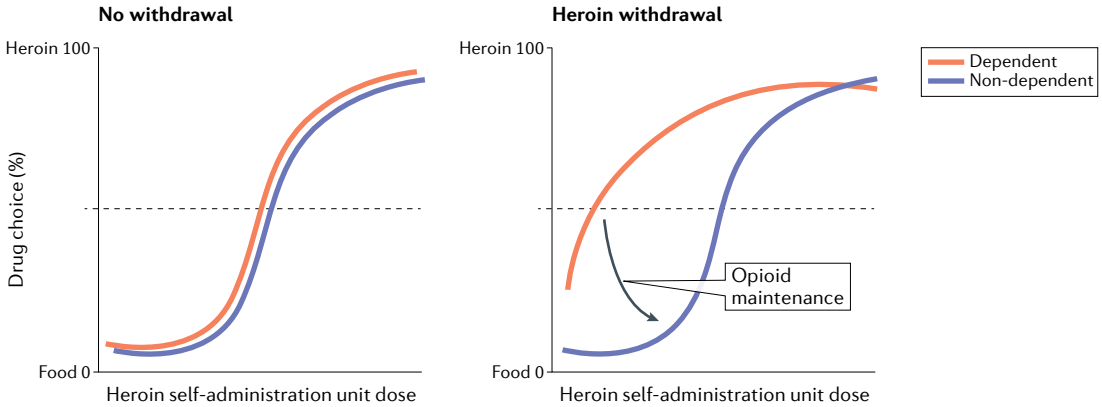

Fig. 3 | **Effect of heroin withdrawal and buprenorphine or methadone maintenance on drug choice in rhesus monkeys.** The percent heroin choice under a heroin self-administration regimen in dependent (orange line) and non-dependent (blue line) monkeys is shown in the left panel. Opioid dependence was achieved by introduction of an additional daily 21-h supplemental heroin self-administration session in addition to the 2-h heroin-choice session. Opioid withdrawal was achieved by suspension of the 21-h supplemental heroin self-administration session for 1 day and was confirmed by scoring somatic behavioural withdrawal signs at various time points over the 22-h opioid withdrawal period. Experimental details and the time course of opioid withdrawal on heroin choice and somatic behavioural withdrawal signs are reported in REF.[129]. At low unit dose of self-administered heroin (*x* axis), monkeys in both conditions prefer food over heroin (*y* axis). Preference switches to heroin as the unit dose of self-administered heroin was increased. The percent heroin choice when heroin self-administration is interrupted in dependent monkeys to induce withdrawal (orange line) is shown in the right panel. Preference for heroin (*x* axis) is already higher in dependent monkeys than in non-dependent monkeys (blue line) at low unit doses of self-administered heroin. Preference for food can be restored to the previously non-dependent levels via 'opioid maintenance therapy' with prolonged administration of either buprenorphine or methadone (black arrow). Preference scale: food (0%) or heroin (100%). The dashed line represents the indifference point. The *x* axis represents heroin self-administration doses and can be generalized to prescription opioids such as fentanyl and oxycodone. See REF.[334].

intensity level (or quinine concentration) under which some rats are punishment resistant (continuing drug self-administration), while others are punishment sensitive[37,164]. Physiological measurements aim to identify differences between the two phenotypes, and experimental manipulations (lesions, pharmacological agents and chemogenetic or optogenetic activation/inhibition) aim to change them[164,177–179]. Punishment studies have identified a role for forebrain serotonin and 5-HT_{2C} receptors[180] and decreased activity in the mPFC (prelimbic area) in punishment-resistant cocaine self-administration[177]. These results, however, were not replicated in another study using brain lesions[181].

There is also evidence for a role of the dorsal striatum and BLA in punishment-resistant cocaine self-administration[181,182]. Studies using home-cage alcohol intake or operant alcohol self-administration showed a role for anterior insular cortex (AIC)-to-NAc core projections and NAc core GRIN2C-containing NMDA receptors[179,183], mPFC to dorsal periaqueductal grey projections[178] and BLA GABAergic transmission[154]. These mechanisms were not engaged during non-punished drug self-administration[154,177–179,181,182]. Finally, Pascoli et al.[184,185] showed that punishment-resistant optogenetic self-stimulation of VTA dopamine neurons is dependent on synaptic plasticity changes in the OFC and its projections to the dorsal striatum (FIG. 2). However, OFC inactivation has no effect on punishment-resistant cocaine self-administration[181]; thus, the relevance of that finding to punishment-resistant drug self-administration is unknown.

In studies of mechanisms of relapse after cessation of drug intake caused by adverse consequences, rats are trained to self-administer a drug and are then exposed to intermittent punishment or electric barrier of increasing shock intensities over days until they 'voluntarily' abstain. During drug-free relapse tests, rats are exposed to drug priming, drug cues or drug contexts in the presence[175] or absence[173,174,186] of foot shock. Circuit studies have identified roles for the lateral hypothalamus, NAc core and shell, ventral subiculum and its projections to the NAc shell, and AIC in context-induced relapse to alcohol seeking after punishment-induced abstinence[171,187–189], and for the ventral pallidum in context-induced relapse to cocaine seeking after punishment[190]. In cocaine-trained rats, reversible inactivation of the BLA and CeA potentiates context-induced relapse to cocaine seeking after punishment-induced abstinence; the same manipulations decreased context-induced reinstatement after extinction[191], assessed by the ABA renewal procedure[192]. Thus, amygdala activity can either promote or inhibit relapse depending on the method used to achieve abstinence. Finally, using the electric barrier model, Saunders et al.[193] showed that cue-induced relapse in the presence of the barrier occurs primarily in rats classified as sign tracking and that this effect is mediated by NAc core dopamine (FIG. 2).

Together, findings from punishment studies identified brain mechanisms that are largely distinct from those controlling drug taking and drug seeking without adverse consequences[37]; this includes a recent demonstration of opposite roles of amygdala activity

Opioid maintenance therapy
Pharmacological treatment method in which long-acting opioid agonists such as methadone or buprenorphine are administered orally or via depot formulation, producing few or no acute subjective effects in tolerant patients but reducing craving for, and use of, other opioids.

ABA renewal
The resumption of a conditioned response in the original training context after extinction in a different context (also called 'context-induced reinstatement').

Sign tracking
Behaviour directed towards a stimulus as a result of a learned association between the stimulus and the reward. Sign-tracking responses develop even though reward delivery is not contingent on a response.

in relapse after punishment-induced abstinence versus extinction-induced abstinence[194]. A question for future research is whether punishment resistance is correlated with increased drug choice. This has been shown for alcohol with saccharin as the alternative reward[154], but not for methamphetamine with social interaction as the alternative reward[44]. As with the intermittent drug access model, the translational utility of the punishment model has yet to be established. However, recent studies suggest that the model has postdictive validity. The MOR antagonist GSK1521498 decreases previously punished seeking responses in the rat model[195] and self-reported responses to alcohol infusions in social drinkers[196]. Additionally, the $GABA_B$ receptor agonist baclofen, which decreases heavy drinking in humans[197], was subsequently shown to decrease quinine-resistant home-cage alcohol drinking in rats[198].

DSM-IV-based individual differences model. Across drug classes, ~20% of recreational drug users progress to addiction as defined by the DSM (currently in the fifth edition)[199]. In animal models, transition to 'addiction' has traditionally been studied using long-term home-cage procedures for oral self-administration of alcohol or opioid solutions[166,200] and with unlimited-access intravenous cocaine self-administration that causes binge-like responding[51,78]. These studies have shown how the transition can be modulated by environmental conditions (drug exposure duration, dose and housing conditions) and by individual characteristics such as place in the social hierarchy[166]. Expanding on this historical background, Deroche-Gamonet et al.[201] in 2004 introduced a rodent model of cocaine addiction that formally adapted the DSM-IV criteria used in humans.

They trained rats over 3 months to self-administer cocaine for three daily 40-min sessions separated by 15-min off periods. They repeatedly evaluated three behaviours on the basis of the DSM-IV criteria: persistent drug seeking during periods of drug unavailability (responding during the 15-min off periods), high motivation to self-administer cocaine (progressive ratio responding) and willingness to take the drug despite adverse consequences (foot shock punishment). They calculated an 'addiction' score (scale 0–3) based on the subjects' percentile in each measure's distribution. They reported that that only ~20% of the rats met all three 'addiction' criteria and these rats showed high relapse vulnerability (that is, reinstatement induced by cues or cocaine priming injections). A follow-up study showed that impulsivity predicted the development of addiction-like behaviour[202], and a recent study showed that the findings generalize to methamphetamine[44].

In mechanistic studies of the DSM-IV model, Kasanetz et al.[203] measured NMDA-dependent long-term depression in the NAc after short-term (17 days) and prolonged (50–72 days) cocaine self-administration. In 'non-addict' rats, the initial impairment in long-term depression recovered over time, while in 'addict' rats (score of 3), it did not. Kasanetz et al.[204] also showed that the 'addict' rats had a selective impairment of mGluR2/3-mediated long-term depression in the mPFC, along with increased local AMPA/NMDA ratio, a measure of synaptic strength. In a follow-up study, Cannella et al.[205] showed that 'addict' rats had greater cue-induced reinstatement and that this effect was decreased by LY379268 (an mGluR2/3 agonist). However, the inhibitory effect of LY379268 was also observed in 'non-addict' rats. Bock et al.[206] reported that synaptic plasticity in NAc D2 dopamine receptor (DRD2)-expressing medium spine neurons contributes to vulnerability/resilience to cocaine taking and seeking in a mouse version of the DSM-IV model. Most recently, using a variation of the 'individual differences' approach based on an intermittent-access drug self-administration model[79], O'Neal et al.[90] showed that in heroin-trained 'addiction-vulnerable' rats, cue-induced reinstatement (but not progressive ratio responding) is bidirectionally modulated via the direct and indirect striatal pathways (FIG. 2).

Together, findings from the DSM-IV model have a significant conceptual impact[207], but have led to very few follow-up brain mechanism studies. At present, neither the postdictive validity nor the translational utility (predictive validity) of the model has been established, and the results from a single pharmacological study with LY379268 confirm those from studies on the efficacy of mGluR2/3 agonists on relapse in rat models[208].

In summary, from a mechanistic perspective, the major conceptual advance from studies using the addiction-related models described here has been the dissociation of circuits controlling traditional limited-access drug self-administration (and drug CPP) from those that control arguably more complex behaviours, such as extended-access escalation of drug self-administration, cue-controlled responding under second-order schedules and drug self-administration despite adverse consequences. The studies reviewed also show that different brain areas and circuits control behaviour in the different models (FIG. 2). Much less is known about the circuit mechanisms of drug choice, and about the 'addicted' phenotype in DSM-IV models. It is also largely unknown whether these more human-relevant models have greater predictive or postdictive validity than those that preceded them. The models have shown good postdictive validity, but, as we noted, have not yet led to approval or dissemination of new treatments (predictive validity). One exception is the choice model, whose results partially inspired the development of contingency management, a highly effective behavioural treatment for most forms of addiction[161]. This model also proved useful in detecting 'false-positive' medications identified in traditional single-lever drug self-administration and reinstatement models that were ineffective in human studies (TABLES 1,3).

The reverse translational approach

Contingency management is one of the success stories in addiction treatment (other successes include opioid agonist maintenance and the community-reinforcement approach) that have led our group to take a 'reverse translational' approach to animal models. For many years, we and others have used the rat reinstatement model to identify unique and shared mechanisms of reinstatement induced by drug priming, stress and drug cues and

Reverse translation
The use of data from humans (for example, that a treatment is effective for a condition) to develop animal models whose goals are to uncover underlying mechanisms and identify new treatments.

G-protein-biased MOR agonist
An agonist of μ opioid receptor (MOR) that preferentially activates the G-protein-coupled intracellular pathway over the β-arrestin pathway.

Daun02 inactivation procedure
A pharmacogenetic lesion approach (conversion of Daun02 into cytotoxic daunorubicin by β-galactosidase) to determine the behavioural relevance of FOS-expressing neuronal ensembles in *FOS–lacZ* rats that express FOS and β-galactosidase in activated neurons.

contexts[209]. However, the clinical studies whose goal was to 'forward translate' findings from the reinstatement model have had, at best, limited success (TABLE 1). Now, through reverse translation of successful human treatments, we aim to clarify their mechanisms and action and identify new treatments. We first describe an animal model of opioid maintenance[210,211] that we recently used to test a new class of MOR agonists that might complement methadone and buprenorphine. Next, we describe our models of contingency management[161] and the community-reinforcement approach[212], which we have used to identify brain mechanisms of relapse after treatment.

Opioid maintenance treatment model. Opioid maintenance can be modelled in rats using osmotic minipumps that provide relatively invariant drug levels and mimic the slow kinetics of clinical regimens. We and others studied the effect of maintenance with heroin[213], methadone[32] or buprenorphine[31] (via minipumps implanted after self-administration of heroin or heroin plus cocaine) on reinstatement after extinction. Opioid maintenance decreased reinstatement induced by drug priming but not foot shock stress. In one study[31], buprenorphine maintenance also decreased extinction responding before reinstatement testing.

Recently[42], we combined the opioid maintenance model with a modification of the context-induced reinstatement model[192,214] to compare the efficacy of buprenorphine with that of the putatively G-protein-biased MOR agonist TRV130 (REF.[215]) (see REF.[216] for an alternative account of the improved safety profile of putative MOR-biased agonists). Minipumps were implanted after oxycodone self-administration training (FR1 reinforcement schedule, 20-s time out; 6 h per day for 14 days), and the effect of buprenorphine and TRV130 maintenance was tested on three relapse-related measures: extinction responding, context-induced reinstatement and reacquisition of oxycodone self-administration. In male rats, buprenorphine and TRV130 decreased extinction responding and reacquisition but had a weaker effect on context-induced reinstatement. In female rats, buprenorphine decreased responding on all three measures, while TRV130 decreased only extinction responding. Because of their lower liability to produce respiratory depression, the clinical implication is that G-protein-biased MOR agonists, currently in development as analgesics[217], should be considered as maintenance medications, although they might be more effective for men than women.

Reverse translation of agonist-based maintenance treatment is also applicable to cocaine. A study at the beginning of this century showed that amphetamine maintenance decreases human cocaine use[218]. Subsequent studies in monkeys and rats showed that prolonged amphetamine delivery decreases cocaine self-administration and choice[219,220]. These findings provide a framework through which an agonist-based maintenance-like model can be used in laboratory animals to identify novel, long-acting dopamine mimics (full or partial agonists at receptors, or blockers or substrates at transporters) for treatment of psychostimulant addiction[221].

Contingency management model. In humans, abstinence is often chosen in order to retain or obtain access to non-drug rewards[28]. This general principle is made concrete and systematic in contingency management, a behavioural treatment in which small prizes or monetary vouchers can maintain abstinence for many months[146]. In 2015, on the basis of previous work using food versus drug choice[23,36] (see above), our group[43] developed a rat model to study incubation of methamphetamine craving and relapse after voluntary abstinence. Our objective was to model craving and relapse after discontinuation of contingency management.

In this model, food-sated rats are trained to self-administer pellets of palatable food for 6 days and then to self-administer methamphetamine for 12 days. Next, relapse to drug seeking is tested twice — after 1 and 21 days of abstinence. Between tests, rats undergo voluntary abstinence (achieved via a discrete-choice procedure between drug and palatable food). In the first study[43], we showed robust incubation of methamphetamine craving in male rats after choice-induced abstinence, an effect decreased by systemic injection of the mGluR2 agonist AZD8529. These data extend previous findings on the efficacy of mGluR2/3 agonists on relapse in rat models[208]. However, AZD8529 appears to have a more favourable profile than the classic mGluR2/3 agonist LY379268 for translation to human relapse prevention: it is more selective on the mGluR2 subtype, has better bioavailability and does not produce tolerance[222]. In the second study[223], we extended the incubation findings (for methamphetamine craving after food choice-induced abstinence) to female rats. We also showed that, for heroin, choice-induced abstinence prevented incubation in both sexes. The clinical implications of these findings are unknown. Contingency management is thought to be similarly efficacious across drug classes[146], but if it had a greater effect on incubation for opioids than for psychostimulants, this difference would be difficult to detect in humans without a specialized study design[224].

We recently used this model to study brain mechanisms of relapse and craving after choice-induced abstinence. Using the Daun02 inactivation procedure[225], we found that incubation of methamphetamine craving requires activation of dorsomedial striatum neuronal ensembles[226]. Using a similar behavioural procedure combined with D1 dopamine receptor (DRD1) and DRD2 antagonists, Rossi et al.[227] demonstrated that incubation also involves the NAc core but not the shell. Using multiple methods, including projection-specific chemogenetic inhibition, we found that relapse to methamphetamine seeking after choice-induced abstinence requires AIC-to-CeA glutamatergic projections[228]. Most recently, we used a disconnection procedure to demonstrate that relapse to fentanyl seeking after choice-induced abstinence requires projections between the piriform cortex and the OFC[229] (FIG. 2).

The community-reinforcement approach model. In the studies just described, 'choice-induced voluntary abstinence' refers to a choice between a drug and palatable

Endophenotype
Also known as intermediate phenotype, a quantitative trait unseen by the unaided eye, located along the pathway between a genomic locus that contributes to the heritability of a complex disease phenotype and the disease itself.

food. The exclusive use of food as the non-drug reward (in our studies and most others) may limit translation, because in most humans, the rewards that compete with drugs are primarily social (for example, family, friends and employment)[230]. Since the early 1970s, this knowledge has been incorporated into the community-reinforcement approach, which harnesses operant principles by increasing volitional contact with social reinforcers such as support groups and positive work environments[212,231].

Similar principles underlie our recently developed operant model of choice between drugs and rewarding social interaction in rats[44]. This model was also inspired in part by studies in laboratory monkeys, dating to the early 1960s, in which social interaction was chosen over food[232]. In our rat model[44,233], the availability of a social-reward choice eliminated drug self-administration, even in rats that met 'addiction' criteria[201], under diverse conditions that included social housing between the choice sessions. Furthermore, after intermittent-access drug self-administration[79], the rats' addiction scores did not predict their liability to shift from social to methamphetamine preference when social interaction was delayed or punished. Another unexpected finding was that abstinence induced by social choice modestly decreased incubation of heroin craving[234] and completely prevented incubation of methamphetamine craving[44].

We have begun to study the neurocircuitry underlying social reward prevention of incubation. It involves the lateral part of the CeA protein kinase Cδ (PKCδ)-expressing neurons[44] (which inhibit the medial part of the CeA output neurons controlling appetitive and aversive behaviours[235]). We first demonstrated this with double-labelling immunohistochemistry of FOS plus PKCδ[44]. We then developed an adeno-associated virus-based short hairpin RNA to inhibit PKCδ expression, and showed that knocking down the enzyme in the lateral part of the CeA reverses the prevention of incubation[236] (FIG. 2). Using similar methods, we also showed a role for the lateral part of the CeA somatostatin-expressing neurons in the classic incubation of craving after home-cage forced abstinence[44,236].

In summary, we described treatment-based reverse translational approaches whose goal is to mimic successful addiction treatments. We propose that these reverse-translated 'treatment' models provide an ecologically relevant platform from which we can improve forward translation using different methods to discover new relapse-related circuits and to identify new medications (for example, G-protein-biased MOR agonists) for relapse prevention in 'treated' or post-'treated' laboratory animals. An unexpected finding from our choice-induced voluntary abstinence models is the drug-specific effects of the food versus social interaction manipulations: food choice prevents the emergence of incubation of heroin craving but not methamphetamine craving, while social choice prevents the emergence of incubation of methamphetamine craving but has a modest effect on incubation of heroin craving[44,223]. The mechanistic basis for this dissociation is a subject for future research. Finally, for a brief discussion of the reverse translational treatment approach within the context of endophenotype-based approaches to animal models of psychiatric disorders[237–239], see Supplementary Box 1.

Implications for human addiction

Pharmacological treatments. Reverse translation builds on interventions with established clinical efficacy, ultimately evidenced by regulatory approval. Few addiction pharmacotherapies fit this bill, but some do, and these offer a starting point. Approval of medications requires 'meaningful clinical benefit'; for addiction (except alcoholism), this is defined by the FDA and European Medicines Agency as sustained abstinence[240]. Draft guidance from the FDA suggests — appropriately — that benefit could be recognized in "patterns" other than complete abstinence[241]. Until such guidance is implemented, we cannot be confident that approval will be granted for a medication that, for example, partially shifts choice allocation towards non-drug rewards (FIG. 3). Nevertheless, non-abstinence outcomes may offer biomarkers for early-stage development[242].

The prototype for reverse translation should probably be methadone, which retains patients in treatment and promotes abstinence from other opioids with effect sizes among the largest in medicine (number needed to treat of 2 or less)[21]. When use of methadone is accompanied by behavioural treatments, outcomes are even better[243]. Of note, many patients taking methadone show substantial functional improvement without complete abstinence from other opioids[244]. Reverse translation can accommodate that reality: in rats, as in humans, suppression of opioid intake and relapse by agonist maintenance is not uniform[32,42], a finding that seems important to explain.

Heterogeneity in response to methadone maintenance, in patients or laboratory animals, underscores the fact that we do not fully understand how methadone maintenance works. Clinically, two mechanisms are thought to be important, both enabled by methadone's slow elimination and its associated sustained MOR activation. First, methadone dampens craving for other opioids without inducing intoxication. Second, by gradually inducing tolerance, methadone — at sufficient doses — decreases the rewarding effects of short-acting opioids[245]. (This 'blockade' is rarely complete; patients can top up.) The relative contributions of these two mechanisms vary between and within patients, adding often unrecognized complexity to methadone's actions.

Buprenorphine, a long-acting high-affinity partial MOR agonist (with KOR antagonistic effects of unknown clinical relevance), highlights some of these complexities. At sufficient doses, its treatment efficacy is similar to that of methadone[246]. Because it is a partial agonist, its ability to suppress craving is inferior to methadone's and requires MOR occupancy greater than 70% (REF.[247]). However, because of its high affinity and limited intrinsic MOR activity[248], buprenorphine becomes a potent antagonist in the presence of other opioids, blocking their short-term rewarding effects and promoting abstinence at doses lower than those required

to suppress craving. This dichotomy has been elegantly borne out by studies of depot buprenorphine[249,250].

Reverse translation of these clinical realities, with accompanying mechanistic work, should be relevant to more than opioid addiction. We recognize major differences in addiction across drug classes[49], but opioid addiction is not the only one treatable by agonist maintenance. Although effect sizes are lower (number needed to treat of 29 (REF.[251])), nicotine addiction can be treated with nicotine replacement therapy, a full-agonist approach that emulates the slow kinetics of methadone. The high-affinity partial α4β2 nicotinic agonist varenicline has similar clinical efficacy[252]. Agonist approaches might also work for alcohol addiction, although the complexity of this condition is greater, because alcohol does not act through a single molecular target[33]. However, through its actions at $GABA_B$ and extrasynaptic $GABA_A$ receptors, sodium oxybate is a partial alcohol mimetic. Recent data support its efficacy[253]. Additionally, as mentioned already, the $GABA_B$ receptor agonist baclofen (a potential alcohol mimetic), decreases heavy drinking in humans[197] and was recently shown to decrease quinine-resistant (compulsive) home-cage alcohol drinking in rats[198]. In cannabis-dependent men, cannabis use is markedly reduced by PF-04457845 (a fatty acid amide hydrolase (FAAH) inhibitor)[254]. FAAH selectively degrades anandamide (an endogenous partial agonist at CB1 receptors) and PF-04457845 increases its plasma levels about tenfold[255]. This can be conceptualized as an indirect agonist maintenance treatment for cannabis addiction. Finally, as discussed in the section entitled "The reverse translational approach", principles of agonist maintenance treatment can also be applied to reverse translational studies aimed at identifying novel treatments for cocaine addiction[145].

The clinical data discussed above can inform reverse translation by pointing to the fact that, across drug classes, 'clinically meaningful benefits are achieved with medications that share two characteristics: they activate, to various degrees, the neurochemical targets of the addictive drug, and they stabilize the activity of those systems to avoid excessive highs and lows. High-affinity, low-efficacy partial agonists such as buprenorphine (and potentially the new generation of MOR agonists[216]) additionally block the rewarding effects of shorter-acting addictive drugs.

Finally, recent studies show that a single ketamine infusion, combined with behavioural treatments, decreases craving and relapse risk in cocaine and alcohol users[256,257]. If this finding can be reverse translated, for example, by demonstrating that acute administration of ketamine decreases incubation of psychostimulant craving after food choice-induced abstinence (contingency management), this could provide an experimental setup to test novel ketamine-like compounds with a more favourable risk–benefit ratio and identify brain mechanisms of ketamine's protective effect.

Psychological treatments. Developing new psychotherapeutic treatments will rarely require animal models. Psychotherapeutic treatments are often based on information conveyed through language and then processed abstractly by the patient/client; some of those processes may be difficult to mimic or measure in laboratory animals[258]. It will usually be more expedient to develop psychotherapies directly in the target population — humans — in accordance with systematic guidelines for formative research[259].

But medications and other biomedical treatments (and perhaps some behavioural treatments that act chiefly through classical or operant conditioning) can and should be screened in animal models that account for how drugs are used in a psychosocial milieu. Support for this point can be seen in findings from our social-choice model: rats uniformly chose social interaction with a peer rather than drugs (unless social interaction was devalued by delay or punishment of the social interaction)[233]. The strength of that finding was puzzling and surprising to many neuroscientists, including us. Many clinicians and drug-policy thought leaders were less impressed; a representative response (via Twitter) was "NIDA needed to do a rat study to discover something that social scientists have known about humans for essentially forever" (that is, that social bonds can protect against addiction). The heuristic value of our finding was audience dependent, but the practical value is not.

The logical testing ground for biomedical treatments is the subset of laboratory animals whose preference for drugs is most inelastic to the availability of non-drug alternatives, social or otherwise. They might represent the subset of patients who need such treatments (FIG. 4). The challenge is to identify those laboratory animals. We do not yet know which (if any) parametric variations can do that, and we cannot find out without assessing predictive validity. That requires iterative, bidirectional translation with a human interventional component, an inherently slow process. This is a reason to start soon.

Concluding remarks

Addiction is a complex and multifaceted psychiatric disorder whose progression and treatment outcomes are dependent on the drug user's social and economic environment, government policies and laws, and human-specific cognitive and language-related processes[258,260]. Animal models, as sophisticated as they have evolved to be over the years, can mimic only some features of this complex human condition. In general, we argue that a more nearly complete understanding of the multiple brain mechanisms of addiction will come from the use of multiple models of the different phases of addiction (FIG. 1) and the realization that terms such as 'brain reward/addiction circuit(s)' or 'addiction genes' are not heuristically useful. This is because different and often dissociable molecules and brain circuits control drug taking and drug seeking in the different animal models (FIG. 2), and, as discussed elsewhere, these mechanisms are also often dissociable across drug classes[49,261].

Our main take-home message is that reverse translation of effective medical and behavioural treatments of addiction to animal models will improve their translational utility. This approach will increase our

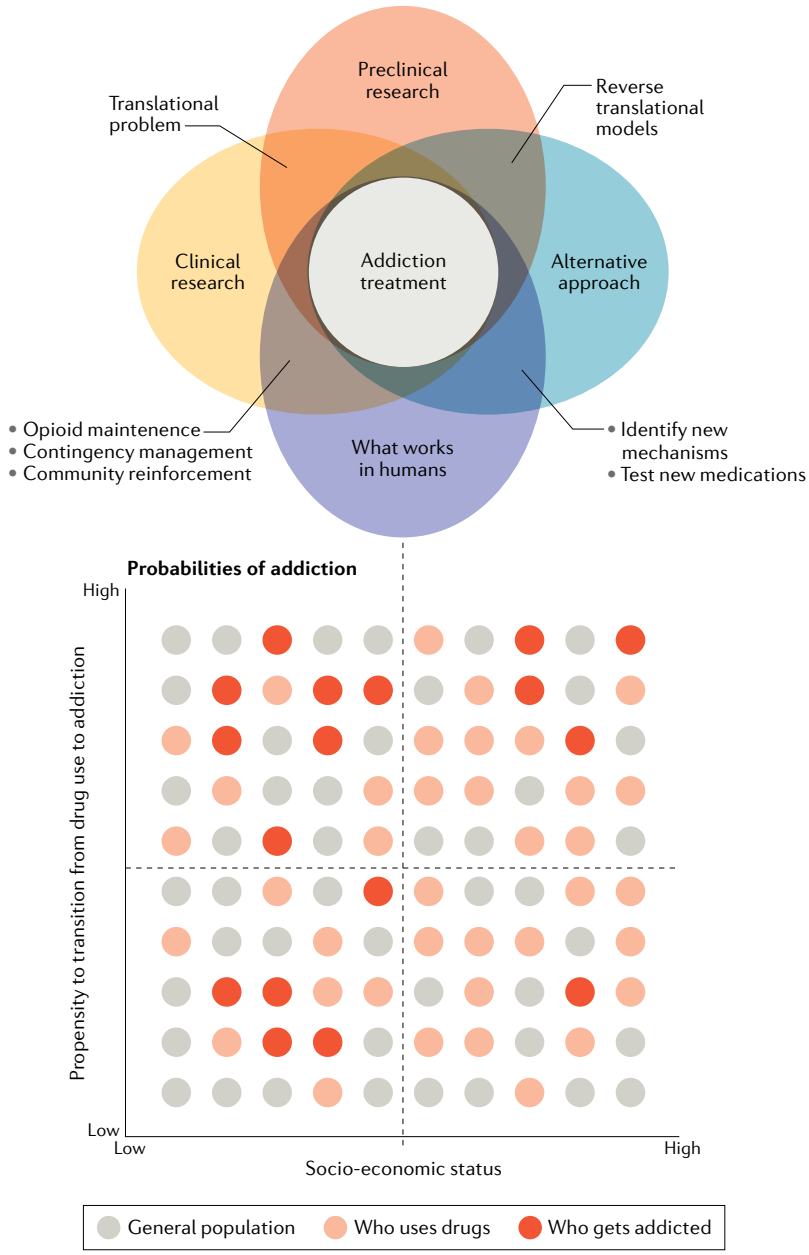

Fig. 4 | **Addiction treatment and animal models.** A Venn diagram representing a vision for translation in addiction treatment is shown in the top panel. The intersection between preclinical (pink oval) and clinical (yellow oval) research represents the current translation problem (that is, that the combination of traditional models with new technologies has yet to improve on current options for addiction treatment). Therefore, it is important to understand and explore the intersection between clinical research and what works in humans (purple oval). Successful treatments include opioid maintenance treatment and behavioural treatments such as contingency management and the community-reinforcement approach. This suggests alternative approaches (blue oval) that can be integrated with preclinical research in a reverse translational approach, the goals of which are to clarify mechanisms of action, test new treatments and forward translate those new treatments to humans in ways that account for differences in treatment needs. In the bottom panel, we operationalize socially based 'recovery capital' as socio-economic status (*x* axis) and plot it against the propensity to transition from drug use to addiction (*y* axis). People whose drug use becomes addictive despite high socio-economic status may disproportionately be those with endogenous (that is, genetic and/or neurobiological) vulnerabilities. A highly biomedicalized approach to addiction treatment (medications or neurostimulation) has an important place in public health, but its benefits are skewed towards the patients for whom those types of treatments may be necessary and nearly sufficient (upper-right quadrant). For other patients, those types of treatments may be necessary but insufficient (upper-left quadrant) or neither necessary nor sufficient (lower-left quadrant). If social-choice models can identify rodents with especially high propensities to resume drug seeking when social rewards are just slightly delayed or devalued, those rodents might be ideal for the screening of new biomedical or behavioural treatments for people whose addictions do not fully respond to psychosocial/psychotherapeutic treatments. Grey dots, general population; pink dots, people who use drugs but do not become addicted; red dots, people who use drugs and become addicted.

mechanistic understanding of effective treatments. In turn, this will allow forward translation of novel medications and behavioural approaches that mimic the efficacy of the established treatments in the animal models. From a clinical perspective, we propose a wider implementation of social-based behavioural treatments, including the community-reinforcement approach and innovative social media-based approaches (already in use for other psychiatric disorders[262]).

Additionally, from a reverse translational perspective, human imaging studies, in combination with social-based behavioural treatments, may help reveal the circuits controlling the protective effects of positive social interaction on drug-taking behaviour, and identify druggable targets that modify these circuits. Furthermore, reverse translation can be improved by including both sexes in testing potential medications in the animal models. For example, we recently reported that females are less sensitive than males to the antirelapse effects of potential medications[42,176].

Finally, we argue that choice-based models may be particularly appropriate for medication testing because they not only mimic the clinical efficacy of contingency management but are also sensitive (in monkey models) to clinically effective opioid agonist therapy. For example, methadone is preferentially effective in physically dependent but not non-dependent monkeys[129]. Remarkably, 65 years after the introduction of methadone[210], and 29 years after the introduction of contingency management[161], little work has been devoted to identifying the circuitry through which these treatments operate. Reverse-translationally informed animal models could address that, and then allow evaluation of new treatments, with potentially reduced risk–benefit ratios[42].

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1. Association, A. P. *Diagnostic and Statistical Manual of Mental Disorders: DSM-5*. (American Psychiatric Association Publishing Incorporated, 2013).
2. Carvalho, A. F., Heilig, M., Perez, A., Probst, C. & Rehm, J. Alcohol use disorders. *Lancet* **394**, 781–792 (2019).
3. Volkow, N. D. & Collins, F. S. The role of science in addressing the opioid crisis. *N. Engl. J. Med.* **377**, 391–394 (2017).
4. Volkow, N. D. Stigma and the toll of addiction. *N. Engl. J. Med.* **382**, 1289–1290 (2020).
5. Heilig, M., Epstein, D. H., Nader, M. A. & Shaham, Y. Time to connect: bringing social context into addiction neuroscience. *Nat. Rev. Neurosci.* **17**, 592–599 (2016).
6. Pickard, H. Responsibility without blame for addiction. *Neuroethics* **10**, 169–180 (2017).
7. Pickard, H. The purpose in chronic addiction. *AJOB Neurosci.* **3**, 40–49 (2012).
8. Leshner, A. I. Addiction is a brain disease, and it matters. *Science* **278**, 45–47 (1997). **An influential opinion piece that popularized the notion of addiction as a brain disease**.
9. Nestler, E. J. & Aghajanian, G. K. Molecular and cellular basis of addiction. *Science* **278**, 58–63 (1997).
10. Koob, G. F. & Le Moal, M. Drug abuse: hedonic homeostatic dysregulation. *Science* **278**, 52–58 (1997).
11. Steketee, J. D. & Kalivas, P. W. Drug wanting: behavioral sensitization and relapse to drug-seeking behavior. *Pharmacol. Rev.* **63**, 348–365 (2011).
12. Russo, S. J. et al. The addicted synapse: mechanisms of synaptic and structural plasticity in nucleus accumbens. *Trends Neurosci.* **33**, 267–276 (2010).
13. Koob, G. F. Neurobiology of opioid addiction: opponent process, hyperkatifeia, and negative reinforcement. *Biol. Psychiatry* **87**, 44–53 (2020).
14. Jaramillo, A. A. et al. Functional role for suppression of the insular-striatal circuit in modulating interoceptive effects of alcohol. *Addict. Biol.* **23**, 1020–1031 (2018).
15. Wise, R. A. & Koob, G. F. The development and maintenance of drug addiction. *Neuropsychopharmacology* **39**, 254–262 (2014).
16. Jonkman, S. & Kenny, P. J. Molecular, cellular, and structural mechanisms of cocaine addiction: a key role for microRNAs. *Neuropsychopharmacology* **38**, 198–211 (2013).
17. Peters, J., Kalivas, P. W. & Quirk, G. J. Extinction circuits for fear and addiction overlap in prefrontal cortex. *Learn. Mem.* **16**, 279–288 (2009).
18. McNally, G. P. Extinction of drug seeking: neural circuits and approaches to augmentation. *Neuropharmacology* **76**, 528–532 (2014).
19. Bossert, J. M., Marchant, N. J., Calu, D. J. & Shaham, Y. The reinstatement model of drug relapse: recent neurobiological findings, emerging research topics, and translational research. *Psychopharmacology* **229**, 453–476 (2013).
20. Dong, Y., Taylor, J. R., Wolf, M. E. & Shaham, Y. Circuit and synaptic plasticity mechanisms of drug relapse. *J. Neurosci.* **37**, 10867–10876 (2017).
21. Epstein, D. H., Heilig, M. & Shaham, Y. Science-based actions can help address the opioid crisis. *Trends Pharmacol. Sci.* **39**, 911–916 (2018).
22. Nestler, E. J. & Hyman, S. E. Animal models of neuropsychiatric disorders. *Nat. Neurosci.* **13**, 1161–1169 (2010).
23. Ahmed, S. H. Validation crisis in animal models of drug addiction: beyond non-disordered drug use toward drug addiction. *Neurosci. Biobehav. Rev.* **35**, 172–184 (2010).
24. Field, M. & Kersbergen, I. Are animal models of addiction useful? *Addiction* **115**, 6–12 (2020).
25. Ahmed, S. H. & Koob, G. F. Transition from moderate to excessive drug intake: change in hedonic set point. *Science* **282**, 298–300 (1998). **An influential article that introduces the escalation model currently used by numerous researchers**.
26. Katz, J. L. & Higgins, S. T. The validity of the reinstatement model of craving and relapse to drug use. *Psychopharmacology* **168**, 21–30 (2003).
27. Venniro, M., Caprioli, D. & Shaham, Y. Animal models of drug relapse and craving: from drug priming-induced reinstatement to incubation of craving after voluntary abstinence. *Prog. Brain Res.* **224**, 25–52 (2016).
28. Epstein, D. H. & Preston, K. L. The reinstatement model and relapse prevention: a clinical perspective. *Psychopharmacology* **168**, 31–41 (2003).
29. Markou, A. et al. Animal models of drug craving. *Psychopharmacology* **112**, 163–182 (1993).
30. Sarter, M. & Bruno, J. P. in *Biolotical Psychiatry* (eds H. D'haenen, J.A. den Boer & Willner, P.) 1-8 (Johns Willey & Sons Ltd., 2002).
31. Sorge, R. E., Rajabi, H. & Stewart, J. Rats maintained chronically on buprenorphine show reduced heroin and cocaine seeking in tests of extinction and drug-induced reinstatement. *Neuropsychopharmacology* **30**, 1681–1692 (2005).
32. Leri, F., Tremblay, A., Sorge, R. E. & Stewart, J. Methadone maintenance reduces heroin- and cocaine-induced relapse without affecting stress-induced relapse in a rodent model of poly-drug use. *Neuropsychopharmacology* **29**, 1312–1320 (2004).
33. Spanagel, R. Alcoholism: a systems approach from molecular physiology to addictive behavior. *Physiol. Rev.* **89**, 649–705 (2009).
34. Jorenby, D. E. et al. Efficacy of varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. *JAMA* **296**, 56–63 (2006).
35. Jonas, D. E. et al. Pharmacotherapy for adults with alcohol use disorders in outpatient settings: a systematic review and meta-analysis. *JAMA* **311**, 1889–1900 (2014).
36. Banks, M. L. & Negus, S. S. Insights from preclinical choice models on treating drug addiction. *Trends Pharmacol. Sci.* **38**, 181–194 (2017).
37. Vanderschuren, L. J. M., Minnaard, A. M., Smeets, J. A. S. & Lesscher, H. M. B. Punishment models of addictive behavior. *Cur Opin. Behav. Sci.* **13**, 77–84 (2017).
38. Kawa, A. B., Allain, F., Robinson, T. E. & Samaha, A. N. The transition to cocaine addiction: the importance of pharmacokinetics for preclinical models. *Psychopharmacology* **236**, 1145–1157 (2019).
39. Ahmed, S. H. Trying to make sense of rodents' drug choice behavior. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **87**, 3–10 (2018).
40. Deroche-Gamonet, V. & Piazza, P. V. Psychobiology of cocaine addiction: contribution of a multi-symptomatic animal model of loss of control. *Neuropharmacology* **76 Pt B**, 437–449 (2014).
41. Perry, W. et al. A reverse-translational study of dysfunctional exploration in psychiatric disorders: from mice to men. *Arch. Gen. Psychiatry* **66**, 1072–1080 (2009).
42. Bossert, J. M. et al. In a rat model of opioid maintenance, the G protein-biased mu opioid receptor agonist TRV130 decreases relapse to oxycodone seeking and taking and prevents oxycodone-induced brain hypoxia. *Biol. Psychiatry* https://doi.org/10.1016/j.biopsych.2020.02.014 (2020). **A recent article where the authors use an animal model of opioid maintenance as a platform to identify new opioid agonist-based treatments**.
43. Caprioli, D. et al. Effect of the novel positive allosteric modulator of metabotropic glutamate receptor 2 AZD8529 on incubation of methamphetamine craving after prolonged voluntary abstinence in a rat model. *Biol. Psychiatry* **78**, 463–473 (2015). **An article where the authors modify the classic food versus drug choice model to study relapse after contingency management (food choice-induced voluntary abstinence)**.
44. Venniro, M. et al. Volitional social interaction prevents drug addiction in rat models. *Nat. Neurosci.* **21**, 1520–1529 (2018). **A recent article where the authors show that rats trained to self-administer heroin or methamphetamine using gold standard addiction models strongly prefer operant social interaction over the drugs**.
45. Deneau, G., Yanagita, T. & Seevers, M. H. Self-administration of psychoactive substances by the monkey. *Psychopharmacologia* **16**, 30–48 (1969). **A seminal early article demonstrating binge-like cocaine self-administration in a non-human primate model**.
46. Yokel, R. A. & Pickens, R. Self-administration of optical isomers of amphetamine and methylamphetamine by rats. *J. Pharmacol. Exp. Ther.* **187**, 27–33 (1973).
47. Johanson, C. E., Balster, R. L. & Bonese, K. Self-administration of psychomotor stimulant drugs: the effects of unlimited access. *Pharmacol. Biochem. Behav.* **4**, 45–51 (1976).
48. Bozarth, M. A. & Wise, R. A. Toxicity associated with long-term intravenous heroin and cocaine self-administration in the rat. *J. Am. Med. Assoc.* **254**, 81–83 (1985).
49. Badiani, A., Belin, D., Epstein, D., Calu, D. & Shaham, Y. Opiate versus psychostimulant addiction: the differences do matter. *Nat. Rev. Neurosci.* **12**, 685–700 (2011).
50. Heilig, M. & Koob, G. F. A key role for corticotropin-releasing factor in alcohol dependence. *Trends Neurosci.* **30**, 399–406 (2007).
51. Tornatzky, W. & Miczek, K. A. Cocaine self-administration "binges": transition from behavioral and autonomic regulation toward homeostatic dysregulation in rats. *Psychopharmacology* **148**, 289–298 (2000).
52. Zernig, G. et al. Explaining the escalation of drug use in substance dependence: models and appropriate animal laboratory tests. *Pharmacology* **80**, 65–119 (2007).
53. Vanderschuren, L. J. & Ahmed, S. H. Animal studies of addictive behavior. *Cold Spring Harb. Perspect. Med.* **3**, a011932 (2013).
54. Pelloux, Y., Everitt, B. J. & Dickinson, A. Compulsive drug seeking by rats under punishment: effects of drug taking history. *Psychopharmacology* **194**, 127–137 (2007).
55. Mantsch, J. R., Baker, D. A., Funk, D., Le, A. D. & Shaham, Y. Stress-induced reinstatement of drug seeking: 20 years of progress. *Neuropsychopharmacology* **41**, 335–356 (2016).
56. Koob, G. F. A role for brain stress systems in addiction. *Neuron* **59**, 11–34 (2008).
57. Wee, S. & Koob, G. F. The role of the dynorphin-kappa opioid system in the reinforcing effects of drugs of abuse. *Psychopharmacology* **210**, 121–135 (2010).
58. Grieder, T. E. et al. VTA CRF neurons mediate the aversive effects of nicotine withdrawal and promote intake escalation. *Nat. Neurosci.* **17**, 1751–1758 (2014).
59. Schlosburg, J. E. et al. Long-term antagonism of kappa opioid receptors prevents escalation of and increased motivation for heroin intake. *J. Neurosci.* **33**, 19384–19392 (2013).
60. Schmeichel, B. E., Herman, M. A., Roberto, M. & Koob, G. F. Hypocretin neurotransmission within the central amygdala mediates escalated cocaine self-administration and stress-induced reinstatement in rats. *Biol. Psychiatry* **81**, 606–615 (2017).
61. Kallupi, M. et al. Nociceptin attenuates the escalation of oxycodone self-administration by normalizing CeA-GABA transmission in highly addicted rats. *Proc. Natl Acad. Sci. USA* **117**, 2140–2148 (2020).
62. Funk, C. K., O'Dell, L. E., Crawford, E. F. & Koob, G. F. Corticotropin-releasing factor within the central nucleus of the amygdala mediates enhanced ethanol self-administration in withdrawn, ethanol-dependent rats. *J. Neurosci.* **26**, 11324–11332 (2006).
63. Hollander, J. A. et al. Striatal microRNA controls cocaine intake through CREB signalling. *Nature* **466**, 197–202 (2010).
64. Im, H. I., Hollander, J. A., Bali, P. & Kenny, P. J. MeCP2 controls BDNF expression and cocaine intake through homeostatic interactions with microRNA-212. *Nat. Neurosci.* **13**, 1120–1127 (2010).
65. Ahmed, S. H. et al. Gene expression evidence for remodeling of lateral hypothalamic circuitry in cocaine addiction. *Proc. Natl Acad. Sci. USA* **102**, 11533–11538 (2005).
66. Ben-Shahar, O. et al. Extended daily access to cocaine results in distinct alterations in Homer 1b/c and NMDA receptor subunit expression within the medial prefrontal cortex. *Synapse* **63**, 598–609 (2009).
67. Calipari, E. S., Ferris, M. J. & Jones, S. R. Extended access of cocaine self-administration results in tolerance to the dopamine-elevating and locomotor-stimulating effects of cocaine. *J. Neurochem.* **128**, 224–232 (2014).
68. Willuhn, I., Burgeno, L. M., Groblewski, P. A. & Phillips, P. E. Excessive cocaine use results from decreased phasic dopamine signaling in the striatum. *Nat. Neurosci.* **17**, 704–709 (2014).
69. Reed, B., Butelman, E. R., Fry, R. S., Kimani, R. & Kreek, M. J. Repeated administration of opra kappa (LY2456302), a novel, short-acting, selective KOP-r antagonist, in persons with and without cocaine dependence. *Neuropsychopharmacology* **43**, 739–750 (2018).
70. Banks, M. L. The rise and fall of kappa-opioid receptors in drug abuse research. *Handb. Exp. Pharmacol.* **258**, 147–165 (2019).
71. Kwako, L. E. et al. The corticotropin releasing hormone-1 (CRH1) receptor antagonist pexacerfont in alcohol dependence: a randomized controlled experimental

medicine study. *Neuropsychopharmacology* **40**, 1053–1063 (2015).
A study, together with that of Schwandt et al. (2016), that shows lack of efficacy of a CRFR1 antagonist (a major target for addiction treatment on the basis of results from animal models since the 1990s) in human laboratory studies.

72. Schwandt, M. L. et al. The CRF1 antagonist verucerfont in anxious alcohol-dependent women: Translation of neuroendocrine, but not of anti-craving effects. *Neuropsychopharmacology* **41**, 2818–2829 (2016).
73. Shaham, Y. & de Wit, H. Lost in translation: CRF1 receptor antagonists and addiction treatment. *Neuropsychopharmacology* **41**, 2795–2797 (2016).
74. Deroche-Gamonet, V. et al. The glucocorticoid receptor as a potential target to reduce cocaine abuse. *J. Neurosci.* **23**, 4785–4790 (2003).
75. Mantsch, J. R. et al. Surgical adrenalectomy with diurnal corticosterone replacement slows escalation and prevents the augmentation of cocaine-induced reinstatement in rats self-administering cocaine under long-access conditions. *Neuropsychopharmacology* **33**, 814–826 (2008).
76. Vendruscolo, L. F. et al. Glucocorticoid receptor antagonism decreases alcohol seeking in alcohol-dependent individuals. *J. Clin. Invest.* **125**, 3193–3197 (2015).
A rare example of a potential successful forward translation (see Vendruscolo et al. (2012)) showing the efficacy of a glucocorticoid receptor antagonist in both an animal model and a clinical study.
77. Vendruscolo, L. F. et al. Corticosteroid-dependent plasticity mediates compulsive alcohol drinking in rats. *J. Neurosci.* **32**, 7563–7571 (2012).
78. Roberts, D. C., Brebner, K., Vincler, M. & Lynch, W. J. Patterns of cocaine self-administration in rats produced by various access conditions under a discrete trials procedure. *Drug Alcohol Depend.* **67**, 291–299 (2002).
79. Zimmer, B. A., Oleson, E. B. & Roberts, D. C. The motivation to self-administer is increased after a history of spiking brain levels of cocaine. *Neuropsychopharmacology* **37**, 1901–1910 (2012).
An important study introducing the increasingly popular intermittent drug access animal model of addiction.
80. Allain, F., Minogianis, E. A., Roberts, D. C. & Samaha, A. N. How fast and how often: the pharmacokinetics of drug use are decisive in addiction. *Neurosci. Biobehav. Rev.* **56**, 166–179 (2015).
81. Kawa, A. B., Valenta, A. C., Kennedy, R. T. & Robinson, T. E. Incentive and dopamine sensitization produced by intermittent but not long access cocaine self-administration. *Eur. J. Neurosci.* **50**, 2663–2682 (2019).
82. Xue, Y., Steketee, J. D. & Sun, W. Inactivation of the central nucleus of the amygdala reduces the effect of punishment on cocaine self-administration in rats. *Eur. J. Neurosci.* **35**, 775–783 (2012).
83. Kawa, A. B., Bentzley, B. S. & Robinson, T. E. Less is more: prolonged intermittent access cocaine self-administration produces incentive-sensitization and addiction-like behavior. *Psychopharmacology* **233**, 3587–3602 (2016).
84. Hao, Y., Martin-Fardon, R. & Weiss, F. Behavioral and functional evidence of metabotropic glutamate receptor 2/3 and metabotropic glutamate receptor 5 dysregulation in cocaine-escalated rats: factor in the transition to dependence. *Biol. Psychiatry* **68**, 240–248 (2010).
85. Allain, F., Roberts, D. C. S., Levesque, D. & Samaha, A. N. Intermittent intake of rapid cocaine injections promotes robust psychomotor sensitization, increased incentive motivation for the drug and mGlu2/3 receptor dysregulation. *Neuropharmacology* **117**, 227–237 (2017).
86. James, M. H. et al. Increased number and activity of a lateral subpopulation of hypothalamic orexin/hypocretin neurons underlies the expression of an addicted state in rats. *Biol. Psychiatry* **85**, 925–935 (2019).
87. Nicolas, C. et al. Incubation of cocaine craving after intermittent-access self-administration: sex differences and estrous cycle. *Biol. Psychiatry* **85**, 915–924 (2019).
88. Calipari, E. S., Ferris, M. J., Zimmer, B. A., Roberts, D. C. & Jones, S. R. Temporal pattern of cocaine intake determines tolerance vs sensitization of cocaine effects at the dopamine transporter. *Neuropsychopharmacology* **38**, 2385–2392 (2013).
89. James, I. E. et al. A first time in human clinical study with TRV734, an orally bioavailable G-protein-biased ligand at the μ-opioid receptor. *Clin. Pharmacol. Drug Dev.* **9**, 256–266 (2019).
90. O'Neal, T. J., Nooney, M. N., Thien, K. & Ferguson, S. M. Chemogenetic modulation of accumbens direct or indirect pathways bidirectionally alters reinstatement of heroin-seeking in high- but not low-risk rats. *Neuropsychopharmacology* **45**, 1251–1262 (2019).
91. Bentzley, B. S., Fender, K. M. & Aston-Jones, G. The behavioral economics of drug self-administration: a review and new analytical approach for within-session procedures. *Psychopharmacology* **226**, 113–125 (2013).
92. Mohammadkhani, A. et al. Orexin-1 receptor signaling in ventral pallidum regulates motivation for the opioid remifentanil. *J. Neurosci.* **39**, 9831–9840 (2019).
93. Townsend, E. A., Negus, S. S., Caine, S. B., Thomsen, M. & Banks, M. L. Sex differences in opioid reinforcement under a fentanyl vs. food choice procedure in rats. *Neuropsychopharmacology* **44**, 2022–2029 (2019).
94. Fragale, J. E., Pantazis, C. B., James, M. H. & Aston-Jones, G. The role of orexin-1 receptor signaling in demand for the opioid fentanyl. *Neuropsychopharmacology* **44**, 1690–1697 (2019).
95. Goldberg, S. R. Stimuli associated with drug injections as events that control behavior. *Pharmacol. Rev.* **27**, 325–340 (1975).
96. Goldberg, S. R. Comparable behavior maintained under fixed-ratio and second-order schedules of food presentation, cocaine injection or d-amphetamine injection in the squirrel monkey. *J. Pharmacol. Exp. Ther.* **186**, 18–30 (1973).
97. Whitelaw, R. B., Markou, A., Robbins, T. W. & Everitt, B. J. Excitotoxic lesions of the basolateral amygdala impair the acquisition of cocaine-seeking behaviour under a second-order schedule of reinforcement. *Psychopharmacology* **127**, 213–224 (1996).
98. Weissenborn, R., Robbins, T. W. & Everitt, B. J. Effects of medial prefrontal or anterior cingulate cortex lesions on responding for cocaine under fixed-ratio and second-order schedules of reinforcement in rats. *Psychopharmacology* **134**, 242–257 (1997).
99. Wise, R. A. et al. Fluctuations in nucleus accumbens dopamine concentration during intravenous cocaine self-administration in rats. *Psychopharmacology* **120**, 10–20 (1995).
100. Ito, R., Dalley, J. W., Howes, S. R., Robbins, T. W. & Everitt, B. J. Dissociation in conditioned dopamine release in the nucleus accumbens core and shell in response to cocaine cues and during cocaine-seeking behavior in rats. *J. Neurosci.* **20**, 7489–7495 (2000).
101. Ito, R., Dalley, J. W., Robbins, T. W. & Everitt, B. J. Dopamine release in the dorsal striatum during cocaine-seeking behavior under the control of a drug-associated cue. *J. Neurosci.* **22**, 6247–6253 (2002).
102. Ito, R., Robbins, T. W. & Everitt, B. J. Differential control over cocaine-seeking behavior by nucleus accumbens core and shell. *Nat. Neurosci.* **7**, 389–397 (2004).
103. Hutcheson, D. M., Parkinson, J. A., Robbins, T. W. & Everitt, B. J. The effects of nucleus accumbens core and shell lesions on intravenous heroin self-administration and the acquisition of drug-seeking behaviour under a second-order schedule of heroin reinforcement. *Psychopharmacology* **153**, 464–472 (2001).
104. Di Ciano, P. & Everitt, B. J. Direct interactions between the basolateral amygdala and nucleus accumbens core underlie cocaine-seeking behavior by rats. *J. Neurosci.* **24**, 7167–7173 (2004).
105. Di Ciano, P. & Everitt, B. J. Contribution of the ventral tegmental area to cocaine-seeking maintained by a drug-paired conditioned stimulus in rats. *Eur. J. Neurosci.* **19**, 1661–1667 (2004).
106. Wise, R. A. Neurobiology of addiction. *Curr. Opin. Neurobiol.* **6**, 243–251 (1996).
107. Peak, J., Hart, G. & Balleine, B. W. From learning to action: the integration of dorsal striatal input and output pathways in instrumental conditioning. *Eur. J. Neurosci.* **49**, 658–671 (2019).
108. Everitt, B. J. & Robbins, T. W. Drug addiction: updating actions to habits to compulsions ten years on. *Annu. Rev. Psychol.* **67**, 23–50 (2016).
109. Zapata, A., Minney, V. L. & Shippenberg, T. S. Shift from goal-directed to habitual cocaine seeking after prolonged experience in rats. *J. Neurosci.* **30**, 15457–15463 (2010).
110. Hodebourg, R. et al. Heroin seeking becomes dependent on dorsal striatal dopaminergic mechanisms and can be decreased by N-acetylcysteine. *Eur. J. Neurosci.* **50**, 2036–2044 (2019).
111. Giuliano, C. et al. The Novel mu-opioid receptor antagonist GSK1521498 decreases both alcohol seeking and drinking: Evidence from a new preclinical model of alcohol seeking. *Neuropsychopharmacology* **40**, 2981–2992 (2015).
112. Murray, J. E., Belin, D. & Everitt, B. J. Double dissociation of the dorsomedial and dorsolateral striatal control over the acquisition and performance of cocaine seeking. *Neuropsychopharmacology* **37**, 2456–2466 (2012).
113. Belin, D. & Everitt, B. J. Cocaine seeking habits depend upon dopamine-dependent serial connectivity linking the ventral with the dorsal striatum. *Neuron* **57**, 432–441 (2008).
114. Murray, J. E. et al. Basolateral and central amygdala differentially recruit and maintain dorsolateral striatum-dependent cocaine-seeking habits. *Nat. Commun.* **6**, 10088 (2015).
115. Lukas, S. E., Mello, N. K., Drieze, J. M. & Mendelson, J. H. Buprenorphine-induced alterations of cocaine's reinforcing effects in rhesus monkey: a dose-response analysis. *Drug Alcohol Depend.* **40**, 87–98 (1995).
116. Newman, J. L., Negus, S. S., Lozama, A., Prisinzano, T. E. & Mello, N. K. Behavioral evaluation of modafinil and the abuse-related effects of cocaine in rhesus monkeys. *Exp. Clin. Psychopharmacol.* **18**, 395–408 (2010).
117. Mello, N. K., Fivel, P. A., Kohut, S. J. & Bergman, J. Effects of chronic buspirone treatment on cocaine self-administration. *Neuropsychopharmacology* **38**, 455–467 (2013).
118. Winhusen, T. M. et al. Multisite, randomized, double-blind, placebo-controlled pilot clinical trial to evaluate the efficacy of buspirone as a relapse-prevention treatment for cocaine dependence. *J. Clin. Psychiatry* **75**, 757–764 (2014).
119. Ling, W. et al. Buprenorphine+naloxone plus naltrexone for the treatment of cocaine dependence: the Cocaine Use Reduction with Buprenorphine (CURB) study. *Addiction* **111**, 1416–1427 (2016).
120. Sangroula, D. et al. Modafinil treatment of cocaine dependence: a systematic review and meta-analysis. *Subst. Use Misuse* **52**, 1292–1306 (2017).
121. Di Ciano, P., Underwood, R. J., Hagan, J. J. & Everitt, B. J. Attenuation of cue-controlled cocaine-seeking by a selective D3 dopamine receptor antagonist SB-277011-A. *Neuropsychopharmacology* **28**, 329–338 (2003).
122. Pilla, M. et al. Selective inhibition of cocaine-seeking behaviour by a partial dopamine D3 receptor agonist. *Nature* **400**, 371–375 (1999).
123. Le Foll, B. et al. Dopamine D3 receptor ligands for drug addiction treatment: update on recent findings. *Prog. Brain Res.* **211**, 255–275 (2014).
124. Leggio, G. M., Bucolo, C., Platania, C. B., Salomone, S. & Drago, F. Current drug treatments targeting dopamine D3 receptor. *Pharmacol. Ther.* **165**, 164–177 (2016).
125. Gilbert, J. G. et al. Acute administration of SB-277011A, NGB 2904, or BP 897 inhibits cocaine cue-induced reinstatement of drug-seeking behavior in rats: role of dopamine D3 receptors. *Synapse* **57**, 17–28 (2005).
126. Newman, A. H., Grundt, P. & Nader, M. A. Dopamine D3 receptor partial agonists and antagonists as potential drug abuse therapeutic agents. *J. Med. Chem.* **48**, 3663–3679 (2005).
127. Spragg, S. D. S. Morphine addiction in chimpanzees. *Comp. Psychol. Mono* **15**, 132 (1940).
128. Griffiths, R. R., Wurster, R. M. & Brady, J. V. Discrete-trial choice procedure: effects of naloxone and methadone on choice between food and heroin. *Pharmacol. Rev.* **27**, 357–365 (1975).
129. Negus, S. S. Choice between heroin and food in nondependent and heroin-dependent rhesus monkeys: effects of naloxone, buprenorphine, and methadone. *J. Pharmacol. Exp. Ther.* **317**, 711–723 (2006).
An important study demonstrating that opioid dependence and withdrawal increase heroin choice in rhesus monkeys and that this effect is reversed by opioid agonist treatment (methadone or buprenorphine).
130. Lenoir, M., Cantin, L., Vanhille, N., Serre, F. & Ahmed, S. H. Extended heroin access increases heroin choices over a potent nondrug alternative. *Neuropsychopharmacology* **38**, 1209–1220 (2013).

131. Townsend, E. A. et al. Conjugate vaccine produces long-lasting attenuation of fentanyl vs. food choice and blocks expression of opioid withdrawal-induced increases in fentanyl choice in rats. *Neuropsychopharmacology* **44**, 1681–1689 (2019).
132. Banks, M. L. & Negus, S. S. Effects of extended cocaine access and cocaine withdrawal on choice between cocaine and food in rhesus monkeys. *Neuropsychopharmacology* **35**, 493–504 (2010).
133. Hutsell, B. A., Negus, S. S. & Banks, M. L. Effects of 21-day d-amphetamine and risperidone treatment on cocaine vs food choice and extended-access cocaine intake in male rhesus monkeys. *Drug Alcohol Depend.* **168**, 36–44 (2016).
134. Cantin, L. et al. Cocaine is low on the value ladder of rats: possible evidence for resilience to addiction. *PLoS ONE* **5**, e11592 (2010).
135. Caprioli, D., Zeric, T., Thorndike, E. B. & Venniro, M. Persistent palatable food preference in rats with a history of limited and extended access to methamphetamine self-administration. *Addict. Biol.* **20**, 913–926 (2015).
136. Badiani, A. & Spagnolo, P. A. Role of environmental factors in cocaine addiction. *Curr. Pharm. Des.* **19**, 6996–7008 (2013).
137. Caprioli, D. et al. Ambience and drug choice: cocaine- and heroin-taking as a function of environmental context in humans and rats. *Biol. Psychiatry* **65**, 893–899 (2009).
138. Johanson, C. E. & Aigner, T. Comparison of the reinforcing properties of cocaine and procaine in rhesus monkeys. *Pharmacol. Biochem. Behav.* **15**, 49–53 (1981).
139. Nader, M. A. & Woolverton, W. L. Cocaine vs. food choice in rhesus monkeys: effects of increasing the response cost for cocaine. *NIDA Res. Monogr.* **105**, 621 (1990).
140. Tunstall, B. J. & Kearns, D. N. Reinstatement in a cocaine versus food choice situation: reversal of preference between drug and non-drug rewards. *Addict. Biol.* **19**, 838–848 (2014).
141. Woolverton, W. L. & Anderson, K. G. Effects of delay to reinforcement on the choice between cocaine and food in rhesus monkeys. *Psychopharmacology* **186**, 99–106 (2006).
142. Lenoir, M., Serre, F., Cantin, L. & Ahmed, S. H. Intense sweetness surpasses cocaine reward. *PLoS ONE* **2**, e698 (2007).
The first in a series of important studies unexpectedly showing that rats strongly prefer palatable food over addictive drugs in the drug self-administration model.
143. Canchy, L., Girardeau, P., Durand, A., Vouillac-Mendoza, C. & Ahmed, S. H. Pharmacokinetics trumps pharmacodynamics during cocaine choice: a reconciliation with the dopamine hypothesis of addiction. *Neuropsychopharmacology* https://doi.org/10.1038/s41386-020-0786-9 (2020).
144. Foltin, R. W. et al. Development of translational preclinical models in substance abuse: effects of cocaine administration on cocaine choice in humans and non-human primates. *Pharmacol. Biochem. Behav.* **134**, 12–21 (2015).
145. Lile, J. A. et al. Pharmacological validation of a translational model of cocaine use disorder: effects of d-amphetamine maintenance on choice between intravenous cocaine and a nondrug alternative in humans and rhesus monkeys. *Exp. Clin. Psychopharmacol.* **28**, 169–180 (2020).
146. Higgins, S. T., Heil, S. H. & Lussier, J. P. Clinical implications of reinforcement as a determinant of substance use disorders. *Annu. Rev. Psychol.* **55**, 431–461 (2004).
147. Guillem, K. & Ahmed, S. H. Preference for cocaine is represented in the orbitofrontal cortex by an increased proportion of cocaine use-coding neurons. *Cereb. Cortex* **28**, 819–832 (2018).
148. Guillem, K. & Ahmed, S. H. A neuronal population code for resemblance between drug and nondrug reward outcomes in the orbitofrontal cortex. *Brain Struct. Funct.* **224**, 883–890 (2019).
149. Cameron, C. M. & Carelli, R. M. Cocaine abstinence alters nucleus accumbens firing dynamics during goal-directed behaviors for cocaine and sucrose. *Eur. J. Neurosci.* **35**, 940–951 (2012).
150. Carelli, R. M., Ijames, S. G. & Crumling, A. J. Evidence that separate neural circuits in the nucleus accumbens encode cocaine versus "natural" (water and food) reward. *J. Neurosci.* **20**, 4255–4266 (2000).
151. Pfarr, S. et al. Choice for drug or natural reward engages largely overlapping neuronal ensembles in the infralimbic prefrontal cortex. *J. Neurosci.* **38**, 3507–3519 (2018).
152. Warren, B. L. et al. Separate vmPFC ensembles control cocaine self-administration versus extinction in rats. *J. Neurosci.* **39**, 7394–7407 (2019).
153. Warren, B. L. et al. Distinct Fos-expressing neuronal ensembles in the ventromedial prefrontal cortex mediate food reward and extinction memories. *J. Neurosci.* **36**, 6691–6703 (2016).
154. Augier, E. et al. A molecular mechanism for choosing alcohol over an alternative reward. *Science* **360**, 1321–1326 (2018).
155. Sikora, M. et al. Generalization of effects of environmental enrichment on seeking for different classes of drugs of abuse. *Behav. Brain Res.* **341**, 109–113 (2018).
156. Chauvet, C., Goldberg, S. R., Jaber, M. & Solinas, M. Effects of environmental enrichment on the incubation of cocaine craving. *Neuropharmacology* **63**, 635–641 (2012).
157. Solinas, M., Chauvet, C., Thiriet, N., El Rawas, R. & Jaber, M. Reversal of cocaine addiction by environmental enrichment. *Proc. Natl Acad. Sci. USA* **105**, 17145–17150 (2008).
158. Zlebnik, N. E. & Carroll, M. E. Prevention of the incubation of cocaine seeking by aerobic exercise in female rats. *Psychopharmacology* **232**, 3507–3513 (2015).
159. Zlebnik, N. E., Anker, J. J. & Carroll, M. E. Exercise to reduce the escalation of cocaine self-administration in adolescent and adult rats. *Psychopharmacology* **224**, 387–400 (2012).
160. Zernig, G., Kummer, K. K. & Prast, J. M. Dyadic social interaction as an alternative reward to cocaine. *Front. Psychiatry* **4**, 100 (2013).
161. Higgins, S. T. et al. A behavioral approach to achieving initial cocaine abstinence. *Am. J. Psychiatry* **148**, 1218–1224 (1991).
162. Townsend, E. A., Negus, S. S., Poklis, J. L. & Banks, M. L. Lorcaserin maintenance fails to attenuate heroin vs. food choice in rhesus monkeys. *Drug Alcohol Depend.* **208**, 107848 (2020).
163. Brandt, L. et al. Effects of lorcaserin on oxycodone self-administration and subjective responses in participants with opioid use disorder. *Drug Alcohol Depend.* **208**, 107859 (2020).
164. Luscher, C., Robbins, T. W. & Everitt, B. J. The transition to compulsion in addiction. *Nat. Rev. Neurosci.* **21**, 247–263 (2020).
165. Smith, S. G. & Davis, W. M. Punishment of amphetamine and morphine self-administration behavior. *Psychol. Rec.* **24**, 477–480 (1974).
166. Wolffgramm, J. & Heyne, A. From controlled drug intake to loss of control: the irreversible development of drug addiction in the rat. *Behav. Brain Res.* **70**, 77–94 (1995).
An important early review of the authors' efforts to develop animal models of compulsive drug use and loss of control.
167. Holtz, N. A. & Carroll, M. E. Escalation of i.v. cocaine intake in peri-adolescent vs. adult rats selectively bred for high (HiS) vs. low (LoS) saccharin intake. *Psychopharmacology* **227**, 243–250 (2013).
168. Vanderschuren, L. J. & Everitt, B. J. Drug seeking becomes compulsive after prolonged cocaine self-administration. *Science* **305**, 1017–1019 (2004).
169. Negus, S. S. Effects of punishment on choice between cocaine and food in rhesus monkeys. *Psychopharmacology* **181**, 244–252 (2005).
170. Woolverton, W. L., Freeman, K. B., Myerson, J. & Green, L. Suppression of cocaine self-administration in monkeys: effects of delayed punishment. *Psychopharmacology* **220**, 509–517 (2012).
171. Marchant, N. J., Campbell, E. J., Pelloux, Y., Bossert, J. M. & Shaham, Y. Context-induced relapse after extinction versus punishment: similarities and differences. *Psychopharmacology* **236**, 439–448 (2019).
172. Jenkins, T. N., Warner, L. H. & Warden, C. J. Standard apparatus for the study of animal motivation. *J. Comp. Psychol.* **6**, 361–382 (1926).
173. Panlilio, L., Thorndike, E. & Schindler, C. Reinstatement of punishment-suppressed opioid self-administration in rats: an alternative model of relapse to drug abuse. *Psychopharmacology* **168**, 229–235 (2003).
174. Marchant, N. J., Khuc, T. N., Pickens, C. L., Bonci, A. & Shaham, Y. Context-induced relapse to alcohol seeking after punishment in a rat model. *Biol. Psychiatry* **73**, 256–262 (2013).
175. Cooper, A., Barnea-Ygael, N., Levy, D., Shaham, Y. & Zangen, A. A conflict rat model of cue-induced relapse to cocaine seeking. *Psychopharmacology* **194**, 117–125 (2007).
176. Fredriksson, I. et al. Effect of the dopamine stabilizer (-)-OSU6162 on potentiated incubation of opioid craving after electric barrier-induced voluntary abstinence. *Neuropsychopharmacology* **45**, 770–779 (2020).
177. Chen, B. T. et al. Rescuing cocaine-induced prefrontal cortex hypoactivity prevents compulsive cocaine seeking. *Nature* **496**, 359–362 (2013).
178. Siciliano, C. A. et al. A cortical-brainstem circuit predicts and governs compulsive alcohol drinking. *Science* **366**, 1008–1012 (2019).
179. Seif, T. et al. Cortical activation of accumbens hyperpolarization-active NMDARs mediates aversion-resistant alcohol intake. *Nat. Neurosci.* **16**, 1094–1100 (2013).
180. Pelloux, Y., Dilleen, R., Economidou, D., Theobald, D. & Everitt, B. J. Reduced forebrain serotonin transmission is causally involved in the development of compulsive cocaine seeking in rats. *Neuropsychopharmacology* **37**, 2505–2514 (2012).
181. Pelloux, Y., Murray, J. E. & Everitt, B. J. Differential roles of the prefrontal cortical subregions and basolateral amygdala in compulsive cocaine seeking and relapse after voluntary abstinence in rats. *Eur. J. Neurosci.* **38**, 3018–3026 (2013).
182. Jonkman, S., Pelloux, Y. & Everitt, B. J. Differential roles of the dorsolateral and midlateral striatum in punished cocaine seeking. *J. Neurosci.* **32**, 4645–4650 (2012).
183. Hopf, F. W. & Lesscher, H. M. Rodent models for compulsive alcohol intake. *Alcohol* **48**, 253–264 (2014).
184. Pascoli, V., Terrier, J., Hiver, A. & Luscher, C. Sufficiency of mesolimbic dopamine neuron stimulation for the progression to addiction. *Neuron* **88**, 1054–1066 (2015).
185. Pascoli, V. et al. Stochastic synaptic plasticity underlying compulsion in a model of addiction. *Nature* **564**, 366–371 (2018).
186. Krasnova, I. N. et al. Incubation of methamphetamine and palatable food craving after punishment-induced abstinence. *Neuropsychopharmacology* **39**, 2008–2016 (2014).
187. Marchant, N. J. et al. Role of ventral subiculum in context-induced relapse to alcohol seeking after punishment-imposed abstinence. *J. Neurosci.* **36**, 3281–3294 (2016).
188. Marchant, N. J. et al. A critical role of lateral hypothalamus in context-induced relapse to alcohol seeking after punishment-imposed abstinence. *J. Neurosci.* **34**, 7447–7457 (2014).
189. Campbell, E. J. et al. Anterior insular cortex is critical for the propensity to relapse following punishment-imposed abstinence of alcohol seeking. *J. Neurosci.* **39**, 1077–1087 (2019).
190. Farrell, M. R. et al. Ventral pallidum is essential for cocaine relapse after voluntary abstinence in rats. *Neuropsychopharmacology* **44**, 2174–2185 (2019).
191. Pelloux, Y., Minier-Toribio, A., Hoots, J. K., Bossert, J. M. & Shaham, Y. Opposite effects of basolateral amygdala inactivation on context-induced relapse to cocaine seeking after extinction versus punishment. *J. Neurosci.* **38**, 51–59 (2018).
192. Crombag, H. & Shaham, Y. Renewal of drug seeking by contextual cues after prolonged extinction in rats. *Behav. Neurosci.* **116**, 169–173 (2002).
193. Saunders, B. T., Yager, L. M. & Robinson, T. E. Cue-evoked cocaine "craving": role of dopamine in the accumbens core. *J. Neurosci.* **33**, 13989–14000 (2013).
194. Pelloux, Y. et al. Context-induced relapse to cocaine seeking after punishment-imposed abstinence is associated with activation of cortical and subcortical brain regions. *Addict. Biol.* **23**, 699–712 (2018).
195. Giuliano, C. et al. Evidence for a long-lasting compulsive alcohol seeking phenotype in rats. *Neuropsychopharmacology* **43**, 728–738 (2018).
196. Ziauddeen, H. et al. Opioid antagonists and the A118G polymorphism in the mu-opioid receptor gene: effects of GSK1521498 and naltrexone in healthy drinkers stratified by OPRM1 genotype. *Neuropsychopharmacology* **41**, 2647–2657 (2016).
197. Leggio, L., Garbutt, J. C. & Addolorato, G. Effectiveness and safety of baclofen in the treatment of alcohol dependent patients. *CNS Neurol. Disord. Drug Targets* **9**, 33–44 (2010).
198. Marti-Prats, L. et al. Baclofen decreases compulsive alcohol drinking in rats characterised by reduced

levels of GAT-3 in the central amygdala. Preprint at https://www.biorxiv.org/content/10.1101/2020.06.29.178236v1 (2020).
199. Anthony, J. C., Warner, L. A. & Kessler, R. C. Comparative epidemiology of dependence on tobacco, alcohol, controlled substances, and inhalants: basic findings from the National Comorbidity Survey. *Drug Alcohol Depend.* **2**, 244–268 (1994).
200. Wikler, A. & Pescor, F. T. Classical conditioning of a morphine abstinence phenomenon, reinforcement of opioid-drinking behavior and "relapse" in morphine-addicted rats. *Psychopharmacologia* **10**, 255–284 (1967).
201. Deroche-Gamonet, V., Belin, D. & Piazza, P. V. Evidence for addiction-like behavior in the rat. *Science* **305**, 1014–1017 (2004).
An important article describing the development of the conceptually influential individual differences DSM-IV rat model.
202. Belin, D., Mar, A. C., Dalley, J. W., Robbins, T. W. & Everitt, B. J. High impulsivity predicts the switch to compulsive cocaine-taking. *Science* **320**, 1352–1355 (2008).
203. Kasanetz, F. et al. Transition to addiction is associated with a persistent impairment in synaptic plasticity. *Science* **328**, 1709–1712 (2010).
204. Kasanetz, F. et al. Prefrontal synaptic markers of cocaine addiction-like behavior in rats. *Mol. Psychiatry* **18**, 729–737 (2013).
205. Cannella, N. et al. The mGluR2/3 agonist LY379268 induced anti-reinstatement effects in rats exhibiting addiction-like behavior. *Neuropsychopharmacology* **38**, 2048–2056 (2013).
206. Bock, R. et al. Strengthening the accumbal indirect pathway promotes resilience to compulsive cocaine use. *Nat. Neurosci.* **16**, 632–638 (2013).
207. Piazza, P. V. & Deroche-Gamonet, V. A multistep general theory of transition to addiction. *Psychopharmacology* **229**, 387–413 (2013).
208. Liechti, M. E. & Markou, A. Role of the glutamatergic system in nicotine dependence: implications for the discovery and development of new pharmacological smoking cessation therapies. *CNS Drugs* **22**, 705–724 (2008).
209. Shaham, Y., Shalev, U., Lu, L., De Wit, H. & Stewart, J. The reinstatement model of drug relapse: history, methodology and major findings. *Psychopharmacology* **168**, 3–20 (2003).
210. Dole, V. P. & Nyswander, M. A medical treatment for diacetylmorphine (heroin) addiction. A clinical trial with methadone hydrochloride. *JAMA* **193**, 646–650 (1965).
211. Jasinski, D. R., Pevnick, J. S. & Griffith, J. D. Human pharmacology and abuse potential of the analgesic buprenorphine: a potential agent for treating narcotic addiction. *Arch. Gen. Psychiatry* **35**, 501–516 (1978).
212. Hunt, G. M. & Azrin, N. H. A community-reinforcement approach to alcoholism. *Behav. Res. Ther.* **11**, 91–104 (1973).
213. Shaham, Y., Rajabi, H. & Stewart, J. Relapse to heroin-seeking in rats under opioid maintenance: The effects of stress, heroin priming, and withdrawal. *J. Neurosci.* **16**, 1957–1963 (1996).
214. Bossert, J. M. et al. Role of mu, but not delta or kappa, opioid receptors in context-induced reinstatement of oxycodone seeking. *Eur. J. Neurosci.* **50**, 2075–2085 (2019).
215. DeWire, S. M. et al. A G protein-biased ligand at the mu-opioid receptor is potently analgesic with reduced gastrointestinal and respiratory dysfunction compared with morphine. *J. Pharmacol. Exp. Ther.* **344**, 708–717 (2013).
216. Gillis, A. et al. Low intrinsic efficacy for G protein activation can explain the improved side effect profiles of new opioid agonists. *Sci. Signal.* **13**, eaaz3140 (2020).
217. Viscusi, E. R. et al. A randomized, phase 2 study investigating TRV130, a biased ligand of the mu-opioid receptor, for the intravenous treatment of acute pain. *Pain* **157**, 264–272 (2016).
218. Grabowski, J. et al. Dextroamphetamine for cocaine-dependence treatment: a double-blind randomized clinical trial. *J. Clin. Psychopharmacol.* **21**, 522–526 (2001).
219. Siciliano, C. A. et al. Amphetamine reverses escalated cocaine intake via restoration of dopamine transporter conformation. *J. Neurosci.* **38**, 484–497 (2018).
220. Negus, S. S. & Mello, N. K. Effects of chronic d-amphetamine treatment on cocaine- and food-maintained responding under a second-order schedule in rhesus monkeys. *Drug Alcohol Depend.* **70**, 39–52 (2003).
221. Tardelli, V. S. et al. Prescription psychostimulants for the treatment of stimulant use disorder: a systematic review and meta-analysis. *Psychopharmacology* **237**, 2233–2255 (2020).
222. Justinova, Z. et al. The novel metabotropic glutamate receptor 2 positive allosteric modulator, AZD8529, decreases nicotine self-administration and relapse in squirrel monkeys. *Biol. Psychiatry* **78**, 452–462 (2015).
223. Venniro, M., Zhang, M., Shaham, Y. & Caprioli, D. Incubation of methamphetamine but not heroin craving after voluntary abstinence in male and female rats. *Neuropsychopharmacology* **42**, 1126–1135 (2017).
224. Bedi, G. et al. Incubation of cue-induced cigarette craving during abstinence in human smokers. *Biol. Psychiatry* **69**, 708–711 (2011).
225. Cruz, F. C. et al. New technologies for examining the role of neuronal ensembles in drug addiction and fear. *Nat. Rev. Neurosci.* **14**, 743–754 (2013).
226. Caprioli, D. et al. Role of dorsomedial striatum neuronal ensembles in incubation of methamphetamine craving after voluntary abstinence. *J. Neurosci.* **37**, 1014–1027 (2017).
227. Rossi, L. M. et al. Role of nucleus accumbens core but not shell in incubation of methamphetamine craving after voluntary abstinence. *Neuropsychopharmacology* **45**, 256–265 (2020).
228. Venniro, M. et al. The anterior insular cortex–>central amygdala glutamatergic pathway Is critical to relapse after contingency management. *Neuron* **96**, 414–427 e418 (2017).
229. Reiner, D. J. et al. Role of projections between piriform cortex and orbitofrontal cortex in relapse to fentanyl seeking after palatable food choice-induced voluntary abstinence. *J. Neurosci.* **40**, 2485–2497 (2020).
230. Stitzer, M. L., Jones, H. E., Tuten, M. & Wong, C. in *Handbook of Motivational Counseling: Goal-Based Approaches to Assessment and Intervention with Addiction and Other Problems* (eds Cox, W. M. & Klinger, E.) (John Wiley & Sons Ltd, 2011).
231. Silverman, K., DeFulio, A. & Sigurdsson, S. O. Maintenance of reinforcement to address the chronic nature of drug addiction. *Prev. Med.* **55**, S46–S53 (2012).
232. Mason, W. A., Hollins, J. H. & Sharpe, L. G. Differential responses of chimpanzees to social stimulation. *J. Comp. Physiol. Psychol.* **55**, 1105–1110 (1962).
233. Venniro, M. & Shaham, Y. An operant social self-administration and choice model in rats. *Nat. Protoc.* **15**, 1542–1559 (2020).
234. Venniro, M., Russell, T. I., Zhang, M. & Shaham, Y. Operant social reward decreases incubation of heroin craving in male and female rats. *Biol. Psychiatry* **86**, 848–856 (2019).
235. Grundemann, J. & Luthi, A. Ensemble coding in amygdala circuits for associative learning. *Curr. Opin. Neurobiol.* **35**, 200–206 (2015).
236. Venniro, M. et al. Abstinence-dependent dissociable central amygdala microcircuits control drug craving. *Proc. Natl Acad. Sci. USA* **117**, 8126–8134 (2020).
237. Leboyer, M. et al. Psychiatric genetics: search for phenotypes. *Trends Neurosci.* **21**, 102–105 (1998).
238. Swerdlow, N. R., Braff, D. L. & Geyer, M. A. Sensorimotor gating of the startle reflex: what we said 25 years ago, what has happened since then, and what comes next. *J. Psychopharmacol.* **30**, 1072–1081 (2016).
239. Anderzhanova, E., Kirmeier, T. & Wotjak, C. T. Animal models in psychiatric research: the RDoC system as a new framework for endophenotype-oriented translational neuroscience. *Neurobiol. Stress.* **7**, 47–56 (2017).
240. Falk, D. E. et al. Evaluation of drinking risk levels as outcomes in alcohol pharmacotherapy trials: A secondary analysis of 3 randomized clinical trials. *JAMA Psychiatry* **76**, 374–381 (2019).
241. Center for Drug Evaluation and Research. Opioid use disorder: endpoints for demonstrating effectiveness of drugs for medication-assisted treatment guidance for industry. *US Food and Drug Association* https://www.fda.gov/regulatory-information/search-fda-guidance-documents/opioid-use-disorder-endpoints-demonstrating-effectiveness-drugs-medication-assisted-treatment (2018).
242. Heilig, M., Sommer, W. H. & Spanagel, R. The need for treatment responsive translational biomarkers in alcoholism research. *Curr. Top. Behav. Neurosci.* **28**, 151–171 (2016).
243. Kakko, J. et al. A stepped care strategy using buprenorphine and methadone versus conventional methadone maintenance in heroin dependence: a randomized controlled trial. *Am. J. Psychiatry* **164**, 797–803 (2007).
244. Zhu, Y. et al. Correlates of long-term opioid abstinence after randomization to methadone versus buprenorphine/naloxone in a multi-site trial. *J. Neuroimmune Pharmacol.* **13**, 488–497 (2018).
245. Donny, E. C., Walsh, S. L., Bigelow, G. E., Eissenberg, T. & Stitzer, M. L. High-dose methadone produces superior opioid blockade and comparable withdrawal suppression to lower doses in opioid-dependent humans. *Psychopharmacology* **161**, 202–212 (2002).
246. Mattick, R. P., Breen, C., Kimber, J. & Davoli, M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database Syst. Rev.* https://doi.org/10.1002/14651858.CD002207.pub4 (2014).
247. Greenwald, M. K., Comer, S. D. & Fiellin, D. A. Buprenorphine maintenance and mu-opioid receptor availability in the treatment of opioid use disorder: implications for clinical use and policy. *Drug Alcohol Depend.* **144**, 1–11 (2014).
248. Kliewer, A. et al. Morphine-induced respiratory depression is independent of beta-arrestin2 signalling. *Br. J. Pharmacol.* **177**, 2923–2931 (2020).
249. Haight, B. R. et al. Efficacy and safety of a monthly buprenorphine depot injection for opioid use disorder: a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* **393**, 778–790 (2019).
250. Lofwall, M. R. et al. Weekly and monthly subcutaneous buprenorphine depot formulations vs daily sublingual buprenorphine With naloxone for treatment of opioid use disorder: a randomized clinical trial. *JAMA Intern. Med.* **178**, 764–773 (2018).
251. Moore, D. et al. Effectiveness and safety of nicotine replacement therapy assisted reduction to stop smoking: systematic review and meta-analysis. *BMJ* **338**, b1024 (2009).
252. Cahill, K., Stevens, S., Perera, R. & Lancaster, T. Pharmacological interventions for smoking cessation: an overview and network meta-analysis. *Cochrane Database Syst. Rev.* https://doi.org/10.1002/14651858.CD009329.pub2 (2013).
253. van den Brink, W. et al. Efficacy and safety of sodium oxybate in alcohol-dependent patients with a very high drinking risk level. *Addict. Biol.* **23**, 969–986 (2018).
254. D'Souza, D. C. et al. Efficacy and safety of a fatty acid amide hydrolase inhibitor (PF-04457845) in the treatment of cannabis withdrawal and dependence in men: a double-blind, placebo-controlled, parallel group, phase 2a single-site randomised controlled trial. *Lancet Psychiatry* **6**, 35–45 (2019).
255. Mayo, L. M. et al. Elevated anandamide, enhanced recall of fear extinction, and attenuated stress responses following inhibition of fatty acid amide hydrolase: a randomized, controlled experimental medicine trial. *Biol. Psychiatry* **87**, 538–547 (2020).
256. Dakwar, E. et al. a single ketamine infusion combined with motivational enhancement therapy for alcohol use disorder: a randomized midazolam-controlled pilot trial. *Am. J. Psychiatry* **177**, 125–133 (2020).
257. Dakwar, E. et al. A single ketamine infusion combined with mindfulness-based behavioral modification to treat cocaine dependence: a randomized clinical trial. *Am. J. Psychiatry* **176**, 923–930 (2019).
258. de Wit, H., Epstein, D. H. & Preston, K. L. Does human language limit translatability of clinical and preclinical addiction research? *Neuropsychopharmacology* **43**, 1985–1988 (2018).
259. Czajkowski, S. M. et al. From ideas to efficacy: The ORBIT model for developing behavioral treatments for chronic diseases. *Health Psychol.* **34**, 971–982 (2015).
260. Cabral, T. S. The 15th anniversary of the Portuguese drug policy: its history, its success and its future. *Drug Sci. Policy Law* https://doi.org/10.1177/2050324516683640 (2017).
261. Badiani, A. Substance-specific environmental influences on drug use and drug preference in animals and humans. *Curr. Opin. Neurobiol.* **23**, 588–596 (2013).
262. Insel, T. R. Digital phenotyping: technology for a new science of behavior. *JAMA* **318**, 1215–1216 (2017).
263. Negus, S. S. Rapid assessment of choice between cocaine and food in rhesus monkeys: effects of environmental manipulations and treatment with d-amphetamine and flupenthixol. *Neuropsychopharmacology* **28**, 919–931 (2003).
264. Collins, G. T., Gerak, L. R., Javors, M. A. & France, C. P. Lorcaserin reduces the discriminative stimulus and

reinforcing effects of cocaine in rhesus monkeys. *J. Pharmacol. Exp. Ther.* **356**, 85–95 (2016).
265. Pirtle, J. L. et al. The serotonin-2C agonist lorcaserin delays intravenous choice and modifies the subjective and cardiovascular effects of cocaine: A randomized, controlled human laboratory study. *Pharmacol. Biochem. Behav.* **180**, 52–59 (2019).
266. Harvey-Lewis, C., Li, Z., Higgins, G. A. & Fletcher, P. J. The 5-HT_{2C} receptor agonist lorcaserin reduces cocaine self-administration, reinstatement of cocaine-seeking and cocaine induced locomotor activity. *Neuropharmacology* **101**, 237–245 (2016).
267. Negus, S. S. & Banks, M. L. Learning from lorcaserin: lessons from the negative clinical trial of lorcaserin to treat cocaine use disorder. *Neuropsychopharmacology* https://doi.org/10.1038/s41386-020-00815-4 (2020).
268. Karila, L. et al. Dopamine transporter correlates and occupancy by modafinil in cocaine-dependent patients: a controlled study with high-resolution PET and [^{11}C]-PE2I. *Neuropsychopharmacology* **41**, 2294–2302 (2016).
269. Hart, C. L., Haney, M., Vosburg, S. K., Rubin, E. & Foltin, R. W. Smoked cocaine self-administration is decreased by modafinil. *Neuropsychopharmacology* **33**, 761–768 (2008).
270. Verrico, C. D. et al. Treatment with modafinil and escitalopram, alone and in combination, on cocaine-induced effects: a randomized, double blind, placebo-controlled human laboratory study. *Drug Alcohol Depend.* **141**, 72–78 (2014).
271. Zhang, H. Y. et al. The novel modafinil analog, JJC8-016, as a potential cocaine abuse pharmacotherapeutic. *Neuropsychopharmacology* **42**, 1871–1883 (2017).
272. Collins, G. T. & France, C. P. Effects of lorcaserin and buspirone, administered alone and as a mixture, on cocaine self-administration in male and female rhesus monkeys. *Exp. Clin. Psychopharmacol.* **26**, 488–496 (2018).
273. Bolin, B. L. et al. Buspirone reduces sexual risk-taking intent but not cocaine self-administration. *Exp. Clin. Psychopharmacol.* **24**, 162–173 (2016).
274. Haney, M., Gunderson, E. W., Jiang, H., Collins, E. D. & Foltin, R. W. Cocaine-specific antibodies blunt the subjective effects of smoked cocaine in humans. *Biol. Psychiatry* **67**, 59–65 (2010).
275. Kosten, T. R. et al. Vaccine for cocaine dependence: a randomized double-blind placebo-controlled efficacy trial. *Drug Alcohol Depend.* **140**, 42–47 (2014).
276. Wee, S. et al. Novel cocaine vaccine linked to a disrupted adenovirus gene transfer vector blocks cocaine psychostimulant and reinforcing effects. *Neuropsychopharmacology* **37**, 1083–1091 (2012).
277. Bergman, J., Kamien, J. B. & Spealman, R. D. Antagonism of cocaine self-administration by selective dopamine D(1) and D(2) antagonists. *Behav. Pharmacol.* **1**, 355–363 (1990).
278. Haney, M., Ward, A. S., Foltin, R. W. & Fischman, M. W. Effects of ecopipam, a selective dopamine D1 antagonist, on smoked cocaine self-administration by humans. *Psychopharmacology* **155**, 330–337 (2001).
279. Nann-Vernotica, E., Donny, E. C., Bigelow, G. E. & Walsh, S. L. Repeated administration of the D1/5 antagonist ecopipam fails to attenuate the subjective effects of cocaine. *Psychopharmacology* **155**, 338–347 (2001).
280. Maldonado, R., Robledo, P., Chover, A. J., Caine, S. B. & Koob, G. F. D1 dopamine receptors in the nucleus accumbens modulate cocaine self-administration in the rat. *Pharmacol. Biochem. Behav.* **45**, 239–242 (1993).
281. Howell, L. L., Wilcox, K. M., Lindsey, K. P. & Kimmel, H. L. Olanzapine-induced suppression of cocaine self-administration in rhesus monkeys. *Neuropsychopharmacology* **31**, 585–593 (2006).
282. Meil, W. M. & Schechter, M. D. Olanzapine attenuates the reinforcing effects of cocaine. *Eur. J. Pharmacol.* **340**, 17–26 (1997).
283. Kampman, K. M., Pettinati, H., Lynch, K. G., Sparkman, T. & O'Brien, C. P. A pilot trial of olanzapine for the treatment of cocaine dependence. *Drug Alcohol Depend.* **70**, 265–273 (2003).
284. Hamilton, J. D., Nguyen, Q. X., Gerber, R. M. & Rubio, N. B. Olanzapine in cocaine dependence: a double-blind, placebo-controlled trial. *Am. J. Addict.* **18**, 48–52 (2009).
285. Glick, S. D., Maisonneuve, I. M., Raucci, J. & Archer, S. Kappa opioid inhibition of morphine and cocaine self-administration in rats. *Brain Res.* **681**, 147–152 (1995).
286. Mello, N. K. & Negus, S. S. Effects of kappa opioid agonists on cocaine- and food-maintained responding by rhesus monkeys. *J. Pharmacol. Exp. Ther.* **286**, 812–824 (1998).
287. Walsh, S. L., Geter-Douglas, B., Strain, E. C. & Bigelow, G. E. Enadoline and butorphanol: evaluation of kappa-agonists on cocaine pharmacodynamics and cocaine self-administration in humans. *J. Pharmacol. Exp. Ther.* **299**, 147–158 (2001).
288. Fotio, Y. et al. Activation of peroxisome proliferator-activated receptor gamma reduces alcohol drinking and seeking by modulating multiple mesocorticolimbic regions in rats. *Neuropsychopharmacology* https://doi.org/10.1038/s41386-020-0754-4 (2020).
289. Schwandt, M. L. et al. PPARgamma activation by pioglitazone does not suppress cravings for alcohol, and is associated with a risk of myopathy in treatment seeking alcohol dependent patients: a randomized controlled proof of principle study. *Psychopharmacology* **237**, 2367–2380 (2020).
290. Schroeder, J. R. et al. Assessment of pioglitazone and proinflammatory cytokines during buprenorphine taper in patients with opioid use disorder. *Psychopharmacology* **235**, 2957–2966 (2018).
291. Scofield, M. D. et al. The nucleus accumbens: mechanisms of addiction across drug classes reflect the importance of glutamate homeostasis. *Pharmacol. Rev.* **68**, 816–871 (2016).
292. LaRowe, S. D. et al. A double-blind placebo-controlled trial of N-acetylcysteine in the treatment of cocaine dependence. *Am. J. Addict.* **22**, 443–452 (2013).
293. Anker, J. J. et al. Cocaine hydrolase encoded in viral vector blocks the reinstatement of cocaine seeking in rats for 6 months. *Biol. Psychiatry* **71**, 700–705 (2012).
294. Simpson, T. L. et al. Double-blind randomized clinical trial of prazosin for alcohol use disorder. *Am. J. Psychiatry* **175**, 1216–1224 (2018).
295. Fox, H. C. et al. Prazosin effects on stress- and cue-induced craving and stress response in alcohol-dependent individuals: preliminary findings. *Alcohol Clin. Exp. Res.* **36**, 351–360 (2012).
296. Kowalczyk, W. J. et al. Clonidine maintenance prolongs opioid abstinence and decouples stress from craving in daily life: A randomized controlled trial With ecological momentary assessment. *Am. J. Psychiatry* **172**, 760–767 (2015).
297. Jobes, M. L. et al. Clonidine blocks stress-induced craving in cocaine users. *Psychopharmacology* **218**, 83–88 (2011).
298. Caprioli, D., Justinova, Z., Venniro, M. & Shaham, Y. Effect of novel allosteric modulators of metabotropic glutamate receptors on drug self-administration and relapse: a review of preclinical atudies and their clinical implications. *Biol. Psychiatry* **84**, 180–192 (2018).
299. Shwe, G. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT02401022 (2017).
300. Shelton, K. L., Hendrick, E. S. & Beardsley, P. M. Efficacy of buspirone for attenuating cocaine and methamphetamine reinstatement in rats. *Drug Alcohol Depend.* **129**, 210–216 (2013).
301. Stopponi, S. et al. Activation of nuclear PPARgamma receptors by the antidiabetic agent pioglitazone suppresses alcohol drinking and relapse to alcohol seeking. *Biol. Psychiatry* **69**, 642–649 (2011).
302. Negus, S. S. & Rice, K. C. Mechanisms of withdrawal-associated increases in heroin self-administration: pharmacologic modulation of heroin vs food choice in heroin-dependent rhesus monkeys. *Neuropsychopharmacology* **34**, 899–911 (2009).
303. Jones, J. D. et al. A randomized, double-blind, placebo-controlled study of the kappa opioid receptor antagonist, CERC-501, in a human laboratory model of smoking behavior. *Addict. Biol.* **25**, e12799 (2020).
304. Czoty, P. W., Stoops, W. W. & Rush, C. R. Evaluation of the "pipeline" for dvelopment of medications for cocaine use disorder: a review of translational preclinical, human laboratory, and clinical trial research. *Pharmacol. Rev.* **68**, 533–562 (2016).
305. Nuijten, M. et al. Sustained-release dexamfetamine in the treatment of chronic cocaine-dependent patients on heroin-assisted treatment: a randomised, double-blind, placebo-controlled trial. *Lancet* **387**, 2226–2234 (2016).
306. Kohut, S. J., Fivel, P. A. & Mello, N. K. Differential effects of acute and chronic treatment with the alpha2-adrenergic agonist, lofexidine, on cocaine self-administration in rhesus monkeys. *Drug Alcohol Depend.* **133**, 593–599 (2013).
307. Wee, S., Mandyam, C. D., Lekic, D. M. & Koob, G. F. Alpha 1-noradrenergic system role in increased motivation for cocaine intake in rats with prolonged access. *Eur. Neuropsychopharmacol.* **18**, 303–311 (2008).
308. Czoty, P. W. & Nader, M. A. Effects of the alpha-2 adrenergic receptor agonist lofexidine on food-cocaine choice in socially housed cynomolgus monkeys. *J. Pharmacol. Exp. Ther.* https://doi.org/10.1124/jpet.120.266007 (2020).
309. Jin, X. et al. The mGluR2 positive allosteric modulator BINA decreases cocaine self-administration and cue-induced cocaine-seeking and counteracts cocaine-induced enhancement of brain reward function in rats. *Neuropsychopharmacology* **35**, 2021–2036 (2010).
310. Bauzo, R. M., Kimmel, H. L. & Howell, L. L. Interactions between the mGluR2/3 agonist, LY379268, and cocaine on in vivo neurochemistry and behavior in squirrel monkeys. *Pharmacol. Biochem. Behav.* **94**, 204–210 (2009).
311. Czoty, P. W., Blough, B. E., Landavazo, A. & Nader, M. A. Effects of the mGluR2/3 receptor agonist LY379268 on the reinforcing strength of cocaine in rhesus monkeys. *Psychopharmacology* **237**, 409–417 (2020).
312. Evans, S. M. et al. Efficacy of an adenovirus-based anti-cocaine vaccine to reduce cocaine self-administration and reacqusition using a choice procedure in rhesus macaques. *Pharmacol. Biochem. Behav.* **150–151**, 76–86 (2016).
313. Thomsen, M. et al. Effects of acute and chronic aripiprazole treatment on choice between cocaine self-administration and food under a concurrent schedule of reinforcement in rats. *Psychopharmacology* **201**, 43–53 (2008).
314. Haney, M., Rubin, E. & Foltin, R. W. Aripiprazole maintenance increases smoked cocaine self-administration in humans. *Psychopharmacology* **216**, 379–387 (2011).
315. Lofwall, M. R., Nuzzo, P. A., Campbell, C. & Walsh, S. L. Aripiprazole effects on self-administration and pharmacodynamics of intravenous cocaine and cigarette smoking in humans. *Exp. Clin. Psychopharmacol.* **22**, 238–247 (2014).
316. Moran, L. M. et al. Aripiprazole for cocaine abstinence: a randomized-controlled trial with ecological momentary assessment. *Behav. Pharmacol.* **28**, 63–73 (2017).
317. Wee, S., Wang, Z., Woolverton, W. L., Pulvirenti, L. & Koob, G. F. Effect of aripiprazole, a partial dopamine D2 receptor agonist, on increased rate of methamphetamine self-administration in rats with prolonged session duration. *Neuropsychopharmacology* **32**, 2238–2247 (2007).
318. John, W. S., Banala, A. K., Newman, A. H. & Nader, M. A. Effects of buspirone and the dopamine D3 receptor compound PG619 on cocaine and methamphetamine self-administration in rhesus monkeys using a food-drug choice paradigm. *Psychopharmacology* **232**, 1279–1289 (2015).
319. Negus, S. S. Effects of the kappa opioid agonist U50,488 and the kappa opioid antagonist nor-binaltorphimine on choice between cocaine and food in rhesus monkeys. *Psychopharmacology* **176**, 204–213 (2004).
320. Negus, S. S., Mello, N. K., Portoghese, P. S. & Lin, C. E. Effects of kappa opioids on cocaine self-administration by rhesus monkeys. *J. Pharmacol. Exp. Ther.* **282**, 44–55 (1997).
321. Banks, M. L. & Blough, B. E. Effects of environmental manipulations and treatment with bupropion and risperidone on choice between methamphetamine and food in rhesus monkeys. *Neuropsychopharmacology* **40**, 2198–2206 (2015).
322. Shoptaw, S. et al. Bupropion hydrochloride versus placebo, in combination with cognitive behavioral therapy, for the treatment of cocaine abuse/dependence. *J. Addict. Dis.* **27**, 13–23 (2008).
323. Stoops, W. W., Pike, E., Hays, L. R., Glaser, P. E. & Rush, C. R. Naltrexone and bupropion, alone or combined, do not alter the reinforcing effects of intranasal methamphetamine. *Pharmacol. Biochem. Behav.* **129**, 45–50 (2015).
324. Elkashef, A. M. et al. Bupropion for the treatment of methamphetamine dependence. *Neuropsychopharmacology* **33**, 1162–1170 (2008).
325. de Moura, F. B. et al. Effects of chronic treatment with bupropion on self-administration of nicotine+cocaine mixtures in nonhuman primates. *Exp. Clin. Psychopharmacol.* https://doi.org/10.1037/pha0000333 (2019).

326. Foltin, R. W. & Fischman, M. W. Effects of buprenorphine on the self-administration of cocaine by humans. *Behav. Pharmacol.* **5**, 79–89 (1994).
327. Schottenfeld, R. S., Pakes, J. R., Oliveto, A., Ziedonis, D. & Kosten, T. R. Buprenorphine vs methadone maintenance treatment for concurrent opioid dependence and cocaine abuse. *Arch. Gen. Psychiatry* **54**, 713–720 (1997).
328. Wee, S., Vendruscolo, L. F., Misra, K. K., Schlosburg, J. E. & Koob, G. F. A combination of buprenorphine and naltrexone blocks compulsive cocaine intake in rodents without producing dependence. *Sci. Transl. Med.* **4**, 146ra110 (2012).
329. Banks, M. L., Blough, B. E., Fennell, T. R., Snyder, R. W. & Negus, S. S. Effects of phendimetrazine treatment on cocaine vs food choice and extended-access cocaine consumption in rhesus monkeys. *Neuropsychopharmacology* **38**, 2698–2707 (2013).
330. Banks, M. L., Blough, B. E. & Negus, S. S. Effects of 14-day treatment with the schedule III anorectic phendimetrazine on choice between cocaine and food in rhesus monkeys. *Drug Alcohol Depend.* **131**, 204–213 (2013).
331. Stoops, W. W. et al. Influence of phendimetrazine maintenance on the reinforcing, subjective, performance, and physiological effects of intranasal cocaine. *Psychopharmacology* **236**, 2569–2577 (2019).
332. Mooney, M. E. et al. Pilot study of the effects of lisdexamfetamine on cocaine use: a randomized, double-blind, placebo-controlled trial. *Drug Alcohol Depend.* **153**, 94–103 (2015).
333. Johnson, A. R. et al. Development of a translational model to screen medications for cocaine use disorder I: choice between cocaine and food in rhesus monkeys. *Drug Alcohol Depend.* **165**, 103–110 (2016).
334. Negus, S. S. & Banks, M. L. Modulation of drug choice by extended drug access and withdrawal in rhesus monkeys: Implications for negative reinforcement as a driver of addiction and target for medications development. *Pharmacol. Biochem. Behav.* **164**, 32–39 (2018).
335. Morgan, D. et al. Social dominance in monkeys: dopamine D2 receptors and cocaine self-administration. *Nat. Neurosci.* **5**, 169–174 (2002).
336. Nader, M. A. et al. Social dominance in female monkeys: dopamine receptor function and cocaine reinforcement. *Biol. Psychiatry* **72**, 414–421 (2012).
337. Nader, M. A. et al. PET imaging of dopamine D2 receptors during chronic cocaine self-administration in monkeys. *Nat. Neurosci.* **9**, 1050–1056 (2006).

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