CHAPTER EIGHT

Bidirectional causality between addiction and cognitive deficits

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Abstract

Cognitive deficits are highly comorbid with substance use disorders. Deficits span multiple cognitive domains, are associated with disease severity across substance classes, and persist long after cessation of substance use. Furthermore, recovery of cognitive function during protracted abstinence is highly predictive of treatment adherence, relapse, and overall substance use disorder prognosis, suggesting that addiction may be best characterized as a disease of executive dysfunction. While the association between cognitive deficits and substance use disorders is clear, determining causalities is made difficult by the complex interplay between these variables. Cognitive dysfunction present prior to first drug use can act as a risk factor for substance use initiation, likelihood of pathology, and disease trajectory. At the same time, substance use can directly cause cognitive impairments even in individuals without preexisting deficits. Thus, parsing preexisting risk factors from substance-induced adaptations, and how they may interact, poses significant challenges. Here, focusing on psychostimulants and alcohol, we review evidence from clinical literature implicating cognitive deficits as a risk factor for addiction, a consequence of substance use, and the role the prefrontal cortex plays in these phenomena. We then review corresponding preclinical literature, highlighting the high degree of congruency between animal and human studies, and emphasize the unique opportunity that animal models provide to test causality

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between cognitive phenotypes and substance use, and to investigate the underlying neurobiology at a cellular and molecular level. Together, we provide an accessible resource for assessing the validity and utility of forward- and reverse-translation between these clinical and preclinical literatures.

1. Introduction

Substance use disorders (SUDs) represent a significant global public health crisis. In the United States alone, the societal cost of SUDs has grown to be in excess of 740 billion dollars annually (NIDA, 2020) and worldwide SUDs exceed all other mental health disorders in regard to premature mortality due to illness (Whiteford et al., 2013). Many treatments for SUDs focus on the management of withdrawal symptoms and the reduction of craving (Beck, Wright, Newman, & Liese, 1993; Haass-Koffler, Leggio, & Kenna, 2014; Myrick, Brady, & Malcolm, 2001; Perkins, Conklin, & Levine, 2008; Phillips, Epstein, & Preston, 2014; Veilleux, Colvin, Anderson, York, & Heinz, 2010), sequelae that are also heavily emphasized in the preclinical addiction literature (Becker, 2000; Lichtman & Martin, 2002; Markou et al., 1993; Markou & Koob, 1991; Venniro, Caprioli, & Shaham, 2016). Although treating withdrawal symptoms in abstinent patients is a critical step toward recovery, relapse often occurs long after these symptoms have subsided and therefore there is increasing interest in other mechanisms that outlast these processes. An ever-growing body of clinical research indicates that the dysregulation of executive function, a diverse set of cognitive processes responsible for purposeful, goal-directed behavior (Diamond, 2013), plays a fundamental role in the development and maintenance of SUDs. The prevalence of cognitive comorbidities across substance classes, their role in the initiation and maintenance of harmful patterns of substance use, and the long-lasting nature of these deficits compared to other consequences of drug use suggests that SUD may be best characterized as a disease of executive dysfunction.

Although it is indisputable that cognitive deficits are comorbid with SUDs, the relationship between the two is complex. It has long been held that prolonged exposure to substances of abuse, such as alcohol and psychostimulants, promote neuroadaptations that produce cognitive abnormalities. However, substantial evidence suggests that executive dysfunction is also a risk factor for SUDs, therefore making it difficult to determine the direction and nature of causality in between these variables in clinical populations. Given this complexity, animal models, where risk factors and exposure

can be fully measured and controlled, offer unique advantages for probing the relationship between cognitive function and substance use.

Here we review the clinical evidence for the integral role of cognitive deficits in both the development and maintenance of stimulant use disorder (StUD) and alcohol use disorders (AUD), as well as survey insights from the clinical and preclinical literatures regarding the underlying neurobiological mechanisms mediating these deficits. We begin with an overview of clinical research examining the interplay between SUDs and cognitive deficits (for more exhaustive reviews see Bates, Bowden, & Barry, 2002; Domínguez-Salas, Díaz-Batanero, Lozano-Rojas, & Verdejo-García, 2016). Guided by this research, we then examine evidence from animal studies and discuss potential neural circuit mechanisms underlying cognitive deficits in SUDs. We focus on the prefrontal cortex (PFC) given its role in mediating cognitive processes and the extensive evidence linking substance use to dysregulation of PFC function and structure (for review of subcortical structures role in addiction see Everitt & Robbins, 2013; Koob & Volkow, 2010; Yager, Garcia, Wunsch, & Ferguson, 2015), and limit our discussion to literature examining alcohol and psychostimulant use (for review of other compounds see Crean, Crane, & Mason, 2011; Gruber, Silveri, & Yurgelun-Todd, 2007; Jasinska, Zorick, Brody, & Stein, 2014; Klugman & Gruzelier, 2003). While cognitive deficits are commonly observed across SUDs (Rolland et al., 2019), we focus on psychostimulants and alcohol because they are well characterized in both the clinical and preclinical literatures, and therefore provide a suitable platform for comparing human and animal studies.

We highlight similarities in findings between preclinical and clinical investigations, which support the validity of animal models, and discuss areas that are understudied regarding the neuronal basis of these phenomena. Our goal is to provide a broad, accessible introduction to evidence from animal and human studies as to the relationships between cognitive function and SUDs, and to provide a resource on the translatability of specific animal models by comparing these literatures.

2. Cognitive deficits and SUDs: Clinical findings

SUDs are often associated with cognitive impairments spanning multiple domains including attention, memory, and executive function (Rolland et al., 2019; Stavro, Pelletier, & Potvin, 2013; Verdejo-Garcia & Rubenis, 2020). Estimates indicate that between 30 and 80% of individuals with AUD (Bruijnen et al., 2019; Fein, Bachman, Fisher, & Davenport, 1990;

Løberg & Miller, 1986; Martin, Adinoff, Weingartner, Mukherjee, & Eckardt, 1986; Meek, Clark, & Solana, 1989; Morgenstern & Bates, 1999) and 30–50% of individuals with StUD (Bruijnen et al., 2019; O'Malley, Adamse, Heaton, & Gawin, 1992; Rippeth et al., 2004; Vonmoos et al., 2013) exhibit some degree of cognitive impairment. Moreover, deficits are observed in laboratory-based decision-making tasks utilizing non-drug reinforcers demonstrating that these cognitive deficits represent a fundamental dysregulation of function that is not restricted to drug-associated contexts or decisions involving drug (Bechara et al., 2001; Brière et al., 2019; Stout, Busemeyer, Lin, Grant, & Bonson, 2004; Verdejo-Garcia et al., 2007). Interest in substance-induced cognitive impairments has been further driven by findings that deficits, particularly in cognitive processes associated with executive function, are linked to poor clinical outcomes (Bates, Pawlak, Tonigan, & Buckman, 2006; Czapla et al., 2016; Domínguez-Salas et al., 2016; Goncalves et al., 2017). For example, deficits in basic (e.g., response inhibition) and higher-order executive functions (e.g., problem solving, decision making) are associated with early relapse and poor treatment adherence in AUD and StUD populations (Rolland et al., 2019; Rubenis, Fitzpatrick, Lubman, & Verdejo-Garcia, 2019; Stevens et al., 2014).

The PFC, a neocortical structure composed of several functionally and structurally diverse subregions, is critically involved in executive function (Diamond, 2013; Robbins, 1998; Stuss, 2011). In healthy adults, greater PFC volume and thickness is associated with better executive performance across a variety of neuropsychological tests (Burzynska et al., 2012; Yuan & Raz, 2014). In addition, the PFC is disproportionately impacted by prolonged use of alcohol and psychostimulants as compared to other brain regions (Chanraud et al., 2007; Ersche, Williams, Robbins, & Bullmore, 2013; Goldstein & Volkow, 2011; Mackey & Paulus, 2013; Oscar-Berman, Kirkley, Gansler, & Couture, 2004; Pfefferbaum, Sullivan, Rosenbloom, Mathalon, & Lim, 1998; Volkow, Mullani, Gould, Adler, & Krajewski, 1988). Significant physiological and morphological differences are commonly observed in the PFC of individuals with AUD or StUD, often coinciding with impaired executive function (Chanraud et al., 2007; Dao-Castellana et al., 1998; Fein, Di Sclafani, & Meyerhoff, 2002; Goldstein & Volkow, 2002; Hanlon, Dufault, Wesley, & Porrino, 2011; Kim et al., 2006; Le Berre et al., 2014).

While it is clear that individuals with AUD and StUD display deficits in cognitive function concomitant with structural and functional dysregulation of regions involved with these processes, the extent to which deficits are

caused by substance use can be difficult to parse. In fact, extant clinical research suggests that deficits in executive function present prior to first drug use (i.e., preexisting) serve as a risk factor that facilitates substance use initiation and confers vulnerability to subsequent development of SUDs. At the same time, these preexisting deficits may be further exacerbated by substance-induced neuroadaptations (Fig. 1). Thus, to understand the complex interplay between cognitive deficits and SUDs, both directions of causality must be considered. Below we discuss the clinical evidence (1) implicating cognitive deficits as a risk factor for SUDs, and (2) as a consequence of prolonged substance use. We do not intend to be exhaustive in our review of the clinical literature; rather, we aim to provide an accessible overview for researchers outside of the immediate field, and to motivate our further discussion of questions that can be uniquely addressed by animal models (see Section 2).

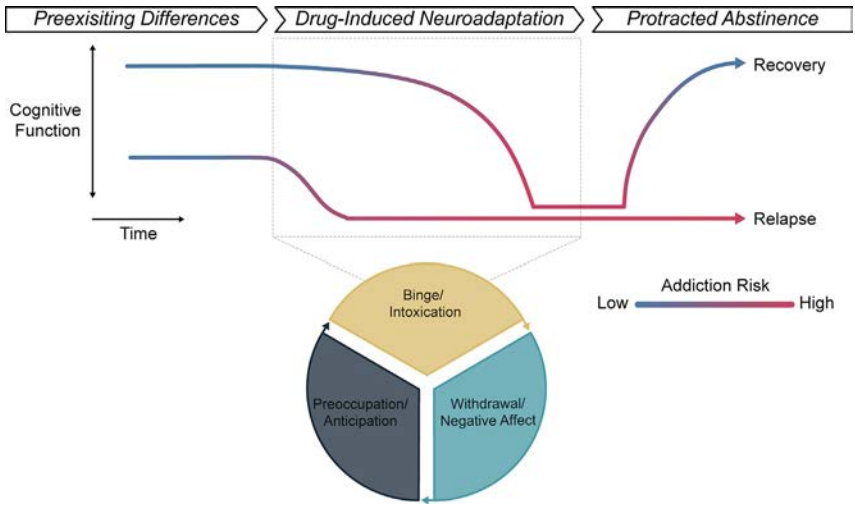

Fig. 1 Interplay between cognitive function, drug use, and addiction outcomes. Variation in cognitive function prior to initial substance use is a critical factor influencing the likelihood of initiation and maintenance of harmful patterns of substance use. Substance-induced neuroadaptations may exacerbate premorbid cognitive deficits or promote the development of cognitive deficits in cognitively normal individuals. Deficits far outlast acute phases of withdrawal and associated negative affect, serving as an enduring risk factor in addiction recovery, and recovery of cognitive function during abstinence is associated with lower rates of relapse; therfore, treatments targeting cognitive dysfunction may significantly improve clinical outcomes.

3. Clinical evidence linking executive dysfunction and addiction vulnerability

Many individuals are exposed to or actively use illicit drugs and alcohol, however only a relatively small subset of these individuals will develop a SUD in their lifetime (SAMHSA, 2019). Thus, to understand, treat, and prevent SUDs, it is imperative to identify behavioral and neurobiological features that may promote the initiation of substance use as well as those that confer resilience or susceptibility to the subsequent development of SUDs. Premorbid deficits in response inhibition (i.e., inhibitory control), one of the core executive functions alongside working memory and cognitive flexibility, have been consistently implicated in SUD vulnerability. Prospective studies have found that relatively poor performance on measures of response inhibition in individuals with minimal substance use history is predictive of the frequency and intensity of later substance use (Nigg et al., 2006; Squeglia, Jacobus, Nguyen-Louie, & Tapert, 2014). Moreover, neuroimaging studies have consistently documented PFC hypofunction in individuals with SUDs during tasks involving response inhibition (Bolla et al., 2004; Fu et al., 2008; Morein-Zamir, Simon Jones, Bullmore, Robbins, & Ersche, 2013; Salo, Ursu, Buonocore, Leamon, & Carter, 2009) and it is thought that decreased activation of the frontal lobe during these tasks may also serve as an important functional marker for susceptibility to problematic substance use. For example, during a go/no-go task in which respondents were required to respond to certain stimuli (go trials) and inhibit responding to others (no-go trials), decreased activity in multiple subregions of the PFC among adolescents was associated with transition to heavy alcohol use ~3 years later (Norman et al., 2011). Similarly, lower activation in the PFC during this task also has been shown to predict heightened substance use and SUD symptoms at an 18-month follow-up (Mahmood et al., 2013). Importantly, differences in task performance and PFC activation in these studies have typically been most pronounced during "no-go" trials, where the subject is required to inhibit a response, suggesting that vulnerability to SUDs is related to deficits in response inhibition rather than poor task performance in general.

For many individuals, substance use initiation begins during adolescence (Johnston et al., 2019), a critical transition period characterized by significant physical, social, emotional, and cognitive development as well as continued brain maturation including the refinement of connectivity in the PFC

(Spear, 2013). Differences in cognitive performance across development provide a unique opportunity to examine the impact of cognitive function on vulnerability to SUDs. For a variety of substances including alcohol and psychostimulants, age of first substance use is correlated with SUD prevalence whereby younger age of onset is associated with a greater likelihood of developing a SUD (Chen, Storr, & Anthony, 2009; Dawson, Goldstein, Chou, Ruan, & Grant, 2008; Flory, Lynam, Milich, Leukefeld, & Clayton, 2004; King & Chassin, 2007; Li, Duncan, & Hops, 2001; Lopez-Quintero et al., 2011). Although many PFC-mediated cognitive processes continue to mature throughout adolescence, the protracted development of cognitive control, juxtaposed with a fully developed and hyperactive reward system, has been proposed to be an underlying factor in adolescent SUD vulnerability (Hammond, Mayes, & Potenza, 2014). Indeed, adolescents display high attraction to rewarding activities associated with novelty and sensation seeking and are less sensitive to negative outcomes of risky choices (Somerville & Casey, 2010). Moreover, prospective studies have demonstrated that high reward-seeking in conjunction with poorer working memory performance is predictive of early substance use progression and the ultimate development of SUDs (Khurana et al., 2015; Khurana, Romer, Betancourt, & Hurt, 2017). While these studies implicate PFC-mediated cognitive processes as important factors in vulnerability to problematic drug use, they also further highlight the difficulty of precisely parsing causal relationships between these variables in human subjects.

Many of the cognitive phenotypes implicated in addiction vulnerability are heritable traits and linked to family history of SUDs (Chassin, Pitts, & Prost, 2002; Clark, Cornelius, Kirisci, & Tarter, 2005; Friedman et al., 2008; Hill, Shen, Lowers, & Locke, 2000). Family history of SUDs is associated with deficits across multiple domains of executive function including cognitive flexibility, response inhibition, and working memory (Corral, Holguín, & Cadaveira, 2003; Ersche, Jones, et al., 2012; Ersche, Turton, et al., 2012; Habeych, Folan, Luna, & Tarter, 2006; Nigg et al., 2006). For example, individuals from families with a history of alcoholism display less improvement in cognitive flexibility during development relative to those without a family history of alcoholism (Corral et al., 2003) as well as aberrant patterns of frontal lobe activation during response inhibition tasks (Schweinsburg et al., 2004; Silveri, Rogowska, McCaffrey, & Yurgelun-Todd, 2011). Along with cognitive/behavioral traits, marked morphological abnormalities have been observed in individuals with a family history of alcoholism including reductions in brain volume and cortical thickness

in frontal regions such as the orbitofrontal cortex (OFC; Henderson et al., 2018; Hill et al., 2009). A recent, landmark longitudinal study revealed that reduced gray matter brain volume in the dorsolateral PFC and insular cortex, brain regions involved in cognitive processes including decision making, reasoning, response inhibition, and working memory (Krawczyk, 2002), was predictive of the initiation of alcohol drinking during adolescence and increased alcohol use during early adulthood (Baranger et al., 2020). These associations were found to be due to shared genetic factors and that genomic risk for greater alcohol use was enriched in genes that were preferentially expressed in the dorsolateral PFC (Baranger et al., 2020). Similarly, lower gray matter volume in the medial PFC of occasional stimulant users predicted future escalation of stimulant use (Becker et al., 2015), suggesting that deficits in cortical function confer vulnerability to SUD across substance classes.

Together, there is extensive evidence demonstrating that executive dysfunction as well as structural and functional abnormalities in the PFC often serve as premorbid factors that facilitate problematic substance use. However, there is a clear need for further prospective investigations of prexisting individual differences in executive function, their role in SUD vulnerability, and how these phenotypes interact with substance-induced alterations in PFC function.

4. Clinical evidence for substance-induced impairments in executive function

Although it is accepted that prolonged substance use contributes to functional and structural brain changes and subsequent cognitive impairments observed in SUDs, many clinical studies have relied heavily on cross-sectional designs that cannot fully dissociate the impact of drug-induced adaptations from preexisting differences. A prominent and often replicated finding is that greater substance use is associated with decline in brain volume in cortical regions as well as with extent of cognitive dysfunction (Albein-Urios, Martinez-González, Lozano, Clark, & Verdejo-García, 2012; Bechara et al., 2001; Bolla, Funderburk, & Cadet, 2000; Fein, Klein, & Finn, 2004; Verdejo-Garcia et al., 2007). For example, heavy alcohol drinking in humans has been linked to widespread reductions in brain volume (Bjork, Grant, & Hommer, 2003; Paul et al., 2008; Pfefferbaum et al., 1998), decreased

gray matter volume in the frontal lobe (Cardenas, Studholme, Meyerhoff, Song, & Weiner, 2005; Kubota et al., 2001; Pfefferbaum et al., 1998), and decreased neuronal density in the OFC (Miguel-Hidalgo, Overholser, Meltzer, Stockmeier, & Rajkowska, 2006). Similarly, psychostimulant use is also associated with reductions in gray matter volume in multiple PFC subregions (Ersche et al., 2013). While there is no question that there is a robust relationship between excessive drug use, dysregulated cortical function, and cognitive deficits, as discussed in the previous section, it is important to consider that some of these effects may be driven by pre-existing differences or may be a result of complex interactions with latent traits which ultimately determine the extent of cognitive dysregulation and propensity to develop a SUD.

One notable study examined cognitive performance in both recreational and dependent cocaine users who differed markedly in their patterns and amount of cocaine use (Vonmoos et al., 2013). Dependent cocaine users exhibited deficits in cognitive performance, including performance on tasks of executive function, relative to recreational users and cocaine-naive individuals. Interestingly, cognitive performance in recreational cocaine users was intermediate to that of cocaine-dependent and cocaine-naive individuals (Vonmoos et al., 2013). In order to parse the contribution of preexisting and substance-induced effects, a handful of longitudinal studies have sought to determine whether the degree of substance use is associated with morphological changes and cognitive deficits over time. A 5-year longitudinal study that tracked cortical gray matter and ventricular changes in men with AUD found that the amount of alcohol consumed throughout this period was predictive of sulci expansion and cortical gray matter loss that were most prominent in prefrontal and frontal regions (Pfefferbaum et al., 1998). Furthermore, high levels of daily alcohol consumption in older adults has been linked to a significant decline in global cognition, executive function, and memory over a 10-year period relative to light-to-moderate drinkers and alcohol abstainers (Sabia et al., 2014). Finally, in cocaine users, increased cocaine use throughout a 1-year period was associated with a reduction in cognitive performance with the greatest impairments observed in working memory (Vonmoos et al., 2014).

Perhaps the strongest approach to isolating drug-induced volumetric and cognitive deficits in SUDs from preexisting differences comes from studies demonstrating that these deficits attenuate during protracted abstinence. In AUD, moderate impairments across multiple cognitive domains including

executive functions, though persistent during early and intermediate sobriety, become less severe after a year (Stavro et al., 2013). This is in line with findings that alcohol-dependent individuals with an average of 6 years of sobriety display normal cognitive functioning (Fein, Torres, Price, & Di Sclafani, 2006). Improvements in verbal memory, executive function, and social cognition have been observed in methamphetamine-dependent individuals after 6 months of continued abstinence (Zhong et al., 2016). In cocaine users, decreased cocaine use has been associated with minor improvements in domains such as attention, declarative memory, and executive function, with the greatest improvements observed in individuals remaining abstinent at a one-year follow-up (Vonmoos et al., 2014).

In contrast to the delayed recovery of cognitive impairments in substance users, regional brain volume increases are evident during early abstinence and continue to improve over time. For example, volume increases occur during alcohol abstinence in multiple brain regions including the dorsolateral PFC, OFC, anterior cingulate cortex, and insula as early as 1 month (Zou, Durazzo, & Meyerhoff, 2018), though improvements in cognitive function do not typically appear until later (discussed above). Importantly, while brain volume continues to increase in these brain regions during long-term abstinence from alcohol, rates of increase are at least 2.5 times higher during short-term vs. long-term abstinence indicating rapid abstinence-induced recovery of frontal and insular brain volumes among individuals with AUD (Zou et al., 2018). Furthermore, increases in gray matter in multiple cortical regions including the anterior and posterior cingulate, insula, and PFC are apparent during early cocaine abstinence and volumetric deficits are fully recovered in as little as 35 weeks after cessation of use (Connolly, Bell, Foxe, & Garavan, 2013). These findings suggest that cognitive improvements during abstinence may be contingent on the recovery of brain regions that subserve affected cognitive domains, but that behavioral recovery may lag significantly behind these morphological changes. Additionally, while evidence indicates that abstinence promotes the recovery of these domains which may, in turn, reduce the likelihood of relapse (Rolland et al., 2019; Rubenis et al., 2019; Stevens et al., 2014), questions remain as to whether comorbid cognitive impairments in SUDs are fully reversible and to what extent residual impairments are substance-induced. It is conceivable that preexisting deficits in executive function are still present throughout prolonged abstinence and therefore not only represent a risk factor for the development of SUDs but also a persistent obstacle in the path to recovery.

5. Insights from preclinical models

As summarized above, there is strong evidence supporting causality for cognitive deficits as a risk factor for SUDs and a consequence of substance use that maintains harmful behavioral patterns. Both directions of causality are accepted to be true. However, parsing the precise contributions of preexisting and substance-induced deficits to SUDs, and investigating the neurobiology underlying the two phenomena, remains a challenge. The use of human subjects poses many roadblocks in the attempt to understand the bidirectional relationship between cognitive dysfunction and SUDs due to a multitude of factors, including the cross-sectional nature of most studies, reliance on self-reports of prior substance use, and the sheer number of variables that must be controlled for. Preclinical studies in animal models, though not without their own limitations, can provide further insight into this relationship whereby a substance naive population can be studied longitudinally, while allowing complete experimenter control over the nature of substance exposure and measurements of cognitive dysregulation. Here, we review the wealth of preclinical literature that has contributed to our understanding of this complex relationship and highlight the congruency between animal and clinical studies.

6. Phenotypic predictors of SUD vulnerability in animal models

While the majority of preclinical literature has examined neuroadaptations underlying drug-induced cognitive impairments, there has also been substantial work probing the role of preexisting variation in a wide array of behavioral traits as predictors of later drug and alcohol self-administration behaviors. These investigations have implicated various aspects of cognitive function such as response inhibition and cognitive flexibility, corroborating and extending clinical findings linking preexisting cognitive deficits with vulnerability to SUDs (for an overview of the tasks used, see Fig. 2). Importantly, in preclinical studies history of substance use is assured, rather than self-reported, and propensity for substance use can be assessed independent from availability due to environmental factors.

As discussed previously, cognitive flexibility, a critical component of executive function that is broadly defined as the ability to make behavioral

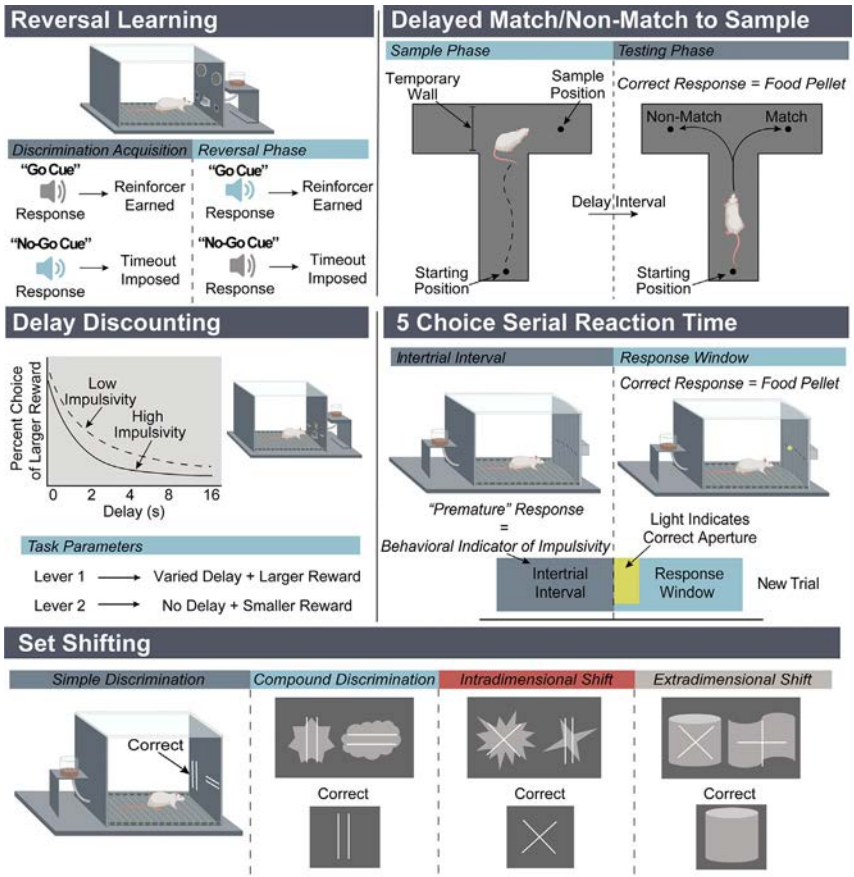

Fig. 2 Behavioral tasks commonly used to assess cognitive function in rodents. Reversal learning tests how quickly rodents can learn a contingency switch as a measure of cognitive flexibility. In the delayed match/non-match to sample task, which is used to measure working memory, animals are shown a sample stimulus and are required to remember the sample throughout a delay period. To receive a reward, they must then return to the sample stimulus (delayed match to sample task) or avoid the sample (delayed non-match to sample task). In delay discounting, animals choose between responding for a small reward delivered immediately or a larger reward delivered after a delay period. Here, impulsivity is measured by how strongly reward magnitude is discounted as a function of wait time. The five-choice serial reaction time task can also be used to assess impulsivity. In this task, animals must withhold responding until the correct response is indicated by brief illumination of a port. Animals must quickly respond after the presentation and the frequency of premature responses is used as a measure of impulsivity. Set shifting is a complex task that requires the subject to learn a set of rules presented within complex stimuli (e.g., the presence of parallel lines indicates the target stimulus) while ignoring irrelevant features (e.g., the shape of the visual stimulus). Intradimensional shifts where the initial rule is altered (e.g., perpendicular lines become the target) or extradimensional shifts where the initial rule is replaced by an entirely new rule (e.g., stimulus shape becomes the relevant feature) are introduced accross sessions and the animals' ability to update behavior is assessed as a measure of cognitive flexibility. Note that many variations of these tasks exist, and exact methodologies can differ greatly.

adaptations in response to changing environmental contingencies (Ragozzino, Detrick, & Kesner, 1999), is impaired in humans with AUD (Fein et al., 2006; Goudriaan, Oosterlaan, Beurs, & Brink, 2006) and StUD (Ersche, Roiser, Robbins, & Sahakian, 2008; Kim et al., 2006). In both humans and animals, commonly used tests of cognitive flexibility include reversal learning and set shifting (explained below). Importantly, evidence from lesion studies of rodents, humans, and non-human primates indicate that performance on these tasks is dependent on the OFC and dorsolateral PFC (medial PFC in rodents) (Bissonette et al., 2008; Dias, Robbins, & Roberts, 1996a, 1996b; McAlonan & Brown, 2003), indicating that these cognitive constructs have validity for cross-species comparisons.

In animal models, reversal learning is typically assessed in tasks wherein the animal learns that one type of response yields a reinforcer (e.g., food) while the other yields a negative consequence (e.g., a timeout period where food cannot be obtained or delivery of an electrical shock). After meeting a learning criterion, typically a high percentage of correct responses, the contingencies are then switched and the ability to quickly update behavioral strategies to match the new rules is used as a measure of cognitive flexibility (Fig. 2). Low cognitive flexibility indicated by poor performance in reversal learning tasks predicts various aspects of drug-taking behaviors in multiple model species [reviewed in (Izquierdo & Jentsch, 2012)]. For example, a higher latency to reach criterion after a contingency switch (i.e., poor performance) is associated with faster acquisition of cocaine self-administration and higher administration rates across sessions in mice (Cervantes, Laughlin, & Jentsch, 2013). Similarly, strain variation across recombinant inbred mice shows phenotypic overlap between poor performance in reversal learning and high levels of alcohol self-administration and cue-induced reinstatement of alcohol seeking (Laughlin, Grant, Williams, & Jentsch, 2011; Loos, Staal, Smit, De Vries, & Spijker, 2013). Together, these findings provide further support for the idea that an impaired ability to update responding following a contingency switch is a predictor of heightened self-administration of both cocaine and alcohol.

Similarly, performance on set-shifting tasks is also predictive of future aspects of substance use in preclinical models. In this task, animals learn by trial and error to attend to a relevant cue in the environment (e.g., shape) while ignoring irrelevant cues (e.g., color) in order to receive a food reward. During an intradimensional shift, animals must maintain the attentional set by learning to ignore a previously reward-paired stimuli (e.g., triangle) to

attend to another stimulus within the same dimension (e.g., circle). This attentional set is then challenged during the extradimensional shift wherein a previously irrelevant dimension (e.g., color) is now relevant. Importantly, this task can be easily applied across multiple species, including in humans as a variation of the Wisconsin Card Sorting Test, therefore presenting a highly translatable approach (Brown & Tait, 2016). In nonhuman primates, lower performance in set-shifting tasks is associated with higher overall preference for alcohol, reduced latency to reach maximum alcohol consumption, and higher overall intake (Shnitko, Gonzales, & Grant, 2019). While these results provide strong evidence that relationships between cognitive performance and SUD vulnerability can be faithfully recapitulated in a range of models, relatively little preclinical work has focused on neural circuit mechanisms mediating these effects prior to first drug use.

Response inhibition, the ability to suppress prepotent responses in order to select more appropriate goal-directed behaviors (Diamond, 2013), has been linked in both clinical and preclinical studies to measures of impulsivity, suggesting they may have similar underlying neural mechanisms (Dalley, Everitt, & Robbins, 2011; Franken, van Strien, Nijs, & Muris, 2008; Horn, Dolan, Elliott, Deakin, & Woodruff, 2003; Izquierdo & Jentsch, 2012). Furthermore, like reversal learning performance, behavioral measures of impulsivity also have well-studied relationships with aspects of SUD vulnerability in animal models, both for psychostimulants and alcohol [reviewed in (Belin, Belin-Rauscent, Everitt, & Dalley, 2016; Winstanley, Olausson, Taylor, & Jentsch, 2010)]. Performance in delay discounting tasks represents one commonly utilized measurement of impulsivity in both clinical and preclinical studies, which is shown to be predictive of aspects of substance use (Vanderveldt, Oliveira, & Green, 2016). In this paradigm, impulsivity is defined as the extent to which time reduces the subjective value (or reward magnitude) of a reinforcer. This is typically assessed by allowing the choice between a smaller reward that will be delivered immediately after the choice is made, or a larger reward that is delivered after a delay period. By varying the length of the delay, discounting of reward value as a function of time is assessed as a measure of impulsivity (Fig. 2) (Bizot, Le Bihan, Puech, Hamon, & Thiébot, 1999; Thiébot, Le Bihan, Soubrié, & Simon, 1985; Vanderveldt et al., 2016).

Early studies in the field found that impulsive performance in a delay discounting paradigm predicts higher alcohol consumption in rats (Poulos, Le, & Parker, 1995; Poulos, Parker, & Lê, 1998). Furthermore, when

animals are selectively bred for alcohol preference, high-alcohol-preferring mouse strains exhibit steeper delay discounting curves (i.e., small, immediate rewards are preferred over large, delayed rewards), even when tested prior to first alcohol exposure (Oberlin & Grahame, 2009; Wilhelm & Mitchell, 2008). Impulsivity can also be measured using the five-choice serial reaction time task wherein an animal is required to select the correct nose-poke port following a brief presentation of a visual cue indicating which option is correct on that trial (typically a light in the response aperture), and withhold responding during the intertrial interval to maximize the number of reinforcers earned. However, it should be noted that impulsivity in this task, as measured by premature, anticipatory responses during the intertrial interval, does not appear to be related to alcohol preference (Peña-Oliver et al., 2015). Altogether, preexisting differences in impulsivity prior to alcohol exposure are predictive of subsequent AUD-like phenotypes in preclinical models, mirroring results in humans, but this relationship may be specific to subdomains within impulsivity or to sensitive to the methodology used to assess impulsivity.

Individual differences in impulsivity also map onto aspects of rodent psychostimulant use. In this body of work, multiple subdomains of impulsivity have been considered, such as attentional impulsivity/impulsive choice and motor impulsivity/inhibitory failure [(Robinson et al., 2009); reviewed in (Dalley et al., 2011)]. In rodents, attentional impulsivity is often defined as steeper delay discounting curves, while motor impulsivity is typically defined in reaction time tasks as high levels of anticipatory/premature motor response behaviors prior to the presentation of stimuli indicating that a reinforcer is available. For cocaine, high attentional impulsivity in delay discounting predicts faster escalation of self-administration (Anker, Perry, Gliddon, & Carroll, 2009; Perry, Larson, German, Madden, & Carroll, 2005; Perry, Nelson, & Carroll, 2008). Moreover, high motor impulsivity in the five-choice serial reaction time task predicts risk to develop compulsive cocaine-taking in outbred rats (Belin, Mar, Dalley, Robbins, & Everitt, 2008; Dalley et al., 2007), mirroring the clinical findings (Nigg et al., 2006). Impulsive performance in this task also correlates strongly with several facets of pathology-like psychostimulant-taking behaviors, including extinction resistance (Broos, Diergaarde, Schoffelmeer, Pattij, & De Vries, 2012), insensitivity to punishment (Belin et al., 2008), as well as higher reinstatement of cocaine-taking after punishment-induced abstinence (Economidou, Pelloux, Robbins, Dalley, & Everitt, 2009).

In sum, individual differences in motor and attentional components of impulsivity appear to predict multiple aspects of drug-taking behavior across substance classes. Specifically, variation in attentional impulsivity has a strong relationship with the preliminary aspects of drug-taking, such as preference and escalation, while motor impulsivity predicts compulsive aspects of drug-taking, such as persistent drug use despite negative consequences. Collectively, these findings suggest that the two proposed components of impulsive behavior are indeed dissociable and should likely be examined separately. In further support of this notion, increased motor impulsivity in the five-choice serial reaction time task fails to predict alcohol preference (Peña-Oliver et al., 2015). Based on the above findings from the cocaine literature, motor impulsivity may instead be associated with likelihood of persistent alcohol seeking, though this remains to be tested. Overall, these results provide strong support for the impact of underlying impulsivity and cognitive inflexibility on vulnerability to addiction and highlight the need for further research into the neurobiological mechanisms underlying these relationships.

7. Substance-induced impairments in cognitive function in animal models

Animal models have provided valuable insight into the nature of substance-induced deficits in PFC function and associated cognitive deficits. Importantly, these studies can definitively parse preexisting traits from substance-induced deficits using longitudinal approaches where genetic and environmental backgrounds can be fully observed and controlled. Findings from this research have revealed that several facets of executive function shown to be impaired in individuals with SUD including cognitive flexibility (Chung et al., 2007; Errico, King, Lovallo, & Parsons, 2002; Ersche et al., 2008), response inhibition (Goudriaan et al., 2006; Lawrence, Luty, Bogdan, Sahakian, & Clark, 2009; Monterosso, Aron, Cordova, Xu, & London, 2005), and working memory (Albein-Urios et al., 2012; Ambrose, Bowden, & Whelan, 2001; Gonzalez, Bechara, & Martin, 2007), are similarly disrupted in rodents and non-human primates following exposure to substances of abuse.

Impaired cognitive flexibility has been observed in alcohol-exposed rodents across ages of exposure, length of exposure, and withdrawal time points. Chronic intermittent ethanol (CIE) exposure is a well-validated model of alcohol dependence where subjects are exposed to multiple cycles

of high concentrations of alcohol vapor followed by abstinence/withdrawal periods (Avegno & Gilpin, 2019; Becker & Lopez, 2004; Gilpin, Richardson, Cole, & Koob, 2008; Lopez & Becker, 2005; Vendruscolo & Roberts, 2013). In rats, CIE exposure during adolescence produces set-shifting impairments in adulthood, enhanced alcohol-seeking behavior, and volumetric reductions in brain regions including the neocortex, thalamus, and hippocampus (Gass et al., 2014). Similar studies conducted in both mice and rats have also revealed that CIE exposure causes impairments in set-shifting performance assessed during brief abstinence (Kroener et al., 2012; Trantham-Davidson et al., 2014) while studies involving voluntary alcohol drinking have revealed reversal learning deficits in rats assessed following more prolonged abstinence periods (Charlton et al., 2019). Notably, these reversal learning deficits coincided with significant cortical cell loss in the OFC, medial PFC, and motor cortex (Charlton et al., 2019).

Similar to alcohol, exposure to psychostimulants produces persistent impairments in cognitive flexibility in rodents and non-human primates. In monkeys, both short-term (2 weeks) or long-term (~5 years) exposure to experimenter-administered or self-administered cocaine, respectively, induced deficits in reversal learning (Gould, Gage, & Nader, 2012; Jentsch, Olausson, De La Garza, & Taylor, 2002). Interestingly, deficits in reversal learning following short-term exposure to cocaine were still evident after a month of abstinence (Jentsch et al., 2002). These findings are in agreement with studies in rats in which experimenter-administered or self-administered cocaine led to reversal learning deficits which persisted 1–3 months after drug cessation (Calu et al., 2007; Schoenbaum, Saddoris, Ramus, Shaham, & Setlow, 2004). Notably, the degree of reversal learning impairment induced by cocaine was indistinguishable from that induced by bilateral OFC lesions (Calu et al., 2007; Schoenbaum et al., 2004; Schoenbaum, Setlow, Nugent, Saddoris, & Gallagher, 2003), suggesting that psychostimulants result in OFC-mediated deficits in cognitive flexibility in both rodents and non-human primates. In addition, performance on tasks of cognitive flexibility thought to be primarily mediated by the medial PFC (i.e., set shifting) are similarly disrupted in psychostimulant-exposed rodents. For example, in rats, methamphetamine self-administration induced set-shifting deficits that were comparable to those observed in animals with lesions to the dorsomedial PFC (Parsegian, Glen, Lavin, & See, 2011). Although it is tempting to conclude from any set of studies that drug-induced deficits in cognitive function can be localized to a single brain region, it is much more likely that deficits in the function of many regions converge to produce rigid behavioral strategies.

In addition to deficits in cognitive flexibility, animal models have also faithfully reproduced substance-induced deficits in working memory commonly observed in individuals with AUD and StUD during protracted abstinence (Chanraud et al., 2007; Fein et al., 2006; Gonzalez et al., 2007; Goudriaan et al., 2006; Rendell, Mazur, & Henry, 2009). Working memory refers to a cognitive system that allows for the temporary storage and manipulation of limited amounts of information required to perform complex cognitive tasks including planning, reasoning, and problem-solving (Cowan, 2014). Lesion studies in rodents and non-human primates have revealed that working memory is dependent on the dorsolateral PFC (medial PFC in rodents) (Tsutsui, Oyama, Nakamura, & Iijima, 2016). In both humans and animals, delayed match to sample and delayed non-match to sample tasks are commonly used to assess working memory performance. These tasks can vary significantly in exact methodology (Fitz, Gibbs, & Johnson, 2008; George et al., 2012; George, Mandyam, Wee, & Koob, 2008; Herndon, Moss, Rosene, & Killiany, 1997; Porter et al., 2011), but typically involve presenting the subject with a stimulus (in rodents this is often one arm of a T-maze) referred to as the sample. In a delayed match to sample task, the subject must then remember the sample stimulus through a given delay period before returning to the sample stimulus to receive a reward. In a delayed non-match to sample task, to receive a reward the subject must avoid the sample stimulus (for example by choosing the opposite arm of the T-maze) (Fig. 2). A similar task, termed spontaneous alternation, is also commonly used in rodents and relies on novelty rather than a food reward to reinforce behavior (Hughes, 2004).

In mice, voluntary alcohol drinking produced persistent deficits in working memory (Dominguez et al., 2017). Notably, these deficits were only evident in animals that underwent a prolonged period of abstinence and not those with continued alcohol access at the time of testing (Dominguez et al., 2017). Impairments in working memory performance have also been observed in rats on a delayed non-match to sample task during acute abstinence after intermittent, but not continuous, access to alcohol; however, these deficits were no longer apparent when tested during more prolonged abstinence periods (George et al., 2012). These findings suggest that alcohol-induced deficits in working memory in rodents may be most pronounced during acute withdrawal, as compared to during maintenance of drinking, but dissipate over protracted abstinence.

Regarding psychostimulants, long-term cocaine self-administration in non-human primates induced deficits on a delayed match to sample task when tested during acute abstinence (Porter et al., 2011). Furthermore, escalation of

cocaine intake during extended access cocaine self-administration in rats was associated with working memory deficits on a delayed non-match to sample task, while limited access self-administration was not (George et al., 2008). Working memory deficits during protracted abstinence from cocaine correlates with a lower density of neurons and oligodendrocytes in the dorsomedial PFC and oligodendrocytes in the OFC (George et al., 2008). As mentioned earlier, deficits in executive functions including working memory gradually improve with extended abstinence in human cocaine users (Vonmoos et al., 2014). Several studies in rodents and non-human primates have also revealed improvements in cocaine-induced working memory deficits following prolonged abstinence. For example, persistent impairments in working memory on a delayed alternation task, a measure of spatial working memory, were observed following short-term cocaine self-administration in rats that dissipated after 6 weeks of abstinence (Fijał, Nowak, Leśkiewicz, Budziszewska, & Filip, 2015). Additionally, non-human primates with long-term exposure to self-administered cocaine displayed improvements in working memory on a delayed match to sample task by 30 days of abstinence (Gould et al., 2012).

Taken together, these findings indicate that both alcohol and psychostimulant exposure across multiple animal models can induce significant impairments in PFC-mediated executive functions. This is consistent with clinical studies in humans that have found that individuals with SUDs commonly display signs of executive dysfunction and confirms that prolonged substance abuse induces cognitive deficits in addition to those that may be preexisting. In several animal studies, substance-induced impairments were comparable to those observed in animals that received selective damage to regions of the PFC that subserve these functions. Furthermore, multiple animal studies reported substance-induced impairments coincident with loss of cortical volume and reductions in cellular density in the PFC (Charlton et al., 2019; Gass et al., 2014; George et al., 2008), consistent with clinical observations (Fein et al., 2002; Kim et al., 2006; Le Berre et al., 2014). This is in agreement with studies revealing that individuals with SUDs display reduced markers of neuronal integrity and viability in the frontal lobe and PFC (Chang, Ernst, Strickland, & Mehringer, 1999; Ernst, Chang, Leonido-Yee, & Speck, 2000; Xia et al., 2012) as well as reductions in brain volume and density in these regions (Hanlon et al., 2011; Matochik, London, Eldreth, Cadet, & Bolla, 2003; Nakama et al., 2011; Pfefferbaum et al., 1998; Pfefferbaum, Sullivan, Mathalon, & Lim, 1997). This suggests that substance-induced alterations to cognitive performance in animal models is associated with morphological and functional alterations to PFC

with a high degree of similarity to alterations observed in individuals with SUDs, further supporting the utility of animal models for mechanistic investigations of these phenomena.

Notably, the aforementioned animal studies utilized a variety of methods to expose animals to alcohol and psychostimulants, and there is significant debate within the field as to which methods are most relevant for human addiction. While there is extensive nuances in the models used, and even how the same model/procedure is performed between laboratories, one major distinguishing feature is whether the drug is used voluntarily (i.e., the animal chooses to consume the drug, by pressing a lever to activate a syringe pump or licking a spout) or non-voluntarily (i.e., the experimenter chooses if the animal is exposed, via injection or filling the homecage with vaporized drug). It is clear that the complexities of SUDs cannot be captured in a single animal model, and that diversity of models to address specific aspects of SUDs is a strength of the preclinical literature. That said, the differential impact of various exposure methods on behavioral and neuronal function is not trivial. Indeed, contingent vs. non-contingent drug exposure can produce distinct neuroadaptations and cognitive deficits (Schweppe et al., 2020; Wiskerke, Schoffelmeer, & De Vries, 2016). Taken together, the ability to specifically isolate and test specific aspects of SUDs is a unique strength of animal models, but the validity and caveats of these procedures should continue to be a matter of discussion and results that are consistent across models should be emphasized.

8. Circuit mechanisms of substance-induced cognitive deficits

As summarized in the sections above, the structure and function of PFC is heavily impacted by psychostimulant and alcohol exposure. Animal models provide an avenue to investigate the specific neural circuits and transmitter systems involved in these adaptations at the cellular and molecular level (Siciliano & Tye, 2019; Spanagel, 2017). The degree of similarity in the behavioral impact of chronic drug use in humans and animals, discussed above, gives confidence that these models are appropriate for investigating the neurobiology underlying these phenomena. Here we provide a brief overview of circuit-specific drug-induced adaptations that have been linked to cognitive deficits in animal models and highlight further convergence with findings in human subjects.

The mesolimbic dopamine system has been extensively implicated in the reinforcing and rewarding aspects of drugs and alcohol as well as craving and seeking (Di Chiara & Imperato, 1988; Nestler, 2005; Siciliano, Calipari, Ferris, & Jones, 2015). In contrast, mesocortical dopamine projections that originate in the midbrain and terminate in the PFC are believed to serve a crucial role in many cognitive processes and in deficits induced by chronic psychostimulant or alcohol use. The PFC, which is composed mostly of glutamatergic pyramidal neurons and GABAergic interneurons, relies on a balance of excitatory and inhibitory neurotransmission for normal physiological and cognitive function. Activity in both of these cell types is modulated via release of dopamine from presynaptic terminals arising from cell bodies in the midbrain. Once released, dopamine acts on D1 and D2-type dopamine receptors located both postsynaptically on interneurons and pyramidal neurons and presynaptically on cortical inputs from upstream regions and interlaminar lateral connectivity (Benes & Berretta, 2001; Gao, Krimer, & Goldman-Rakic, 2001; Paspalas & Goldman-Rakic, 2005; Seamans & Yang, 2004; Vander Weele, Siciliano, & Tye, 2019). Human neuroimaging studies have consistently demonstrated that individuals with SUDs exhibit abnormal patterns of PFC activity under baseline conditions, while performing cognitively demanding tasks, and during exposure to drugs and drug-associated cues that often differ between subregions (Bolla et al., 2003; Childress et al., 1999; Ersche et al., 2005; Goldstein et al., 2007; Goldstein & Volkow, 2002; Grant et al., 1996; Kilts et al., 2001; London, Ernst, Grant, Bonson, & Weinstein, 2000; Paulus et al., 2002; Salo et al., 2009; Volkow et al., 1992, 2005). For example, stimulant-dependent individuals commonly display greater activation in the OFC and reduced activation in the medial and dorsolateral PFC during decision making tasks (Bolla et al., 2003; Ersche et al., 2005). Such observations may be due, in part, to substance-induced alterations in dopamine signaling (Volkow et al., 2001, 1993, 1996) and further evidence suggests that preexisting variation in dopamine signaling may confer susceptibility or resiliency to SUDs in humans (Volkow et al., 2006).

In animal models, dysregulated dopamine release and receptor function in the medial PFC is associated with impairments in multiple cognitive domains including working memory, cognitive flexibility, and decision making (Floresco, 2013). Notably, mesolimbic and mesocortical dopamine neurons undergo contrasting plasticity after exposure to substances of abuse (Lammel, Ion, Roeper, & Malenka, 2011). Growing evidence suggests that

alterations in dopamine release in the PFC in conjunction with a reduced ability of dopamine receptors to modulate neuronal activity in this region are a major factor mediating substance-induced deficits in executive function. For example, chronic alcohol exposure is associated with reduced firing of midbrain dopamine neurons and decreased dopamine transmission in the dorsolateral PFC, medial PFC, and OFC (Narendran et al., 2014; Trantham-Davidson & Chandler, 2015) whereas repeated exposure to methamphetamine is associated with progressive cell death and reductions in dopamine terminal density in the medial PFC (Kadota & Kadota, 2004). Amphetamine and cocaine have also been demonstrated to reduce the influence of midbrain dopamine neuron activation on postsynaptic excitability in medial PFC neurons (Nogueira, Kalivas, & Lavin, 2006; Tse, Cantor, & Floresco, 2011). Together these data suggest that alcohol and psychostimulants significantly disrupt dopaminergic regulation of the PFC. Moreover, reduced expression and impaired function of dopamine receptor subtypes in the medial PFC have been linked to deficits in executive function in cocaine and alcohol-exposed rodents during abstinence (Briand et al., 2008; Trantham-Davidson et al., 2014). These substance-induced deficits are likely mediated, in part, by impaired dopamine receptor modulation of excitatory inputs to the PFC. For example, repeated amphetamine exposure has been shown to diminish the ability of D1 and D2 receptors to modulate basolateral amygdala inputs to medial PFC during abstinence in rodents that exhibited impaired decision making (Tse et al., 2011). Similar alterations may also disrupt hippocampal- PFC circuits involved in working memory (Seamans, Floresco, & Phillips, 1998).

Changes in dopaminergic activity as well as many other systems converge to ultimately produce dysregulated and aberrant activity of cortical neurons. Indeed, methamphetamine- induced alterations in neuronal firing patterns in the dorsomedial PFC have been associated with impaired set-shifting performance and enhanced drug seeking (Parsegian et al., 2011) while rescue of cocaine-induced reductions in medial PFC excitability decreased compulsive drug-taking behavior (Chen et al., 2013). Similarly, rescue of cocaine-induced reductions in OFC excitability ameliorates deficits in Pavlovian summation in rats, thought to be a measure of insight or reasoning (Lucantonio et al., 2014). Interestingly, activity and synaptic connectivity in distinct PFC subregions are uniquely affected by psychostimulants such as cocaine and amphetamine. For example, repeated exposure to amphetamine produced enhanced inhibitory and excitatory responses in the medial PFC and OFC, respectively, that were associated with progressive impairments in

instrumental responding (Homayoun & Moghaddam, 2006). Furthermore, amphetamine and or cocaine exposure increase the number of dendritic branches and the density of dendritic spines on pyramidal neurons in the medial PFC and medium spiny neurons in the nucleus accumbens, effects that are still evident after a month of abstinence (Crombag, Gorny, Li, Kolb, & Robinson, 2005; Robinson, Gorny, Mitton, & Kolb, 2001; Robinson & Kolb, 1997, 1999). This is in contrast to the OFC where amphetamine reduces spine density (Crombag et al., 2005). Mirroring findings in clinical studies examining risk factors for SUDs (Baranger et al., 2020), the activity in medial PFC during initiation of alcohol use is a marker of compulsive drinking vulnerability in mice (Siciliano et al., 2019).

One plausible take away from these findings is that substance-induced alterations to PFC structure and function commonly found in SUDs are, in part, a consequence of impaired dopamine neuromodulation of PFC neuronal networks and region-specific changes in synaptic connectivity. The combined influence of these changes could drastically impact excitatory drive in the PFC leading to behavioral inflexibility and impaired decision making that may ultimately undermine rehabilitation efforts and increase risk of relapse. While preclinical studies have consistently demonstrated that executive functions are compromised in a variety of animal models following both short- and long-term exposure to alcohol and psychostimulants, a more robust understanding of the neural circuitry involved and how substance-induced neuroadaptive changes evolve over time is needed.

9. Concluding remarks

While animal studies have greatly expanded our knowledge of the circuit mechanisms mediating drug and alcohol-induced cognitive deficits, this realm is dramatically understudied in the preclinical literature in comparison with drug-taking and seeking processes. Both clinical and preclinical studies are needed to develop a comprehensive understanding of how addiction impacts the brain to elucidate what areas of cognition are both predictive of subsequent use and most affected by continued use. Extensive clinical research so far has cogently demonstrated that PFC-mediated executive dysfunction and impulsivity are most heavily impacted by continued substance use, and cross-sectional work further indicates dysfunction in these faculties may confer individual vulnerability to SUD development, particularly during adolescence when substance use is most often initiated. Meanwhile, preclinical studies can effectively recapitulate these phenotypes in animal

models, allowing us to address questions of causality, illuminate underlying mechanisms, as well as characterize the longitudinal nature of these deficits.

However, there is still much we do not understand. While years of research have illuminated how drugs of abuse hijack natural reinforcement circuitry and drive maladaptive behaviors, there is still a lack of understanding why only a subset of individuals that experiment with these drugs will go on to develop an addicted phenotype. There is a strong need for more longitudinal work from the clinical research side, which contends with issues of subject recruitment and continued retention, to understand the complex and bidirectional factors that lead an individual to develop these problematic patterns of use and identify how substances can confer vulnerability to relapse through exacerbated executive dysfunction. Understanding the longitudinal nature of these cognitive deficits, both prior to and after exposure, can then inform experimental design in the preclinical realm, and lead to greater understanding and enhanced treatment development. Additionally, in the preclinical field, much work is needed to delineate the distinct nature of the relationships among the various classes of drugs and across the lifespan. Due to technical limitations, including issues with ecological validity in behavioral task design and lack of complete understanding for the mechanisms of these functions, While there is much more work that needs to be done, communication between preclinical and clinical researchers will be critical in the search for potential treatments for this set of disorders.

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