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CAN WE ENHANCE THE CLINICAL EFFICACY OF COGNITIVE AND PSYCHOLOGICAL APPROACHES TO TREAT SUBSTANCE USE DISORDERS THROUGH UNDERSTANDING THEIR NEUROBIOLOGICAL MECHANISMS?

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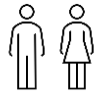
Clinical behavioral-oriented interventions	**Translationally relevant preclinical models**
Contingency management 	Contingency management-like intervention – Rodent model (Caprioli et al., 2015) 
Community-reinforcement approach 	Social-choice induced abstinence – Rodent model (Venniro et al., 2018) 
Cognitive bias modification 	Model of attentional bias - Non-human primate (Baeg et al., 2020). 

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ABSTRACT

MADDERN, X.J. et al., Enhancing the clinical efficacy of cognitive and psychological approaches to treat substance use disorders through mechanism-guided interventions. NEUROSCI BIOBEHAV REV ..(..) XXX-XXX, 2022. - Despite decades of research in the field of addiction, relapse rates for substance use disorders remain high. Consequently, there has been growing focus on providing evidence-based treatments for substance use disorders, resulting in the increased development and use of cognitive and psychological interventions. Such treatment approaches, including contingency management, community-reinforcement approach, and cognitive bias modification, have shown promising clinical efficacy in reducing substance use and promoting abstinence during treatment. However, these interventions are still somewhat limited in achieving sustained periods of abstinence post-treatment. The neurobiological mechanisms underpinning these treatment approaches remain largely unknown and under-studied, in part, due to a lack of translational animal models. The adoption of a reverse translational approach may assist in development of more representative models that can facilitate elucidation of the mechanisms behind these clinically relevant interventions. This review examines our current understanding of addiction neurobiology from clinical, preclinical research and existing animal models, and considers how the efficacy of such behavioral-oriented interventions alone, or in combination with pharmacotherapy, may be enhanced to improve treatment outcomes.

Keywords: Substance use disorder, contingency management, community-reinforcement approach, cognitive bias modification, reverse translation, combinatory treatment

1. INTRODUCTION

Substance use disorders are chronic and relapsing in nature, characterized by persistent drug use despite adverse consequences (DSM-5, 2013). A substance use disorder, and its severity, is diagnosed based on the number of DSM-5 listed symptoms (11 in total) an individual presents with (DSM-5, 2015). Addiction is a severe form of substance use disorder, and is diagnosed upon the exhibition of six or more DSM-5 symptoms (DSM-5, 2015). Substance use disorders are a major risk factor for disability and premature loss of life (Lim et al., 2016). Concerningly, deaths from substance use disorders have increased from 280,000 globally in 2007 to 352,000 in 2017 (Roth et al., 2018). Furthermore, in 2016, 31.8 million disability-adjusted life years were attributable to drug use, whilst 99.2 million were attributable to alcohol use (GBD, 2018). The COVID-19 pandemic appears to have exacerbated this issue, with evidence of up to a 36% increase in substance use problems in adults and older adolescents compared to pre-pandemic levels (Dodge et al., 2021).

Despite many people consuming alcohol and drugs globally (Peacock et al., 2018), only a subset of the population develop substance use disorders (Anthony et al., 1994, Nutt et al., 2007). A hallmark feature of addiction is the return to drug seeking following a period of abstinence, known as relapse, which can occur even following years of abstinence (O'Brien et al., 1992). Relapse rates remain quite high (McLellan et al., 2000), however, remission rates are gradually improving, increasing by almost 10% from the 1970's to 2000's, to approximately 50%, with only 30% of those remaining completely abstinent (White, 2012). Thus, further focus on how treatment can facilitate accelerated progression to remission would be beneficial.

Growing attention has been directed toward delivering evidence-based treatments for substance use disorders, leading to further advancement and application of cognitive and psychological interventions (Jhanjee, 2014). In this regard, psychosocial interventions can promote favorable behavioral changes in substance use disorder treatment, e.g. reduced substance use and increased full-time employment (Hubbard et al., 1997; Marsch and Dallery, 2012). Cognitive and psychological approaches are flexible and efficacious in clinical application, capable of being utilized in various treatment settings as either stand-alone interventions, or in combination with pharmacotherapies (Jhanjee, 2014). Interestingly, behavioral-oriented interventions based on alternative reinforcement (contingency management and community-reinforcement approach) are amongst the most effective in reducing drug use in individuals with a substance use disorder (Christie et al., 2020, Dutra et al., 2008, Lubman et al., 2007, Nall et al., 2019, Prendergast et al., 2006). However, whilst these approaches are effective in reducing substance use and promoting abstinence during treatment, their long-term benefits post-treatment appear to be somewhat inconsistent and mixed in nature (Benishek et al., 2014, Davis et al., 2016, Ginley et al., 2022, McLellan et al., 2000, Minozzi et al., 2016, Nall et al., 2019, Prendergast et al., 2006, Rains et al., 2020, Sayegh et al., 2017). Therefore, despite promising clinical efficacy, inconsistency in achieving sustained abstinence and reduced, or controlled, substance use post-treatment presents an opportunity for further refinement and improvements in outcomes.

The search for more effective treatment could be facilitated by a deeper understanding of the neurobiological actions (such as circuitry and mechanisms) underpinning these treatment approaches. However, these remain

largely unknown and under-investigated (Venniro et al., 2020, Wiers et al., 2015). This may stem from a lack of relevant animal models appropriately capturing the application of these interventions to the human condition. Consequently, the continued development and refinement of translationally relevant preclinical models to elucidate exactly how these approaches operate, including the neurobiological changes associated with positive treatment outcomes, may ultimately assist to unlock their full potential in clinical practice. In this respect, it is also important for preclinical modelling to consider differences in the addictive properties of substances, as an individual with lived experienced recently stated, '[they] would have likely continued to use [cocaine] despite no longer enjoying its effect and despite not wanting to continue to use it. This [being] the state closest to compulsion that [they] experienced, and [they] found it to be unique to short-acting stimulants.', but not opioids (Smith, 2022). Thus, animal models developed may consequently experience a degree of drug specificity in their utility and effectiveness.

By way of contrast, there is extensive research exploring pharmacological therapies in preclinical models and perhaps this reflects the ease of administration of a drug in the experimental setting, Accordingly, pharmacotherapy will not be explored in this review.

This review will explore three different behavioral-oriented interventions: contingency management, community-reinforcement approach and cognitive bias modification. Whilst cognitive-behavioral therapy and motivational interviewing are also widely used treatment approaches, they are structurally challenging to model preclinically as by necessity they involve a language component that cannot be represented in an animal model (Perry and Lawrence,

2020). Therefore, this review focuses upon commonly utilized behavioral clinical interventions with components that are amenable to preclinical modelling (Figure 1). For each treatment approach, we will discuss the clinical literature, preclinical research and existing animal models, plus what is known in terms of underlying neurobiology. We will highlight how the efficacy and utility of pharmacotherapy may be enhanced through behavioral-oriented interventions. Finally, we will highlight the importance of translationally relevant preclinical models in enabling the neurobiology underpinning these treatment approaches to be elucidated and speculate how this may lead to improved treatment outcomes.

2. Contingency management

2.1. Background & clinical research

Contingency management is a widely used behavioral therapy for treating substance use disorders and is regarded as effective in clinical application (Ainscough et al., 2017, Petry, 2011). Contingency management involves operant conditioning through the systematic delivery of alternative reinforcers that are contingent upon the performance of a target response/behavioral change (Higgins et al., 1994, Higgins & Silverman, 1999, Petry et al., 2018). The alternative reward is intended to act as a positive reinforcer that directly competes with the reinforcing effects of a drug, thus increasing the likelihood of abstinence being initiated and maintained (Bigelow et al., 1981). Contingency management is designed to be delivered as an augmentation of standard treatment services, as it complements and combines well with a range of psychosocial treatments, including the community-reinforcement approach and cognitive-behavioral therapy, as well as pharmacotherapies (Rash and DePhilippis, 2019).

Clinically, there are two main variations; voucher-based and prize-based (Regier and Redish, 2015). The voucher-based approach involves clients being awarded points for providing a drug-negative bodily sample, these points accumulate and can be exchanged for a voucher reward (Higgins et al., 1991, Higgins et al., 1993, Higgins et al., 1994, Iguchi et al., 1997, Regier and Redish, 2015). The prize-based approach consists of clients earning the chance to win a prize reward with each drug-negative sample provided, with the probability to win higher-valued prizes being lower than lower-valued prizes (Chen et al., 2013, Killeen et al., 2012, McDonell et al., 2013, Petry et al., 2000, Petry et al., 2004, Petry et al., 2005, Petry et al., 2012, Petry & Martin, 2002).

Contingency management is efficacious in the treatment of many substance use disorders, including psychostimulant, opioid, cannabis, nicotine, alcohol as well as polydrug use disorders (Benishek et al., 2014, Cahill et al., 2015, Dutra et al., 2008, Gates et al., 2016, Lussier et al., 2006, Petry et al., 2000, Prendergast et al., 2006, Schierenberg et al., 2012). For example, in cocaine-dependent individuals, contingency management significantly increased both the rates and duration of abstinence compared to standard treatment (Higgins et al., 2000, Silverman et al., 1996). Similarly, improvements have been seen in treatment retention and abstinence outcomes, including abstinence duration, in methamphetamine, amphetamine and cocaine using clients (Petry et al., 2005, Pierce et al., 2006). Contingency management also appears to be effective regardless of client background characteristics, pre-existing health conditions or presenting comorbidities, and is capable of being implemented in complex treatment settings (Bolivar et al., 2021, Hunt et al., 2019, Petry et al., 2018). However, contingency management does have several limitations. Firstly, once

contingency management treatment is discontinued, and the alternative reinforcer is removed, there are inconsistent and mixed findings in regards to the positive long-term treatment outcomes achieved (Benishek et al., 2014, Davis et al., 2016, Ginley et al., 2022, Minozzi et al., 2016, Prendergast et al., 2006, Rains et al., 2020, Roll, 2007, Sayegh et al., 2017). Accordingly, studies examining different durations of intervention delivery are warranted to establish optimal protocols. Additionally, there are considerable barriers to implementing the intervention in clinical practice, including the personnel time required to collect bodily samples, financial costs associated with the alternative reinforcer, political and social will, and the stigma associated with providing positive reinforcement to stop drug and/or alcohol use (Petry, 2010, Petry et al., 2005, Pierce et al., 2006). Consequently, despite the effectiveness of contingency management in reducing substance use and achieving abstinence during treatment, rates of post-treatment abstinence remain modest. Interestingly, a variation of traditional contingency management methodology, involving individuals having access to paid work contingent upon abstinence may achieve more enduring positive treatment outcomes (Silverman et al., 2001). Furthermore, the recent expansion and advancement of technology-based contingency management treatment does provide promise to increase access to the intervention whilst also enabling remote delivery of incentives, which may facilitate extended treatment (see Dallery et al., 2019, McPherson et al., 2018 for recent reviews). The development of more innovative contingency management approaches targeting non-abstinence outcome behaviors has also been shown to be capable of improving treatment attendance (Pfund et al., 2022), highlighting the flexibility in utility of this intervention.

2.2. Preclinical modelling

Translational preclinical models of contingency management can elucidate the neural circuitry and neurobiological mechanisms that promote abstinence during treatment, and those that ultimately contribute to subsequent relapse following treatment cessation. Indeed, the neural mechanisms underlying relapse following contingency management remain largely unknown, with no preclinical model recapitulating aspects of contingency management until the last decade (Ahmed et al., 2013, Venniro et al., 2016).

Preclinical procedures modelling choice-based suppression of drug intake are widely thought to emulate the voluntary abstinence commonly observed in clients undertaking contingency management (Caprioli et al., 2015). In these models, the drug remains readily available in the environment but is forgone in favor of non-addictive alternative rewards (Caprioli et al., 2015, Carroll et al., 1989, Carroll and Lac, 1993, Epstein and Preston, 2003, Lenoir et al., 2007, Lenoir et al., 2013b, Marlatt, 1996). Recently, Caprioli and colleagues published a nuanced rodent model of craving and relapse following a contingency management-like intervention, based on the principle of choice-based suppression of drug intake (Caprioli et al., 2015, Venniro et al., 2020). In this model, rats were trained to self-administer palatable food pellets, then subsequently trained to self-administer a drug via a different lever (Caprioli et al., 2015, Lenoir et al., 2013b). Rats were tested for drug seeking behavior and then exposed to a discrete-choice procedure where they could respond for either food or drug reward (Caprioli et al., 2015). Interestingly, male and female rats displayed a preference for palatable food over methamphetamine, heroin and fentanyl, and voluntarily abstained from drug intake, when this non-drug reward

was available (Caprioli et al., 2015, Caprioli et al., 2017, Reiner et al., 2020, Venniro et al., 2018). However, similar to observations in the human condition, "relapse" in rodents occurred following cessation of this contingency management-like procedure (Caprioli et al., 2015, Caprioli et al., 2017, Reiner et al., 2020, Venniro et al., 2017).

2.3. Preclinical investigation of the underlying neurobiology

Using this preclinical model, the neurobiological underpinnings of relapse following a contingency management-like intervention have begun to be investigated for methamphetamine and fentanyl seeking. Neuronal ensembles in the dorsomedial striatum seemingly mediate the incubation of methamphetamine craving observed after cessation of the contingency management-like intervention (Caprioli et al., 2017). There was also increased activation of dopamine D1 receptor expressing neurons in the medial and lateral subregions of the central amygdala associated with relapse to methamphetamine seeking following the contingency management-like intervention (Venniro et al., 2017). Intracranial infusion of a D1 receptor antagonist into the central amygdala decreased relapse-associated increases in central amygdala neuron activation, and relapse following intervention cessation (Venniro et al., 2017). More recently, increased activation of D1 and D2 receptor expressing medium spiny neurons in the nucleus accumbens core has been associated with incubation of methamphetamine craving following the contingency management-like intervention (Rossi et al., 2020). Further, reversible inactivation of the nucleus accumbens core, but not the nucleus accumbens shell, selectively reduced incubation and relapse to methamphetamine seeking (Rossi et al., 2020). Moreover, antagonism of D1, D2 or both receptors in the

nucleus accumbens core decreased methamphetamine craving and seeking to a similar extent (Rossi et al., 2020). However, direct D1 and D2 receptor antagonism is not a viable treatment target due to their critical role in key functions of daily life, including locomotion, memory, learning and attention (Mishra et al., 2018). Nonetheless, there is much work to be done utilizing this preclinical model to elucidate more feasible treatment targets, as further expanded upon below.

From a circuitry perspective, selective activation of the projection from the ventral anterior insular cortex to central amygdala is associated with methamphetamine craving and seeking (Venniro et al., 2017). Both reversible inactivation, and chemogenetic inhibition, of this projection decreased relapse and relapse-associated neural activation in the central amygdala following the contingency management-like intervention (Venniro et al., 2017). These studies have postulated that ventral anterior insular cortex projections to the central amygdala release glutamate preferentially to the lateral part of the central amygdala, and this plays a critical role in relapse to methamphetamine seeking in this preclinical model (Venniro et al., 2017). Subsequently, evidence to date suggests that the dorsomedial striatum, medial and lateral central amygdala, and nucleus accumbens core appear to be important neurobiological loci in this contingency management-like intervention with regards to methamphetamine.

Interestingly, potentially different neurobiological mechanisms and circuitry may be involved in fentanyl craving and relapse following cessation of this contingency management-like intervention, with the orbitofrontal cortex showing increased Fos protein expression, a marker of neuronal activation, associated with fentanyl craving and relapse (Reiner et al., 2020). However, Fos

protein is a relatively blunt tool, as it does not label cells with a net inhibitory synaptic or transcriptional drive, nor does it indicate transcriptional activation of genes in cell populations of interest but only provides evidence of trans-synaptic activation generally (Kovacs, 1998). In this instance, heightened activation of piriform cortex neurons projecting to the orbitofrontal cortex was observed and functional inactivation of the orbitofrontal cortex significantly reduced fentanyl seeking (Reiner et al., 2020). Anatomical disconnection of the piriform cortex to the contralateral orbitofrontal cortex pathway also decreased relapse, suggesting that these projections are a critical motivation-related pathway in relapse to opioid seeking following the contingency management-like intervention (Reiner et al., 2020). Importantly, these findings were shown in both male and female rats, implying a conserved mechanism across sexes. Therefore, there may be drug-dependent neurobiological mechanisms involved in this preclinical model of a contingency management-like intervention based upon what has been observed to date with methamphetamine compared to fentanyl. Further investigation into other drugs, such as alcohol and cocaine, would consequently be enlightening.

2.4. Directions for future research

Despite these mechanistic advances, to date, a viable molecular treatment target has yet to be identified and validated. This may require molecular phenotyping of cell populations implicated in relapse following a contingency management-like treatment. Such data would likely provide the foundational basis for exploration of the afferent and efferent connectivity of these cells, aiding elucidation of the functional neural circuit(s) involved. Cell-type specific investigations may also assist the discovery of more amenable therapeutic

targets. A gap in our understanding also remains as to individual differences in the susceptibility of a contingency management-like intervention in rats, and contingency management in humans, to evoke abstinence (Forster et al., 2020, Luo et al., 2014). For example, why do some rats and humans not develop a favorable preference toward the non-addictive alternative reinforcer over a drug? This may reveal the molecular mechanisms that facilitate the development of this favorable preference toward a non-addictive alternative reinforcer, even when a drug is readily available in the same environment. Alternatively, it may highlight the underlying neurobiology explaining the pro-drug choice over the alternative reinforcer observed in some rats and humans. Positron emission tomography signal in the ventral striatum has been shown to accurately predict individual treatment response to contingency management in individuals with a cocaine dependence (cross-validated correct rate = 82%, Luo et al., 2014). Thus, this may be a key node informing the clinical efficacy and utility of contingency management in each individual, at least in those with a cocaine dependence. Determining whether a minority of rats that appear resistant to the contingency management-like intervention display a higher "addiction score", prior to the discrete-choice procedure, compared to those that develop the favorable choice, would be instructive. Investigating the neurobiological differences that exist when a rat voluntarily abstains during the discrete-choice procedure to one that relapses following cessation of the contingency management-like intervention could be informative (Bouton et al., 2021). This may highlight mechanisms that promote abstinence in the presence of an alternative non-drug reward, to those that contribute to eliciting relapse when it is removed. Understanding these neurobiological mechanisms

underpinning contingency management, and other behavioral-oriented interventions, would be of value in the clinical setting as it could inform the specific neurobiological actions of these interventions and who may benefit the most from these approaches, thus enhancing delivery of personalized treatment. This may assist in determining existing pharmacotherapies that would be most efficacious and thereby further enhance treatment outcomes, while also providing a roadmap to assess novel pharmacological interventions against newly identified targets.

An equally important question is the extent to which preclinical choice models can be used to develop behavioral innovations that improve contingency management efficacy. To this end, the incentivized choice model developed by Bouton and Thraikill holds promise. This model has only been studied with non-drug rewards. It differs from the procedures described above because it obtains voluntary abstinence without requiring mutually exclusive choice. In this model, animals are first trained to respond for one reward (R1- reward). In a second phase, a new response is introduced and earns a larger reward (R2 - reward+). Critically, the original response, R1 remains available and reinforced if chosen. The difference in reward magnitude is sufficient to incentivize choice of R2 over R1, effectively suppressing R1 in both rats (Bouton et al., 2017) and humans (Thraikill and Acala, 2021). Relapse also occurs from this choice but can be reduced by presenting 'free' (i.e. unearned) rewards during the second phase (Bouton et al., 2017). Thus, this preclinical model may provide a useful behavioral assay to investigate contingency management treatment innovations to delay relapse, and enhance behavioral change, whilst also more accurately emulating clinical treatment settings.

3. Community-reinforcement approach

3.1.Background & clinical research

The community-reinforcement approach is another alternative reinforcement-oriented intervention that aims to change the lifestyle/environment of drug-dependent individuals to reduce substance use and facilitate abstinence (Roozen et al., 2003). This approach attempts to develop alternative rewarding social activities that are incompatible with substance use, this being essential in initiating and maintaining abstinence (Schottenfeld et al., 2000). The overarching goal is to assist individuals suffering from a substance use disorder to discover and adopt an alternative lifestyle that is more rewarding than their current drug-oriented lifestyle, through altering environmental contingencies in various aspects of their life (Kraan et al., 2018, Roozen et al., 2003).

These foundational principles of the community-reinforcement approach are supported by clinical research, as people with substance use disorders are less engaged in pleasant, or otherwise rewarding, activities (i.e. taking a vacation, visiting friends, participating in organized sports, intimacy) compared to people without substance use disorders (Roozen et al., 2008, Van Etten et al., 1998). Furthermore, enriching the environment of individuals with a substance use disorder with non-drug related rewarding alternatives encourages reductions in substance use (Correia et al., 2005, Vechinich and Tucker, 1996). The community-reinforcement approach is more effective than standard treatment in reducing alcohol consumption in humans (Azrin, 1976, Azrin et al., 1982, Hunt & Azrin, 1973). In a study of homeless individuals with alcohol dependence, the community-reinforcement approach significantly outperformed standard treatment on numerous drinking measures across five follow-up timepoints, ranging from two months to a year post-treatment (Smith

et al., 1998). Standard treatment in this study consisted of the day shelter's services (i.e. free meals and shower), offering of individual sessions with a Master's-level 12-step, on-site Alcoholics Anonymous meetings, temporary employment job programs and case managers for those dually diagnosed (Smith et al., 1998). Similarly, in clients with opioid dependence on methadone maintenance, the community-reinforcement approach reduced the number of opiate positive urinalyses and improved Addiction Severity Index scores, compared to standard treatment (Abbott et al., 1998). In outpatients with cocaine dependence, combination of the community-reinforcement approach and contingency management significantly improved treatment outcomes, such as treatment retention and reductions in substance use, compared to contingency management alone (Higgins et al., 2003). However, no difference was observed in treatment retention or substance use reductions between the community-reinforcement approach and group drug counselling in individuals with opioid- and cocaine-dependence (Schottenfeld et al., 2000). Despite the lack of difference in treatment outcomes between these interventions, the total number of hours engaged in non-drug related activities was significantly higher for community-reinforcement approach-treated clients that achieved abstinence compared to community-reinforcement approach-treated clients that never achieved abstinence (Schottenfeld et al., 2000). This highlights the cruciality of participation in non-drug related activities in the success and treatment outcomes achieved through the community-reinforcement approach. Interestingly, the combinatory treatment of the community-reinforcement approach and contingency management outperforms standard treatment in numerous studies (Higgins et al., 1991, Higgins et al., 1993, Higgins et al.,

1994), appearing to be effective at promoting abstinence for a range of substance use disorders (Bickel et al., 1997, Bickel et al., 2008, Budney et al., 2006, Garcia-Rodriquez et al., 2009). Furthermore, a recent meta-analysis found that treatment of cocaine and/or amphetamine dependence with the community-reinforcement approach alone, or in combination with contingency management, were more effective than standard treatment approaches (i.e. non-contingent rewards, cognitive behavioral therapy, 12-step program, meditation-based treatments, supportive-expressive psychodynamic therapy, treatment as usual, and different combinations of these) in achieving positive treatment outcomes at the longest follow-up timepoint post-intervention (De Crescenzo et al., 2018). Consequently, a large body of evidence supports the community-reinforcement approach's ability to reduce drug use and promote abstinence during treatment, and for a period of time post-treatment, however the rates of sustained abstinence remain low (McLellan et al., 2000, Nall et al., 2019).

3.2. Preclinical modelling

Clinical and preclinical research have demonstrated that adverse social interactions and social isolation promote drug self-administration, consumption and relapse, whilst positive social interactions can be protective against these maladaptive behaviors (Bardo et al., 2013, Heilig et al., 2016, Marlatt et al., 1988, Miczek et al., 2008, Nader and Banks, 2014, Venniro et al., 2018, Venniro and Golden, 2020). This is a foundational principle of the community-reinforcement approach, as it harnesses operant conditioning principles through increasing volitional contact with favorable social reinforcers, i.e. support groups and positive work environments (Stitzer et al., 2011, Venniro et al., 2018). However, due to its complex and comprehensive nature, preclinical

research has, and should continue to, focus on modelling facets that are amenable to preclinical modelling, i.e. social reinforcement, rather than the specific human modality of the community-reinforcement approach. Broadly, in preclinical research, group housing in an enriched home-cage environment decreased drug self-administration, reinstatement of drug seeking and conditioned place preference (Alexander et al., 1978, Alexander et al., 1981, Hadaway et al., 1979, Solinas et al., 2008, Venniro et al., 2018, Zlebnik and Carrol, 2015). Furthermore, the presence of a drug naïve peer in the testing chamber decreased cocaine self-administration (Smith, 2012, Strickland and Smith, 2014). Together, these findings highlight that in rodents, experimenter-controlled social interactions can decrease drug seeking and intake, by reducing the reward attributed to a drug (Venniro et al., 2018). Recently, an operant preclinical model involving a series of mutually exclusive choice tasks between drug and social interaction has been developed to emulate the community-reinforcement approach as applied in the human condition (Venniro et al., 2018).

This model aims to probe the social aspect of the community-reinforcement approach, in terms of how an alternative social reward competes with a drug to reduce drug use and promote abstinence. Similar to the contingency management-like preclinical model, rodents are trained to lever press for a social interaction reward, and then trained to self-administer a drug via a different lever (Venniro et al., 2018). Rats are then tested for drug seeking behavior (Venniro et al., 2018). Following this, rats are exposed to a series of mutually exclusive choice tasks, where they can lever press for either a social interaction or drug delivery (Venniro et al.., 2018). The availability of an

alternative social reward significantly reduced cocaine, methamphetamine and heroin self-administration in male and female rats, even in those displaying an addiction-like phenotype (Venniro et al., 2018, Venniro et al., 2021).

3.3. Preclinical investigation of the underlying neurobiology

Social-choice induced abstinence prevented the incubation of methamphetamine and cocaine craving and relapse, whilst more modestly decreasing these two measures for heroin (Venniro et al., 2018, Venniro et al., 2021). Interestingly, after two weeks of social-choice induced abstinence training rats were protected against incubation of methamphetamine craving for at least one month (Venniro et al., 2018). This protective effect was associated with the recruitment of protein kinase C-δ-expressing inhibitory neurons in the lateral part of the central amygdala, and decreased activation of the ventral anterior insular cortex during relapse (Venniro et al., 2018). Targeted knockdown of protein kinase C-δ within the central amygdala eliminated the protective effect, demonstrating the critical involvement of these cells in the social-choice mediated reduction of methamphetamine seeking (Venniro et al., 2020). Interestingly, the contingency management-like and social-choice induced abstinence paradigms elicited differential effects on the incubation of methamphetamine seeking, yet both appeared to involve the central amygdala.

Recent evidence supports the central amygdala as a hub for incubation of methamphetamine craving and relapse, with cell-type specific microcircuits implicated (Venniro et al., 2020). However, despite these abstinence-dependent microcircuits being dissociable, there appears to be a degree of inter-relatedness. Incubation of methamphetamine craving and relapse following the

contingency management-like intervention appeared to be induced through increased activation of glutamatergic projections from the ventral anterior insular cortex to the lateral central amygdala (Venniro et al., 2017). This likely heightened activity of D1 receptor-expressing neurons in the lateral central amygdala that may have in turn increased activation of D1 receptor-expressing neurons in the medial central amygdala (Venniro et al., 2017, Walker, 2021). This may resultingly disinhibit the medial central amygdala and enhance efferent projections to downstream brain regions potentially involved in the incubation of methamphetamine craving and relapse. Interestingly, incubation of methamphetamine craving and relapse also occurs following forced abstinence, apparently driven by heightened activation of somatostatin-expressing neurons in the lateral and medial central amygdala (Venniro et al., 2020). Indeed, knockdown of somatostatin-expressing neurons in the lateral central amygdala reduced activation of medial central amygdala output neurons, and prevented the incubation of methamphetamine craving and relapse, likely through dampening the downstream projections of the medial central amygdala (Venniro et al., 2020). Contrastingly, social-choice induced abstinence decreased ventral anterior insular cortex activity, which may indicate reduced sensitivity to drug-associated cues of glutamatergic ventral anterior insular cortical projections to the lateral central amygdala (Venniro et al., 2018). Dampened glutamatergic input from this projection may facilitate increased recruitment of protein kinase C-δ-expressing neurons in the lateral central amygdala, which has been hypothesized to prevent the activation of somatostatin-expressing neurons, and consequently, medial central amygdala output neurons (Grundemann and Luthi, 2015, Venniro et al., 2018). In fact,

knockdown of protein kinase C-δ in the lateral central amygdala increased activation of medial central amygdala output neurons and eliminated the protective effect of social-choice induced abstinence (Venniro et al., 2020). Therefore, these findings from different models of abstinence suggest that downstream targets of the medial central amygdala may be functionally involved in the incubation of methamphetamine craving and relapse. The medial central amygdala projects to numerous brain regions, providing for multiple candidates to be investigated. For example, there is a known projection from the medial central amygdala to the lateral hypothalamus, an area also implicated in relapse to drug seeking and appetitive motivated behavior (Campbell et al., 2020, Harris et al., 2005, Khoo et al., 2017, Krettek and Price, 1978, Marchant et al., 2009, Marchant et al., 2014, Pitkanen et al., 2000, Tsumori et al., 2006, Wise, 1996). The medial central amygdala also projects to the periaqueductal gray and bed nucleus of the stria terminalis, brain regions associated with aversive, and potentially appetitive, motivated behaviors (Ahrens et al., 2018, Assareh et al., 2016, Ch'ng et al., 2018, Kim et al., 2013, Penzo et al., 2014). The medial central amygdala also projects to the nucleus accumbens core (Borrego et al., 2022), implicated in reward processing (Wise, 2002). Thus, future research directed toward determining the contribution of downstream targets of the medial central amygdala in the incubation of methamphetamine craving and relapse would be informative in further deciphering the neural circuit driving this phenomenon. Additionally, such research may potentially uncover novel treatment candidates to pursue, at least with regards to methamphetamine.

3.4. Directions for future research

It remains unknown whether the protective effect of social-choice induced abstinence on methamphetamine seeking is conserved across other drugs and if so, whether the underlying neurobiology is similar. Additionally, it is not yet known whether there are differential patterns of neuronal activation between when an animal makes a social interaction response compared to a drug response, with this being potentially informative as to understanding why most animals voluntarily abstain when an alternative social reward is available.

4. Cognitive bias modification

4.1. Background & clinical research

Cognitive bias modification is a more recently adopted approach in the treatment of substance use disorders. Initially designed and developed to assist in the treatment of anxiety disorders (MacLeod et al., 2002), this attempts to change disorder-specific maladaptive cognitive biases through repeated training on specific cognitive tasks (Beard, 2011, MacLeod and Mathews, 2012, Wiers et al., 2013). In the treatment of substance use disorders, cognitive bias modification has been used to change biases that could supplement treatments targeting more controlled cognitive-motivational processes, such as complex goal-directed thought and behavior (Wiers et al., 2020). Two commonly seen cognitive biases in individuals suffering from a substance use disorder are; attentional bias (i.e. being drawn to substance-related cues in the environment, such as advertisements), and approach bias (i.e. greater tendency to approach rather than avoid substances and substance-related stimuli, e.g. being compelled to enter a store that sells alcohol when walking down the street) (Field et al., 2008, Lubman et al., 2000, Watson et al., 2013).

Cognitive bias modification includes a variety of computerized training paradigms aimed at reducing the attention, approach and/or evaluative biases triggered by addiction-related cues in the environment (Boffo et al., 2019). A commonly used cognitive bias modification training paradigm is the approach-avoidance task, which aims to reduce and eliminate the approach bias toward drug-related cues seen in individuals with substance use disorder (Wiers et al., 2010). This approach bias toward drug-related cues has been positively associated with drug craving (Wiers et al., 2015). The approach-avoidance task targets approach bias through having subjects implicitly learn to push away, and hence avoid, drug-associated cues using a joystick, whilst pulling toward them alternative cues, e.g. an image of a soft drink (Manning et al., 2021, Wiers et al., 2011, Wiers et al., 2015). It is believed that these types of cognitive bias modification treatment methods can more effectively target impulsive processes, that are considered less amenable to change with traditional psychosocial interventions (Christea et al., 2016).

To date, clinical trials have predominantly investigated two different forms of cognitive bias modification, those being approach bias and attentional bias modification. Approach bias modification attempts to alleviate the approach bias toward drug-related stimuli through the approach-avoidance task as described above (Manning et al., 2016, Manning et al., 2021, Wiers et al., 2011). Attentional bias modification aims to eliminate the attentional bias toward substance-related cues in the environment (Hietmann et al., 2018). A commonly utilized attentional bias modification intervention is a modified version of the dot probe paradigm (Hietmann et al., 2018, MacLeod et al., 1986, MacLeod et al., 2002). Here, two pictorial stimuli are displayed concurrently, one being

substance-related and one being substance-unrelated (Hietmann et al., 2018). Both stimuli are then removed from the screen, and the probe is typically presented behind the substance-unrelated stimuli, with participants then asked to identify the position of the probe as quickly as possible (Hietmann et al., 2018). This intends to train participants to shift their attention from the substance-related to the substance-unrelated stimuli (Hietmann et al., 2018). The first randomized-controlled trial of approach bias modification in participants with alcohol dependence found those that received cognitive bias modification treatment in addition to standard treatment (an abstinence-oriented cognitive behavioral therapy-based treatment), had fewer relapse episodes one year following treatment discharge compared to participants who received standard treatment alone, or with a sham cognitive bias modification training (Wiers et al., 2011). These findings were later replicated in a larger follow-up study, that also showed the long-term effect of cognitive bias modification to be dependent upon the change in alcohol-approach bias (Eberl et al., 2013). Those that had a stronger initial bias towards alcohol experienced greater change and improved treatment outcomes (Eberl et al., 2013). The use of approach and attentional bias modification training, either individually or in combination, reduced relapse rates one-year following treatment cessation compared to sham or no training (Rinck et al., 2018). In a separate randomized-controlled trial, 12 sessions of approach bias modification delivered during residential treatment led to reduced rates of relapse at 1-year follow-up, particularly among patients with co-morbid anxiety or depression (Salemink et al., 2021). Additionally, 4 sessions of approach bias modification was effective when added to inpatient alcohol withdrawal treatment, with significantly higher abstinence rates

achieved compared to those that undertook sham training (Manning et al., 2016), and later replicated in a larger multi-site trial (Manning et al., 2021, Manning et al., 2022).

Similarly, there are signals that attentional and approach bias may be beneficial for other substance use disorders through reducing cognitive biases and rates of relapse (Ghaffari-Touran et al., 2021, Manning et al., 2019, Sherman et al., 2018, Ziaee et al., 2016). In a single-arm open-label pilot study in residential treatment setting for methamphetamine withdrawal, 4 sessions of approach bias modification training resulted in abstinence rates of 61% at 2 weeks and 54% at 3-months post-discharge (Manning et al., 2019). The 3-month abstinence rates observed in this study were far greater than the 18% reported in detoxified methamphetamine users in a large treatment outcome study (McKetin et al., 2012). However, uptake and completion of approach bias modification training was lower than comparable trials for residential alcohol withdrawal. In terms of cannabis use disorder, following 4 sessions of approach bias modification training a reduction in cannabis cue reactivity was seen compared to sham training (Sherman et al., 2018). However, this effect was not sustained at a two-week follow-up timepoint, highlighting its transient nature (Sherman et al., 2018). Interestingly, men and women with a cannabis use disorder were found to have differential responses to approach bias modification training, as males reported fewer cannabis use sessions per day compared to women at the conclusion of training which was not observed in the sham condition (Sherman et al., 2018). There is also promising evidence supporting the utility of attentional bias modification training in the treatment of opioid use disorder (Ziaee et al., 2016). The addition of 3 sessions of attentional bias modification

training to standard treatment resulted in a reduction in attentional bias for drug-related stimuli, temptations to use, and number of lapses compared to those that only underwent treatment as usual (Ziaee et al., 2016).

In a study of people seeking treatment for methamphetamine dependence, Dean and colleagues observed that attentional bias modification did not improve several clinically relevant outcomes, including cravings and attentional biases (Dean et al., 2019). Similarly, attentional bias modification training did not reduce attentional bias craving or other drug use behaviors in people in treatment for cocaine use disorder compared to a control therapy (Mayer et al., 2016, Mayer et al., 2020), nor did it differentially affect functional activation during cue reactivity or multisensory cognitive control tasks compared to a control therapy in a fMRI study (Mayer et al., 2020). A meta-analysis found there to be no clinical benefits of cognitive bias modification interventions for either addiction outcomes or cravings (Christea et al., 2016). However, this meta-analysis included both proof-of-principle studies and randomized-controlled studies. The inclusion of proof-of-principle studies, that are typically conducted outside of clinical settings and do not evaluate the effects of a treatment on symptomatology, likely led to imprecise estimates of treatment effect sizes (Wiers et al., 2018). Indeed, when randomized-controlled studies are considered independently, the addition of cognitive bias modification to treatment resulted in long-term improvements of those same treatment outcomes (Wiers et al., 2018). Therefore, based upon the clinical literature thus far, there is an expanding evidence base supporting the clinical efficacy and validity of cognitive bias modification in the treatment of alcohol use disorder in a variety of settings (Eberl et al., 2013, Manning et al., 2016, Manning et al.,

2021, Wiers et al., 2011). However, the literature surrounding its effectiveness in treating opioid use, cannabis use and stimulant use disorders is far less consistent, reliable and robust (Verdejo-Garcia et al., 2019).

Despite several (*n*=6) clinical randomized-controlled trials providing evidence supporting the potential clinical efficacy of cognitive bias modification, at least for alcohol use disorder, it remains unclear exactly how it affects brain functioning (Wiers et al., 2015). Both alcohol-dependent and control participants displayed alcohol cue reactivity in the amygdala and nucleus accumbens, that positively correlated with craving and arousal in response to alcohol-related cues (Wiers et al., 2015). Interestingly, cognitive bias modification decreased alcohol-related cue induced amygdala activity specifically in alcohol-dependent participants (Wiers et al., 2015). Decreased activity in the right amygdala correlated with decreased alcohol craving scores in cognitive bias modification treated alcohol-dependent participants, but not in sham treated participants (Wiers et al., 2015). Cognitive bias modification also reduced activation in the medial prefrontal cortex (Wiers et al., 2015). Together, these findings suggest that cognitive bias modification reduces motivational salience of alcohol cues, and these reductions were associated with craving and approach bias scores respectively (Wiers et al., 2015, Wiers and Wiers, 2017).

These correlative findings from human fMRI studies provide neural targets for preclinical research to functionally interrogate and further elucidate the specific neurobiological actions of cognitive bias modification. However, a major difficulty lies in modelling cognitive biases using simple behavioral protocols in non-human animals (Noworyta et al., 2021). Preclinical research should therefore focus on developing models that capture specific cognitive biases

individually, such as a dedicated model of approach bias, to ensure that it is most accurately reflecting what is seen in the human condition. Recently, Baeg and colleagues published the first non-human primate model of attention bias to drug cues, finding that the orbitofrontal cortex is selectively activated in the attentional bias toward cocaine-related cues (Baeg et al., 2020).

4.2. Preclinical modelling & investigation of the underlying neurobiology

In terms of rodent models, two behavioral paradigms have been developed that attempt to emulate how drug exposure can result in the formation of an approach bias, those being a mixed-valence radial arm maze and modified mixed-valence runway procedure (Nguyen et al., 2015). The mixed-valence radial arm maze assesses approach-avoidance behavior in rodents through a conflict test, where a rodent's willingness to approach and enter a mixed-valence arm presenting both a cue previously associated with a positive consequence and one previously associated with a negative consequence, is measured (Nguyen et al., 2015). Similarly, the modified runway procedure measures the inclination of rodents to approach and enter a goal compartment that is associated with a positive reward (e.g. sucrose) and a negative consequence (footshock; Choi et al., 2022, Nguyen et al., 2015). Rodents that spend a greater proportion of time in the mixed-valence arm in the radial arm maze, and those that display no difference in latency to enter the goal compartment when a negative consequence is introduced in conjunction with the reward in the modified runway procedure, are considered to have aberrant approach-avoidance behavioral tendencies (Nguyen et al., 2015). Cocaine pre-exposure attenuated the acquisition of an aversive association and enhanced positive incentive

motivation in tests of motivational conflict (Nguyen et al., 2015). Male Long-Evans rats with a history of alcohol exposure displayed a greater approach bias toward cues predicting conflict compared to females in the radial arm maze (McNamara and Ito, 2021). Interestingly, alcohol drinking did not affect cued-conflict preference in this paradigm (McNamara and Ito, 2021). However, the preclinical literature specifically investigating approach-avoidance behavior, and its associated bias, with regards to addiction remains limited. A functional role of D1 and D2 receptor mechanisms in the nucleus accumbens in the presentation of cued-approach conflict behavior has been observed in the absence of prior drug exposure (Nguyen et al., 2018). Intracranial nucleus accumbens D1 receptor antagonism resulted in an avoidance of the conflict cue which was suggested to reflect a suppression of cue-induced reward seeking; whilst intracranial nucleus accumbens D2 receptor antagonism led to a preference toward the conflict cue (Nguyen et al., 2018). Inactivation of the ventral CA1 of the hippocampus resulted in avoidance of the conflict cue, whilst inactivation of CA3 led to a preference toward the conflict cue in the radial arm maze (Schumacher et al., 2018). Interestingly, in the modified runway procedure, a corticothalamic pathway from the prelimbic cortex to the paraventricular nucleus of the thalamus modulated decision-making behavior under motivational conflict, promoting decision safety over decision speed (Choi et al., 2022). Molecular phenotyping of this corticothalamic pathway may be informative in further elucidating the exact mechanistic action of this projection. Furthermore, investigating its functional involvement in decision-making under motivational conflict following drug exposure is also of interest

to examine whether prior drug exposure alters the modulatory role of this projection in approach-avoidance behavior.

4.3. Consideration of key elements required in a translationally relevant preclinical model of cognitive bias modification

Despite the development of animal models of approach-avoidance behavior providing some insight as to how an approach bias can arise with prior drug exposure, there does remain a lack of relevant rodent models attempting to encapsulate cognitive bias modification as observed in the human condition. Representative rodent models could be achieved utilizing a treatment-based reverse translational approach, which attempts to emulate successful treatments of substance use disorders clinically in preclinical models (Venniro et al., 2020, Walker et al., 2020). As previously alluded to, modelling complex cognitive biases in simple behavioral paradigms is difficult (Noworyta et al., 2021). Therefore, directing attention toward creating models that target specific cognitive biases individually may enhance the translatability of a preclinical model.

For example, considering a rodent preclinical model of attention bias and a cognitive bias modification-like intervention, there are a number of key factors that need to be accounted for. Firstly, extended exposure and voluntary intake of the drug of interest is preferrable to develop an addiction-like phenotype. Rodents would then need to develop an association between responding to a specific cue and the delivery of a drug reward, whilst also being presented a variety of distractor cues that elicit no consequence/alternative reward of less value, similar to the training procedure published by Baeg and colleagues

(2020). To assess the development of an attentional bias in the rodents, a test would need to be performed, likely under extinction conditions, to measure whether rodents display a preference toward the drug-associated cue over the distractor cues. If an attentional bias toward the drug-associated cue was seen, this could be used to elucidate the underlying neurobiology of this bias compared to control animals. Importantly, however, a representative translational model would incorporate a cognitive bias modification-like intervention that would attempt to alleviate and eliminate the existing attentional bias toward a drug-associated cue. To achieve this, a second phase of training may be included that either punishes the rodent for making a drug-associated cue response, rewards them with an alternative reinforcer for making a response to a specific distractor cue, or they have to make a differential response to the drug-associated cue to avoid punishment ('push away'). This phase of training would attempt to eliminate the original attentional bias through reducing/suppressing responding to the drug-associated cue. Then to assess whether the attentional bias has been attenuated, another extinction test could be performed, to measure whether the rodent reverts back to responding to the drug-associated cue in the absence of a punisher/alternative reinforcer.

4.4. Directions for future research

Equally important in understanding approach biases is consideration of the actual mechanics of choice. In most of the preclinical models described here, the emphasis is simply on what the animal chooses. These models typically do not measure or address how the animals make the choice between approaching and consuming drug and non-drug reward. This is despite a large literature base showing that choices are richer than just what we choose. For example, choice

involves trade-offs between choice speed and choice outcome, and sequential effects whereby past choice history biases subsequent choice outcome and/or yields increased choice volatility. This is an exciting opportunity to formalize the study of choice in preclinical models of drug taking. Formal mathematical models of decision-making, such as diffusion or ballistic accumulators, can decompose these choices into their latent psychological processes (e.g. Brown and Heathcote, 2008, Forstmann et al., 2016). These models can be integrated into behavioral tasks to reveal these latent psychological processes and combined with modern techniques to advance neurobiological understanding of choice (e.g. Choi et al., 2022). For example, this approach can tease out the roles played by excessive salience or value of drug outcomes (i.e. evidence accumulation rates) guiding choice versus overall levels of caution or impulsivity (evidence threshold or response caution) exercised in making these choices (see Field et al., 2020, Hogarth and Field, 2020).

Through the formulation of preclinical models emulating individual cognitive biases, this may facilitate the discovery and elucidation of the neural mechanisms and circuitry underpinning each type of cognitive bias observed in the human condition. This targeted approach may also improve the likelihood of finding new, viable candidates for specific pharmacological interventions to be investigated and developed.

5. Improving pharmacotherapy and psychological/cognitive interventions outcomes through combinatory treatment

Previously, substance use disorder treatments were developed as single-focused interventions (Covington, 2008). However, due to the complex nature of

substance use disorders, treatment needs to be delivered using a multi-dimensional approach that recognizes the subjectivity associated with the experience of substance use disorders between individuals. One way to deliver this type of multi-dimensional approach is through combinatory treatment utilizing both pharmacotherapy and targeted behavioral-oriented interventions. An integrated treatment approach of pharmacotherapy and psychosocial components may alleviate and address the limitations of each treatment modality when applied alone (Carroll, 1997, Starosta et al., 2006). For example, the efficacy of pharmacotherapy relies heavily upon treatment compliance, consequently the adjacent application of a behavioral-oriented intervention, such as contingency management, can be used to assist in improving treatment compliance (Carroll, 1997, Starosta et al., 2006).

5.1. Combinatory treatment with contingency management

The enhanced efficacy and utility of treatment combining existing pharmacotherapy and psychosocial interventions has been demonstrated in numerous trials. The dual treatment of contingency management with desipramine in buprenorphine-maintained cocaine using clients with opiate dependence, significantly increased cocaine-free urine tests over a 12-week treatment period, compared to treatment involving only one of these interventions (Kosten et al., 2003). Similarly, the combinatory treatment of contingency management with citalopram in clients with cocaine dependence had a comparable effect in reducing the number of positive urine tests, compared to singular intervention treatment (Moeller et al., 2007). Interestingly, dual treatment with levodopa and voucher-based contingency management resulted in higher proportions of cocaine-negative urine tests and longer periods

of abstinence compared to levodopa with cognitive behavioral therapy, or placebo with either contingency management or cognitive behavioral therapy, in clients with cocaine dependence (Schmitz et al., 2008, Schmitz et al., 2010). Comparably, in opiate- and cocaine-dependence, contingency management combined with levo-alpha-acetylmethadol, buprenorphine or methadone, resulted in longer periods and rates of abstinence, and increased proportions of negative urine samples (Oliveto et al., 2005, Poling et al., 2006, Schottenfeld et al., 2005). Those combinations found to be efficacious in the clinical setting could be reverse translated in preclinical models utilizing the contingency management-like intervention described above, to expand and improve our understanding as to why and how these combinations work.

5.2. Combinatory treatment with the community-reinforcement approach

With regards to the community-reinforcement approach, dual treatment with disulfiram significantly improved pharmacotherapy compliance, resulting in near-total sobriety in a study in outpatients at a rural community alcoholism treatment clinic (Azrin et al., 1982). For nicotine and heroin dependence, treatment with both the community-reinforcement approach and naltrexone increased rates of abstinence (Roozen et al., 2003, Roozen et al., 2006). However, there are also several studies that did not see enhanced efficacy with combinatory pharmacotherapy and psychosocial treatment in cocaine (Mancino et al., 2014, Mooney et al., 2009, Walsh et al., 2012, Wardle et al., 2017), cocaine and opioid (Umbricht et al., 2014), cocaine and alcohol (Schmitz et al., 2009), or methamphetamine dependence (Heinzerling et al., 2012, Shoptaw et al., 2008). It is important to note, that although there was no significant positive

effect observed in these studies, combinatory treatment did not have a negative effect on treatment outcomes. The somewhat inconsistent findings of dual treatment in studies of substance use disorders, may potentially highlight the importance of delivering personalized treatment plans/methods when treating substance use disorders. Pharmacotherapy and psychosocial interventions delivered individually, or in combination, may only be effective in certain clients but not others. Thus, tailoring treatment to individual needs and circumstances is essential in maximizing treatment efficacy.

Overall, adopting treatment programs that combine behavioral-oriented therapies with existing pharmacotherapies can broaden the utility and success of each intervention approach compared to when they are applied individually (Carrol, 1997). In addition, a better understanding of the neurobiological underpinnings of behavioral-oriented interventions may inform new treatment targets for drug discovery as well as improving behavioral interventions via iterative refinement. This could be facilitated through future preclinical research investigating the neurobiological actions and behavioral effects of numerous combinatory treatments, incorporating both translational models of behavioral-oriented treatments and clinically relevant pharmacotherapies.

6. Conclusion

Cognitive and psychological approaches to treat substance use disorders, such as contingency management, community-reinforcement approach and cognitive bias modification, provide promising non-pharmacological interventions with strong evidence that they can indeed promote favorable behavioral changes in individuals with a substance use disorder (Hubbard et al., 1997, Marsch and

Dallery, 2012). However, the functional neurobiology underpinning how these behavioral-oriented treatments act remains largely unknown (Venniro et al., 2020, Wiers et al., 2015). Importantly, translational preclinical models of key aspects of these clinically relevant treatment approaches continue to be refined to enable neurobiological investigation of these interventions. By doing so, this may ultimately unlock the full potential of cognitive and psychological treatment approaches in clinical application, and when combined with pharmacotherapy in a client-tailored manner, may lead to improved and sustained treatment outcomes.

FIGURE LEGEND

Figure 1: Schema aligning current preclinical models with relevant clinical behavioral interventions.

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