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The neurobiology of impulsivity and substance use disorders: implications for treatment

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Abstract

Impulsivity is strongly associated with substance use disorders (SUDs). Our review discusses impulsivity as an underlying vulnerability marker for SUDs, and treatment of co-occurring impulsivity in SUDs. Three factors should be considered for the complex relationship between impulsivity and a substance use disorder (SUD): (1) the trait effect of impulsivity, centering on decreased cognitive and response inhibition; (2) the state effect resulting from either acute or chronic substance use on brain structure and function; and (3) the genetic and environmental factors (e.g., age and sex) may influence impulsive behavior associated with SUDs. Both subjective and objective measures are used to assess impulsivity. Together, treatment developments (pharmacological, behavioral, and neurophysiological) should consider these clinically relevant dimensions assessed by a variety of measures, which have implications for treatment matching in individuals with SUD. Despite its heterogeneity, impulsivity is a marker associated with SUDs and may be understood as an imbalance of bottom-up and top-down neural systems. Further investigation of these relationships may lead to more effective SUD treatments.

Graphical abstract:

Despite its heterogeneity, impulsivity is a marker associated with substance used disorders (SUDs) and may be understood as an imbalance of bottom-up and top-down neural systems. Our review discusses the multifaceted construct of impulsivity as an underlying vulnerability marker within

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Competing interests

The authors declare no competing interests

the various stages of SUDs. We emphasize a transdiagnostic model for understanding impulsivity and addiction risk.

Keywords

impulsivity; substance use disorders; treatment; tobacco; cannabis; alcohol

Introduction

Substance misuse occurs in over a quarter of a billion people worldwide, with 0.6% suffering from substance use disorders (SUDs)[1]. A significant challenge to understanding the etiology of this disorder relates to the complex interplay between environmental and genetic risk factors[2]. The behavioral and neurobiological relationships between impulsivity and addictive behaviors have been well established [3]. Impulsivity is often equated as bottom-up control mechanisms being suppressed by automatic or reward-driven responses with diminished cognitive control to demands that may not be appropriate (disinhibition) [4,5]. Moreover, impulsivity may be divided into four constructs: lack of meditation, lack of perseverance, sensation seeking, and urgency [6,7]. Notably, sensation seeking has recently been recognized as a separate construct of impulsivity [8]. Moreover, urgency has been recognized as having two traits, positive and negative [9]. Positive urgency refers to the disposition to act rashly to extreme positive effect. Negative urgency refers to the disposition to act rashly to extreme negative effect [10]. However, this review will use the Brewer and Potenza framework, thereby using the four constructs aforementioned and referring to urgency in general rather than specifically to positive or negative urgency.

Furthermore, brain injury and several mental illnesses may predispose individuals to disruptions in these inhibitory control (IC) mechanisms, resulting in impulsive behaviors [11,12]. For instance, early stages of recreational drug use may be mediated by impulsive behavior [11]. Regardless of an individuals' awareness of the harms directly related to their drug habit (e.g., effects on health, finances, and interpersonal relationships), continued drug use and repeated failure of reduced intake or quit attempts, may also be mediated by deficient IC over the immediate reinforcing effects from drug use [11].

Many models have been used to link impulsive behavior to the prevalence of SUD, encompassing neurobiological mechanisms of causation versus risk. One explanation posits drug administration resulting in neurobiological and structural changes affecting behavioral self-control [13]. The alternative explanation suggests deficits in impulsive control may have already been present prior to drug initiation, representing a vulnerability marker for SUDs [14]. Neurobiological (e.g., dopaminergic (DAergic)) [15] and glutamatergic [16] neurocircuitry involved in reward-related learning), genetic, preclinical, and clinical studies have all extensively been conducted to try to disentangle the complicated relationship of initiation, continuation, addiction, and relapse to substances in relation to impulsive behavior [14]. Ultimately, these different addiction phases have many clinical implications for treatment approaches (e.g., pharmacological, neurophysiological, and behavioral) [17,18].

Our review discusses the multifaceted construct of impulsivity as an underlying vulnerability marker within the various stages of SUD. We emphasize a transdiagnostic model for understanding impulsivity and addiction risk. This review is novel compared with previous reviews [11,19,20] since: (1) we review the literature on the development and efficacy of treatment options for the co-occurrence of impulsivity in SUD including pharmacological, neurophysiological, and behavioral approaches, and (2) we provide a theoretical framework of what dimension of impulsivity was measured in the various treatment trials for the co-occurrence of impulsivity and SUDs, thereby providing novel insights into which treatment options are most promising to pursue, while considering the interrelationship of trait, state and other effects, such as environmental and genetic factors (e.g., a transdiagnostic model).

Definitions of impulsivity and outcome measures

Impulsivity is a multidimensional construct, incorporating state and trait classifications, and a variety of associated behaviors [21–24]. Despite agreement regarding the multifaceted perception of impulsivity, there is no consensus on classification [22,25,26]. Further complicating its classification is the predisposition of impulsivity towards maladaptive, risky behavior relative to normal behavioral responses [21,22,26]. Accordingly, measurements of impulsivity reflect the variability in definitions of the term and comprise various forms that range from self-report assessments to behavioral measures and electrophysiological analyses (Table 1) [21,25]. Self-report relies upon an individual's accurate recall of one's own behavior, while behavioral measures are more objective [27]. There is often little overlap between self-report and behavioral measures of impulsivity [28,29].

One common definition of impulsivity is the lack of behavioral inhibition leading to the tendency to act on impulse [21,25,26,30–32]. The Diagnostic and Statistical Manual of Mental Disorders, Fifth edition (DSM-5) describes impulsivity as a lack of behavioral inhibition [33]. Additionally, impulsivity has been considered a "failure of the inhibitory process" [32], as it involves implications in the frontostriatal circuitry leading to the dysfunction of top-down cognitive control [31]. Motor (behavioral) impulsivity relates to the failure of motor inhibition (impulsive action) associated with dorsolateral prefrontal lobe activity [34] that is equivalent to response inhibition and often studied in preclinical models [35]. Behavioral tasks involve terminating prepotent motor responses, using measures such as the stop signal reaction time (SST) task [36], the go/no-go task [37] as well as the continuous performance task (CPT).

Another common theme relates to decision-making lacking sensitivity to negative consequences and processing of long-term outcomes [21,25,26,30–32]. The DSM-5 also describes impulsivity as dysfunctional decision making while incorporating a dimension of urgency and harmful behavior during emotionally charged situations [33]. Some common self-report assessments include the Barratt impulsiveness scale (BIS-11) [23,38], Eysenck impulsiveness questionnaire (I_7) [39], multidimensional personality questionnaire (MPQ) [40], and the UPPS impulsive behavior scale of impulsivity (IBS) [41]. In terms of behavioral tasks, impulsive decision making is commonly measured by the delayed discounting of reward tasks, which comprises the favoring of smaller rewards in the near future compared with larger rewards in the extended future [21,42,43]. Forms of this task involve the full permuted decision-making tasks [44,45] and the shorter Kirby monetary choice questionnaire [46].

Impulsivity is associated with attentional dysfunction [21,25,26,30–32], and the inability to follow instructions [33]. Recent findings suggest that these three domains—personality traits, discounting preferences, and response inhibition tasks—represent three conceptually related, but quantitatively distinct domains of impulsivity [47].

Neurobiology

The overlap between brain circuits and neurotransmitter systems involved in impulsivity and addiction risk [48] have provided a targeted engagement approach through which addiction risk may be remediated [49]. This includes three neurobiological systems: (1) the regulatory system mediated by the medial and ventral prefrontal cortices; (2) the reward system via ventral striatum and midbrain DAergic system; and (3) the threat system via the amygdala [50] (Fig. 1). Regarding the four constructs of impulsivity, urgency (e.g., relating to the tendency of responding to negative emotions irrationally resulting in problematic outcomes[7]) has been associated with excessive recruitment of lateral prefrontal cortex (PFC) activity resulting in self-regulatory failure (e.g., substance misuse) [51]. Lack of premeditation has been associated with decreased gray-matter volumes in the insula and putamen and postulated to relate to the efficacy of decision-making processes [52–54]. Lack of perseverance or lack of conscientiousness is linked to impaired anterior cingulate cortex (ACC) function, and the left ventrolateral and left anterior prefrontal cortices, relating to risky behaviors [55]. Finally, sensation-seeking has been associated with activation of regions related to motivation, arousal, and reinforcement such as the posterior medial orbitofrontal cortex (OFC) and insula [56]. Ultimately, inefficient control, strong reward and weak harm-avoidance signals have been proposed to contribute to substance use. This leads to an imbalance between the PFC top-down cognitive control systems and subcortical bottom-up incentive–reward system leading to risky behaviors such as drug experimentation [57,58].

Recent models of addiction and impulsivity have focused on glutamatergic and gamma-aminobutyric acid-ergic (GABAergic) mechanisms in key structures (ACC), given their role in impulsivity, craving and drug seeking. Human studies have shown that elevated glutamate levels relating to an imbalance between synaptic and nonsynaptic levels are associated with dysregulation between the PFC and nucleus accumbens (NAcc) found in substance dependence [59,60]. Glutamate levels in the dorsal ACC have also been associated with delay discounting (DD) in SUDs [61]. Such findings support the potential of antiglutamatergic agents for the treatment of SUDs. In addition, reduced levels of inhibitory neurotransmitter GABA in the dorsolateral prefrontal cortex (DLPFC) [62] are associated with impulsivity [63]. Increasing evidence supports the modulation of GABAergic systems for the treatment of SUDs and impulsive behaviors. For instance, GABA reuptake inhibitor tiagabine has shown to reduce cocaine use and control impulsive aggression [64]. As such, these findings suggest possible functions of glutamatergic and GABAergic systems underlying comorbid impulsivity and addictive behaviors.

Another relevant neurotransmitter is dopamine (DA). The D2-like (D_2) DA receptor is crucial for drug reinforcement [65]. A core predisposition to addictive and impulsive behaviors is centered on a set of genes that promote feelings of well-being via DA release [65] from NAcc neurons through neurotransmitter interactions in the mesolimbic system. Furthermore,

the reward cascade involves the release of serotonin resulting in hypothalamus stimulation of encephalin and inhibition of GABA at the substantia nigra, thus fine-tuning NAcc DA release. This has given rise to the hypothesis that genetic variation relating to DA may link impulsivity with addiction risk [66]. A single nucleotide polymorphism (rs1800497) has been linked to addiction [67], impulsivity [68], and D_2 receptor density [69]; this variant is not in *DRD2* gene itself, but is part of an evolutionarily conserved gene cluster on chromosome 11 that includes *DRD2* and putatively functionally co-regulate DA neurotransmission [70]. Support for the relevance of this gene cluster was present in a recent study of impulsivity in relation to this region, revealing two significantly associated haplotypes, with the association of one being driven by rs1800497 and the other being driven by a newly identified SNP (rs1079597) [71]. Thus, dysfunction in the brain reward cascade caused by certain genetic variants may cause a hypo-DAergic drive that is behaviorally reflected in greater impulsivity and accordingly leads to greater drug-seeking behavior. Alcohol, cocaine, cannabis, and nicotine stimulate DA release, and thus putatively might remediate this drive.

There is controversy as to whether hyper- or hypoactivation of ventral striatal and DA functioning conveys addiction risk. Among adolescents, an imbalance of immature top-down and hyperactive bottom has been suggested to lead to increased susceptibility to SUD [58]. In adolescents and adults, ventral striatal hypoactivation is linked to impulsivity and SUD,[58] such as alcohol use disorder (AUD) [72], amongst those at risk [73], in youth [74], and in gambling [75]. Reward deficiency syndrome has been proposed which postulates that hypo-DAergic activity results in decreased sensitivity to natural reinforcers, contributing to withdrawal and the perpetuation of drug use [76]. Decreased DA activity may relate to D2 reductions in the anterior cingulate gyrus and OFC, thereby providing a mechanism by which DA disruptions lead to compulsive drug use [76]. In rodent studies, reduced D2DR availability has been associated with trait-like impulsivity [63], while in stimulant use disorders striatal D2DR availability has been negatively correlated with impulsivity [77].

Another non-DA system potentially involved in impulsivity and SUDs includes norepinephrine. This neurotransmitter has been linked to impulsive behaviors and addictions mediating stimulant effects such as drug-seeking behavior [78]. Moreover, clinical trials using adrenergic modulators have shown promise as substance cessation aids, with reduced use of cocaine [79]. Finally, similar to glutamate and GABA, serotonin or 5-hydroxytryptamine (5-HT) levels have also been associated with SUDs. Specifically, clinical, animal and genetic studies have indicated that low levels of the 5-HT transmission have been linked to impulsive choices and addictions such as early onset alcoholism [78,80]. Selective 5-HT receptor agonists and antagonists have demonstrated elevated and blocked impulsiveness, respectively[57]. Moreover, both human and animal trials have demonstrated that upregulated 5-HT receptor mechanisms contribute to the development of SUDs via dysregulated IC associated with impulsivity [81].

Does impulsivity contribute to addiction risk or vice versa?

There have been three well-accepted premises regarding impulsivity and SUDs: (1) impulsivity causes SUDs; (2) SUDs cause impulsivity; and (3) impulsivity is related to a third factor governing SUDs [3]. The behavioral traits of impulsivity have been widely

associated with SUDs and addictive behaviors (e.g., gambling). Notably, these traits vary throughout the life span, with enhanced impulsivity observed during adolescence coinciding with increased drug use [82].

Impulsivity contributes to SUD

Both cross-sectional and longitudinal studies have supported the idea of linking trait impulsivity to drug use. It has been widely recognized that deficient IC in SUDs includes a component of preexisting impulsivity that may predict initial substance use [83], the development of SUDs, risk for addiction [84], chronic use [85], relapse rates, [86] and treatment retention [87]. In comparison with nonpsychiatric controls, higher levels of impulsivity have been found in individuals with SUD involving stimulant, opiate, and alcohol use [11], and greater discounting of delayed rewards has been found amongst individuals with SUD in tobacco [45], alcohol [88], cocaine [89], opiates [90], and methamphetamine [91]. Similarly, increased impulsivity levels have been found amongst cannabis- [92], alcohol- [93], cocaine- [94], and opiate-dependent [95] individuals. Highly impulsive individuals with poor IC may be more sensitive to attention-grabbing properties of substance-related stimuli than those not using substances [96]. Moreover, studies have found that discounting levels vary by a type of SUDs, with particularly cannabis, opiates and cocaine being associated with most impulsivity [90,92]. Thus, impulsivity may potentially represent an endophenotype for SUDs and persist with symptom remissions, evidenced as heritable; conferring an increased risk of developing SUDs compared with the general population [97]. A genetic basis of impulsivity is suggested given the early rs1800497 (*DRD2*/*ANKK1*) findings and putative reward deficiency syndrome.[71] Heritable risk factors for SUDs involving inhibitory deficits prevalent in childhood disruptive behavior disorders, such as attention-deficit/hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), and conduct disorder (CD) have also been suggested given these disorders are familial in nature, commonly comorbid with SUD, and present in early life [98]. Ortal and colleagues also found that certain impulsivity constructs (e.g., disinhibition, impulsive choice, and sensation seeking) indexed via abnormal brain activity indicate shared neurophysiological deficits between ADHD and SUD [99]. Moreover, several neurocognitive tests in clinical settings have consistently demonstrated deficits in impulsivity amongst individuals with SUD, indicative of preexisting PFC deficiencies [20,100]. Advances in neuroanatomy and molecular pharmacology [101] as well as extending to imaging studies (e.g., positron emission tomography and functional magnetic resonance imaging (fMRI) studies) have correlated cognitive activity in the brain to substance addictions. Dom and colleagues found that among 52 studies reviewed, most demonstrated significant deficits in decision making involving the OFC among individuals with SUDs [102]. Several studies have found deficits in impulsivity indexed by the stop-signal reaction-time task within alcohol [103], cocaine [104,105], and methamphetamine [106] addictions.

With respect to the four categories mentioned of impulsivity, all have been linked to substance use disorders [107]; a moderate to strong prediction has been found between negative urgency and lack of perseverance, respectively, and problematic substance use (e.g., alcohol), while the lack of premeditation and sensation seeking has been correlated with increased frequency of substance use. Nonetheless, it is important to note that various stages

of addiction (acquisition, escalation, abstinence, relapse, and treatment), vary in the impact of impulsive behavior and its constituents [3].

In SUD stages, the acquisition phase, which involves the progression of initial drug use to the maintenance of use, animal models suggest that impulsivity may predate substance use [3]. After screening for high or low measures of impulsivity, subsequent initiation of drug use has been monitored [3]. For instance, a more rapid onset and greater cocaine self-administration were found in a high-impulsive group of rats compared with the low-impulsive group [108]. Similarly, this same model has been translated to human behavior, with studies finding that impulsive choice to initiate substance use, and immediate euphoric effects of a drug, out-value future larger benefits, such as personal, educational, social, and economic success [109]. Furthermore, initiation of substance-taking typically occurs during adolescence, which is a high-risk period for the development of SUD due to the immaturity of prefrontal cortical systems responsible for IC [110] as evidenced with fMRI scanning in young children, adolescents, and young adults [11].

Loss of control of drug use is another stage of addiction that posits impulsivity leading to SUD [3]. No human studies have been conducted to support this premise; however, rat trials have demonstrated escalation of drug use in response to increased impulsivity, implicating that highly impulsive individuals may be more prone to accelerating drug use/SUD [111,112].

Levels of impulsivity have also been related to the stages of abstinence, relapse and treatment success. For instance, nicotine deprivation among smokers was found to increase the frequency at which smokers discounted delayed choices [113]. One study also found that DD deficits amongst schizophrenia patients were linked with high rates of cigarette smoking and difficulty of maintaining abstinence [114]. Similarly, chronic methamphetamine users who were abstinent for 5–7 days were found to have deficits in their response inhibition [106]. Symptoms experienced via abstinence, such as increased levels of withdrawal [115] and craving, have also been suggested to be associated with self-reported impulsivity amongst many SUDs including alcohol [116], cocaine, and methamphetamine users.[117] That is to say, those who are more impulsive tend to experience greater levels of craving during withdrawal, and a greater likelihood of relapse [3]. Moreover, individuals with higher impulsivity scores based on questionnaires, have also been more likely to have poorer treatment retention for cocaine misuse, than those with lower impulsivity scores [118].

SUDs contribute to impulsivity.—It is also possible that substance use has a state effect on impulsivity [3]. It has been repeatedly shown that psychoactive substance exposure (e.g., alcohol and cannabis) during adolescent and adulthood results in greater brain vulnerability to changes in white matter integrity, morphology, and activation during cognitive assessments [58]. In particular, chronic neurobiological effects of drug self-administration may mediate structural change to the PFC, via direct neurotoxicity, cell death, or tissue shrinkage, resulting in a gradual attrition of behavioral self-control [13,119]. Numerous studies have found that SUD alters performance in humans across several independent behavioral measures of impulsivity, relating to cognitive outcomes such as DD, behavioral inhibition, and lapses of attention, thus demonstrating that impulsivity may result from drug use [21]. Moreover, both brain imaging and post-mortem studies have shown reduced regional brain volumes, gray

(~20%) and white (~10%) matter densities in individuals with SUDs, such as alcohol, ecstasy, and opiates [120–122]. Changes in gene expression as a consequence of reduced IC within SUD have also been found [11]. Thus there has been a strong indication within human trials that drug use increases levels of impulsive behaviors, which in turn facilitates drug use [19]. In contrast, although increased levels of impulsivity in humans have been found amongst those who use drugs, there is evidence of reduced drug use with increased impulsivity [123]. However, one may argue that these results reflect dysregulated regions of the brain and subsequent cognitive processes given chronic drug use. Consistent with this assertion, animal trials have demonstrated SUD may cause impulsivity a short-term drug administration suggest the emergence of IC deficits [124,125]. Ultimately, these findings depend on the dose, participant samples, and specific testing parameters in order to account for the various effects of SUDs on impulsivity. Taken together, drug use may impair IC resulting in functional consequences [21].

Impulsivity related to a third (independent) factor governing SUD.—Finally, the environment may contribute to impulsivity and SUDs [3]. In both animal and human substance consumption, sex appears as a major factor with females exhibiting greater drug-seeking behavior than males [126,127]. Men report more problems with SUDs compared with women; however, women are more likely to transition to continued misuse than men. Furthermore, preclinical models have shown that amongst females, drug self-administration, escalated drug intake, and higher reinstatement rates are more likely than in males [128–131]. Clinical studies have also produced mixed results [132–134].

Another factor relating to impulsivity and SUDs is a hormonal status. The presence of estrogen, progesterone, and circulating gonadal hormones has been found to play a major role in SUD, with facilitated acquisitions of drug self-administration [135], escalation [136], reinstatement [137], and attenuating effects [136]. For instance, higher levels of testosterone have been associated with greater levels of impulsivity, while another study has found the effect to be baseline dependent [138,139].

Risk of SUD and high levels of impulsivity have also been commonly associated with early life experiences such as prenatal drug exposure (e.g., alcohol) and impoverished rearing conditions (e.g., physical abuse) [140,141].

Epigenetic factors also contribute to impulsivity and addiction. In a longitudinal cohort, Wang *et al.* found that impulsivity mediated the relationship between family disorganization and subsequent alcohol use, specifically amongst individuals at low genetic risk based on polygenic risk scores for impulsivity [142].

Finally, other comorbidities such as ADHD, conduct disorders, oppositional deviant disorder, and other childhood behavior problems, may pose as risk factors for SUD through the role of impulsivity [99]. Constructs of impulsivity such as sensation seeking and conduct problem symptoms prevalent among individuals with ADHD have also been suggested to predict the increased risk for SUD, including misuse of stimulants [143].

Trait factors in impulsivity as targets for SUD treatment development

There are three main approaches to assessing impulsive behavior. The first one focuses on translational between animal and human models [3]. This includes targeting underlying processes involved in impulsivity and SUDs (i.e., working memory (WM) and attention) to validate behavioral measures of impulsivity [3]. For instance, WM training can improve SUD outcomes [144,145]. The second approach, behavioral measures are easy to administer in both species, thus requiring a modest amount of training, which may allow the ability to determine the efficacy of individualized treatments targeting impulsivity and SUD. [3] Finally, these tasks do not rely on retrospective measures or recalling of past events, but focus on the current state in the third approach. This would confirm the validity of assessing changes in impulsivity [3].

Genetic factors implicated in the development of SUD may also be a target for SUD treatment development. One sibling study found that impulsivity may be exacerbated with chronic substance use as evidenced by siblings of chronic stimulant users reporting significantly higher levels of trait impulsivity than controls [84]. Furthermore, biological predisposition to impulsivity and SUD, relate to dysregulated function of the frontal control over corticolimbic circuitry contributed by DAergic projections from the ventral tegmentalVTA to the Nacc and also involves serotonergic, GABAergic, and glutamergic processes. As such targeting these various regions of the brain indirectly using medications or behavioral treatments may result in enhanced cognition via decision making thereby serving as effective treatment strategies [146]. For instance, opioid receptor antagonists (naltrexone) and glutamatergic compounds (N-acetyl cysteine (NAC)) influence mesolimbic DA function indirectly and shown to target reward-seeking addictive behaviors [147,148].

Behavioral data also suggests that recognizing high impulsive behavior may predict the initiation and progression of SUD, thus early detection may serve as an effective means of treatment [146]. Studies relating to patients with diagnoses that include aspects of impulsivity or related constructs, such as ADHD, have indicated an association with later developments of SUD [14,146]. Finally, studying impulsivity in children and adolescents is important to consider, as it may help produce biological explanations of later developing SUD [58]. Taken together, these trait factors offer several dimensions for the progressive treatment developments in SUDs, which have expanded to pharmacological, behavioral and neurophysiological mechanisms.

Treatment of co-occurring impulsivity and substance use disorders

There are strong overlaps in the neural circuitry and functional mechanisms between impulsivity traits and addiction [49], which has directed treatment approaches. However, one of the major difficulties when studying impulsivity and its relation to SUD is the inherent multiplicity of factors related to impulsivity. We review pharmacological (Table 2), behavioral (Table 3), and neuromodulation interventions.

Pharmacological treatments

Tobacco and nicotine.—Preclinical studies have highlighted the effect that nicotine has on increasing impulsive action [149,150]. This effect might be mediated by cholinergic receptors, specifically the nicotinic α4β2 receptors [151,152]. Research studies using animal models have found that antagonists at this receptor reduce self-administration of nicotine and relapse behavior [153,154], indicating its potential as a treatment option with a dual effect on impulsivity and attenuating tobacco use in humans.

There have been two clinical studies in human subjects that have investigated pharmacological treatments targeting impulsivity in smokers. In a retrospective study exploring this topic, researchers looked at data from adolescents with ADHD and found that individuals that were taking methylphenidate exhibited lower rates of tobacco use when compared with non-medicated individuals [155]. To follow up with these findings, a group of researchers conducted a trial of methylphenidate in current smokers with ADHD and found a reduction in ADHD symptoms, but no effect on tobacco use outcomes [156]. These findings suggest that stimulant agents for ADHD may exert protective effects against later substance use in these patients [49]. In another clinical study, researchers created a personality profile for the level of novelty seeking of each participant and assigned them to either a modified treatment condition targeting impulsivity with bupropion and tailored behavioral therapy or to a standard treatment group [157]. The researchers found no differential response to either treatment condition for the novelty-seeking profile [157]. As such, further studies conducted in humans should potentially investigate the role of cholinergic receptors on impulsivity and substance-related outcomes.

Cannabis.—One human study has examined pharmacological treatments for cannabis users with high impulsivity [158]. The study was a clinical trial involving two treatment groups of contingency management (CM), but one including NAC administration[158]. They found no differences between the treatment groups, indicating the lack of efficiency of NAC on impulsive cannabis users [158]. Preclinical animal studies have found an association between CB1 receptors and increases in impulsivity [159]. Additionally, administering CB1 receptor antagonists, such as rimonabant, in animal models has been shown to reduce baseline impulsivity [160] and self-administration of several classes of substances [161]. Further research in human models is warranted to investigate the role that the endocannabinoid system has on impulsivity and substance use as well as the potential to develop treatments targeting this system.

Alcohol.—Five studies have been conducted in humans to find a treatment for impulsivity and AUD [162–166]. The first study compared 6 months of lithium, busiprone, or placebo on individuals with AUD [162]. They found no difference between treatment groups, and that individuals high in the novelty-seeking trait were more likely to drop out of the study [162]. Zorlu and colleagues conducted an open-label study of naltrexone for AUD and compared treated patients with naltrexone-naive patients and healthy controls [163]. They found that naltrexone had no effect on alcohol use outcomes with impulsivity as a mediator [163]. Rubio and colleagues [166] investigated the effects of topiramate compared with placebo and found that the treatment group significantly improved alcohol use outcomes, which were mediated

by performance on an objective test of behavioral inhibition. They also found that the treatment group performed better on two behavioral tasks related to impulsivity across the study period [166]. Another placebo-controlled trial investigated the effects of modafinil on impulsive drinkers with AUD and also found that the treatment group improved abstinence outcomes, which were associated with response inhibition [164]. Modafinil was also found to improve self-reported measures of impulsivity but had no effect on behavioral measures of impulsivity [164].

Finally, Anton and colleagues [165] conducted a placebo-controlled trial with aripiprazole and brought participants into a laboratory bar paradigm at the end of the study, where they were asked to choose between an immediate drink or a delayed monetary reward. Aripiprazole reduced drinks consumed and increased the duration to drink in individuals rated high on impulsivity in the bar laboratory paradigm [165]. Thus, there are promising pharmacological treatments for impulsivity in this population, but further research should be conducted to replicate these findings.

Stimulants.—In animal models, there has been evidence to demonstrate that pharmacological agents that modulate noradrenaline levels, such as selective noradrenaline reuptake inhibitors (NRIs) are effective at reducing impulsivity [167–171]. Interestingly, the NRI atomoxetine has been found to inhibit cue-induced cocaine self-administration in mice [172,173]. Three drug trials in human subjects have been conducted, all with a focus on improving impulsivity in cocaine users [174–176]. Schmitz and colleagues [174] conducted an RCT comparing citalopram with cognitive behavioral therapy (CBT) and CM to a placebo with CBT and CM. They found no differences between treatment groups, but that baseline impulsivity was predictive of better outcomes. Another RCT compared modafinil with CBT to CBT alone in crack cocaine users and found no improvement in impulsivity measures [175]. Finally, an open-label trial was conducted with D-amphetamine in cocaine users, but they also found that the drug had no effect on impulsivity [176]. No human studies have yet investigated the effects of NARIs in individuals with stimulant use disorders.

Opioids.—No human studies have been conducted on pharmacological treatments to improve impulsivity in opioid users. However, preclinical research has shown some promise in μ- and δ-opioid receptor antagonists, as they have been found to reduce drug self-administration and relapse behaviors [177–180].

Problem gambling.—A pilot study comparing paroxetine to placebo found that drug-related improvement in gambling severity was significantly associated with changes in impulsiveness scores [181].

Taken together, further research is needed on pharmacological agents that target impulsivity in individuals with SUDs. There are promising findings in preclinical research that show promise for drugs that target the cholinergic, noradrenergic, and opioid neurotransmitter systems for this population [153,154,167–173,177–180]. Additionally, there has been convincing evidence that suggests the potential for prescribed amphetamines to prevent the onset of substance use disorders in individuals diagnosed with ADHD [49,155,156]. Finally, the only positive findings in human drug trials that have been found to reduce impulsivity and

improve substance use outcomes have been topiramate, modafinil, and aripiprazole for AUD [164–166] as well as paroxetine for problem gamblers [181].

Behavioral treatments

Tobacco.—Two treatment studies in smokers have demonstrated in the post-hoc analysis that baseline impulsivity levels may be predictive of poorer abstinence outcomes. These findings warrant the consideration of targeting impulsivity to improve outcomes in this population. Two studies have been conducted that focus on the effect of a behavioral treatment on impulsive individuals [182,183]. Helstrom and colleagues [182] compared motivational enhancement therapy (MET) session with a tobacco educational control condition. They found unexpectedly that individuals high in impulsivity showed improved tobacco use outcomes in the educational control, indicating that MET may not be an effective strategy in impulsive individuals [182]. Another study [183] found that CBT in combination with CM is more effective at improving abstinence rates in impulsive individuals compared with CBT alone. Further investigation is needed to solidify an effective treatment for impulsive smokers.

Cannabis.—Two studies have been conducted exploring behavioral treatments for cannabis users with high impulsivity traits. The first study was an RCT that included four conditions comparing CBT with a combination of two different CM strategies, which were CM with reinforcement for attendance, and CM with reinforcement for abstinence [184]. They found that pretreatment impulsivity, using an objective delay discounting test (DDT), was not associated with cannabis use outcomes, but that both CM conditions prevented DD from worsening over time [184]. The second study was a cluster-RCT that examined a personality-targeted intervention that was implemented in 21 secondary schools and was based on a four-faceted high-risk profile (anxiety, hopelessness, impulsivity, and sensation seeking) [185]. They found that in students with a high sensation-seeking profile, the targeted intervention delayed the onset of cannabis use [185]. Further clinical studies should be carried out to identify the psychological mechanism behind this association with impulsivity and cannabis use.

Alcohol.—Two RCTs have been conducted exploring behavioral treatment for impulsivity and AUDs. First, Feldstein and colleagues [186] compared motivational enhancement therapy (MET) to an alcohol educational control condition. They also found that individuals high in novelty seeking showed improved alcohol use outcomes in the educational control condition, and low novelty-seeking individuals fared better with MET [186]. Second, another RCT was conducted examining the effects of a mindfulness intervention compared in AUD patients when considering several impulsivity traits [187]. They found that negative urgency was associated with an increased urge to drink in the mindfulness intervention, indicating that mindfulness treatments may not be effective in highly impulsive drinkers [187]. Thus far, there have been no effective behavioral treatments found for this population.

Stimulants.—Three studies have been conducted investigating behavioral treatments for impulsivity and stimulant use. Black and Rosen [144,188,189] conducted an RCT of the Advisor-Teller monetary manager (ATM) intervention compared with a control condition in

cocaine users. ATM addresses money management problems in substance abuse and provides help from therapists with planning and monitoring budgets [188]. They found that the ATM condition produced reductions in DD and cocaine use compared with the control condition and that these effects were association [188]. Another prospective study compared CM with low- versus high-magnitude vouchers in cocaine users [189]. They found that in individuals with high impulsivity had reduced abstinence rates in the low magnitude condition, but not in the high-magnitude condition, signifying that high magnitude CM might be more effective in impulsive cocaine users [189]. Finally, Brooks and colleagues investigated the effects of WM cognitive training (CT) compared with treatment as usual in methamphetamine users and healthy controls [144]. They found that the WM CT was effective at improving self-reported impulsivity scores [144]. Stimulant users appear to be responsive to behavioral treatments targeting impulsivity, and further research should work to develop evidence-based treatments.

Opioids.—Three studies on behavioral treatments for impulsivity in opioid use disorders have been conducted [190,191]. One of these studies involved three study conditions all including buprenorphine with CM in one of three conditions: (1) contingent reinforcement vouchers; (2) reduced value contingent reinforcement vouchers; and (3) non-contingent voucher [190]. They found no differences in impulsivity across the treatment groups [190]. In contrast, a secondary analysis reviewing the effects of two RCTs involving buprenorphine and CM on DD outcomes found that all treatments equally lead to reductions in DD [191]. Finally, a group of researchers conducted a pilot study in substance-using patients enrolled in a methadone maintenance program which provided spiritual self-schema (3-S^+) therapy compared with a standard care control condition [192]. They found that the 3-S^+ therapy group demonstrated reduced impulsivity and substance use, indicating the importance of incorporating elements of self-schema into mindfulness interventions in impulsive drug users [192]. Opioid users appear to be responsive to behavioral treatments that aim to modify impulsivity, and further research should be conducted to develop treatments.

Overall, the behavioral treatment with the most supporting evidence for impulsive individuals with SUDs is CM, particularly with high-value rewards [184,189,190]. There is little support to show that MET on its own provides any benefit to this population, and in two cases an education control condition has been shown to be more effective. The ATM[188] and 3-S^+ [192] are novel treatment paradigms that show promise for this population, but further research should be conducted across various SUDs.

Neuromodulation treatments

A review by Brevet-Aeby et al.[24] suggested that non-invasive brain stimulation may lead to improvements in impulsivity in humans on dimensions of attention, planning, IC, risk taking, and DD after stimulation to prefrontal regions (e.g., DLPFC) [24]. Several studies have found improvements in impulsive and risky behavior upon continuous theta burst stimulation (TBS) to DLPFC [193], transcranial direct current stimulation (tDCS) over the right inferior frontal gyrus (rIFG)[194,195] and the DLPFC [196–200], as well as repetitive transcranial magnetic stimulation (rTMS) over the dorsal frontomedial cortex [201], rIFG [202], DLPFC, and lateral PFC.[203,204] In two studies analyzing cocaine use, rTMS and tDCS of the DLPFC led

to decreased levels of measured impulsivity post-treatment [205,206]. In additional two studies focusing on cigarette consumption, rTMS over the DLPFC also led to decreased impulsivity [207]; however, tDCS over the same region did not show any changes in the second study [208]. A study on cannabis use found that TBS over the DLPFC increased risky behavior [209] and another study looking at gambling disorder found neither rTMS nor TBS led to decreased impulsivity measures [210]. From these results, regions implicated in impulsivity and targeted by certain neurophysiological treatments have spanned the frontal cortex, however, there lacks consistency in hemispheric localization and specificity of brain regions related to impulsivity. Despite the collection of studies analyzing general cognition in healthy individuals as described, neurophysiological treatments studies for substance use disorders that include assessment of impulsivity pre- and post-treatment are lacking. Moreover, a recent review of non-invasive neuromodulation techniques has highlighted the several gaps and high variability in the literature examining the effects of these methods to treat SUD [211], indicating the need for further research in this potentially promising area.

Implications of a transdiagnostic model for impulsivity and addiction risk

There are several primary measures included under the rubric of impulsivity (response inhibition, inattention, urgency, lack of premeditation and perseverance, and sensation seeking) [115]. Impulsivity has been suggested as a trait vulnerability marker for addiction risk involving underlying brain circuits and neurotransmitter systems (e.g., DAergic), which may result in greater risk for SUD. Similarly, stage effects of SUD including the development/acquisition, escalation, abstinence, and relapse and treatment phases amongst both chronic and acute substance-using individuals, comprise state changes to specific brain regions resulting in declined cognitive abilities and increased impulsivity. Moreover, evidence suggests that chronic substance use (binge drinking) results in impairments of specific regions of the brain (PFC projection to the ACC and OFC) which contribute to an imbalance of craving–limbic drive and frontal cortical attention and executive function such as IC [212]. Finally, other environmental and genetic factors may influence the initiation and progression of both SUD and impulsive behavior that further complicates this complex relationship [213]. Understanding the interrelationships between these three components may lead to the development of targeted treatments (Fig. 2). Certain treatment modalities may target common neurotransmitter deficiencies present in dimensions of impulsive behavior and in SUDs. For instance, the dysfunctional reward pathway of the brain (centering on DLFPC) has been indicated in impulsivity and SUDs (e.g., cocaine craving) [205]. Thus treatments such as rTMS, which have been found to activate these regions directly, may posit as an effective transdiagnostic model targeting the same underlying deficiencies in co-occurring impulsivity and SUD.

Conclusions

Taken together, there is increasing evidence supporting pharmacological and behavioral treatments for impulsivity in SUDs. However, further research is needed. Future pharmacological research should focus on investigating the neurotransmitter systems and pharmacological agents (e.g., topiramate, modafinil, and aripiprazole) that have been shown efficacious in preclinical studies. This research could better our understanding of the

etiology of impulsivity in addiction and potentially provide tailored treatments for these individuals. Behavioral treatments should focus on novel therapies that target the root of the impulsivity trait to produce behavioral change in patients.

However, there are several gaps to address in future research. First, there is not always a consistent relationship between behavioral measures and self-report given the circumscribed definition of impulsivity, as well as an individual's ability to report the cognitive processes underlying their behavior [3]. The multiplicity of impulsivity measures besides the defined ones (e.g., urgency, sensation seeking, lack of perseverance, and lack of premeditation) provides an inconsistency amongst trials with conceptual/methodological heterogeneity. Second, there are individual differences on laboratory measures of impulsive choice and inhibition, indicating the importance of using several models to obtain convergent validity, and identifying how these behavioral measures relate, if at all [3]. For instance, experimental conditions played a role in the determination of sex differences, with women discounting delayed hypothetical reinforcers at higher rates than men, while the reverse was found when real reinforces were offered [214]. Third, studies will often assess impulsivity in the demographic assessments made at the beginning of the study, but fail to measure impulsivity after treatment. Thus a potential recommendation for future studies is to complete such measurements both pre- and post-study intervention. Moreover, measurement time frame should be considered given that some measures, like DDT, go/no-go, and SST are amenable to change but personality traits may have too broad a time window or be subject to demand characteristics.

It is not clear to what extent impulsivity is a result of chronic SUDs or a predisposing risk factor. Future studies should consider the multifaceted construct of impulsivity in parallel with the relationship of the various stages of addiction. This will ultimately provide a better understanding of the gaps that exist in understanding SUDS and impulsivity and for developing more effective treatments.

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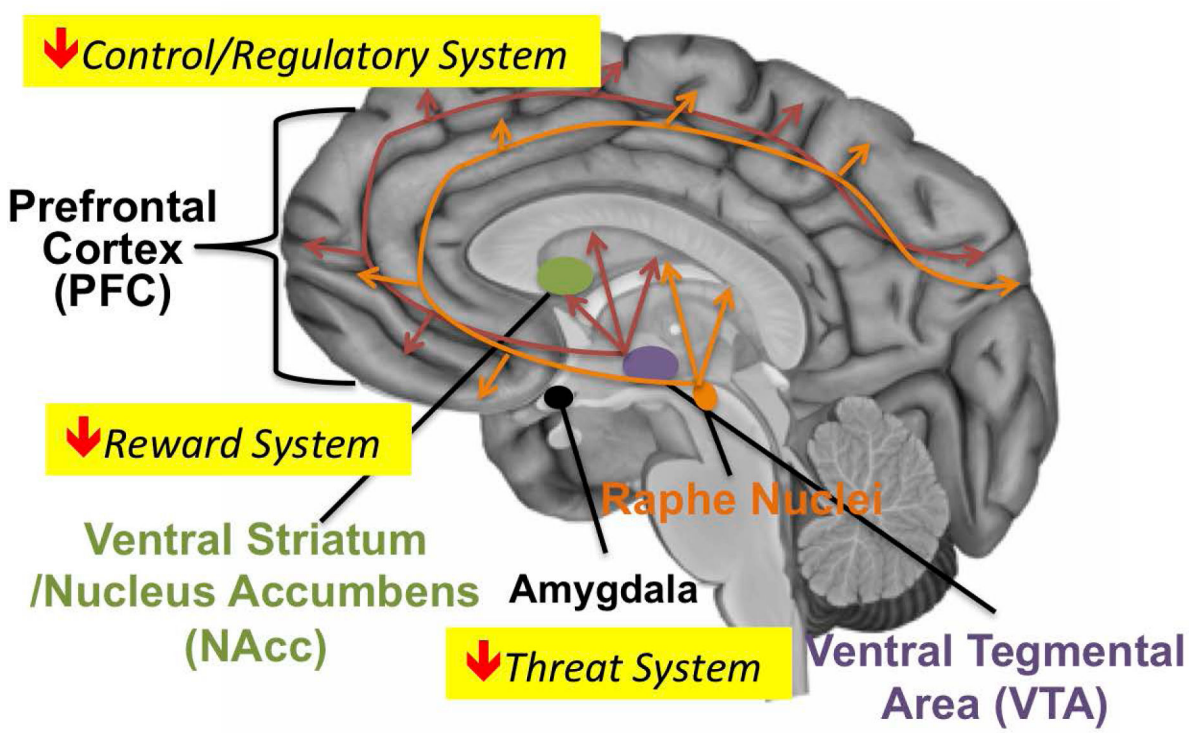

Figure 1.

Brain diagram to illustrate pathways leading to impulsive behaviors (adapted from Ref. 57). Three neurobiological systems including the control/regulatory, reward, and threat systems, mediated by the medial and ventral prefrontal cortices, the ventral striatum and midbrain dopaminergic system, and the amygdala, respectively, provide an overlapping pathway linking brain circuitries and neurotransmitter systems associated with addiction risk and impulsivity.

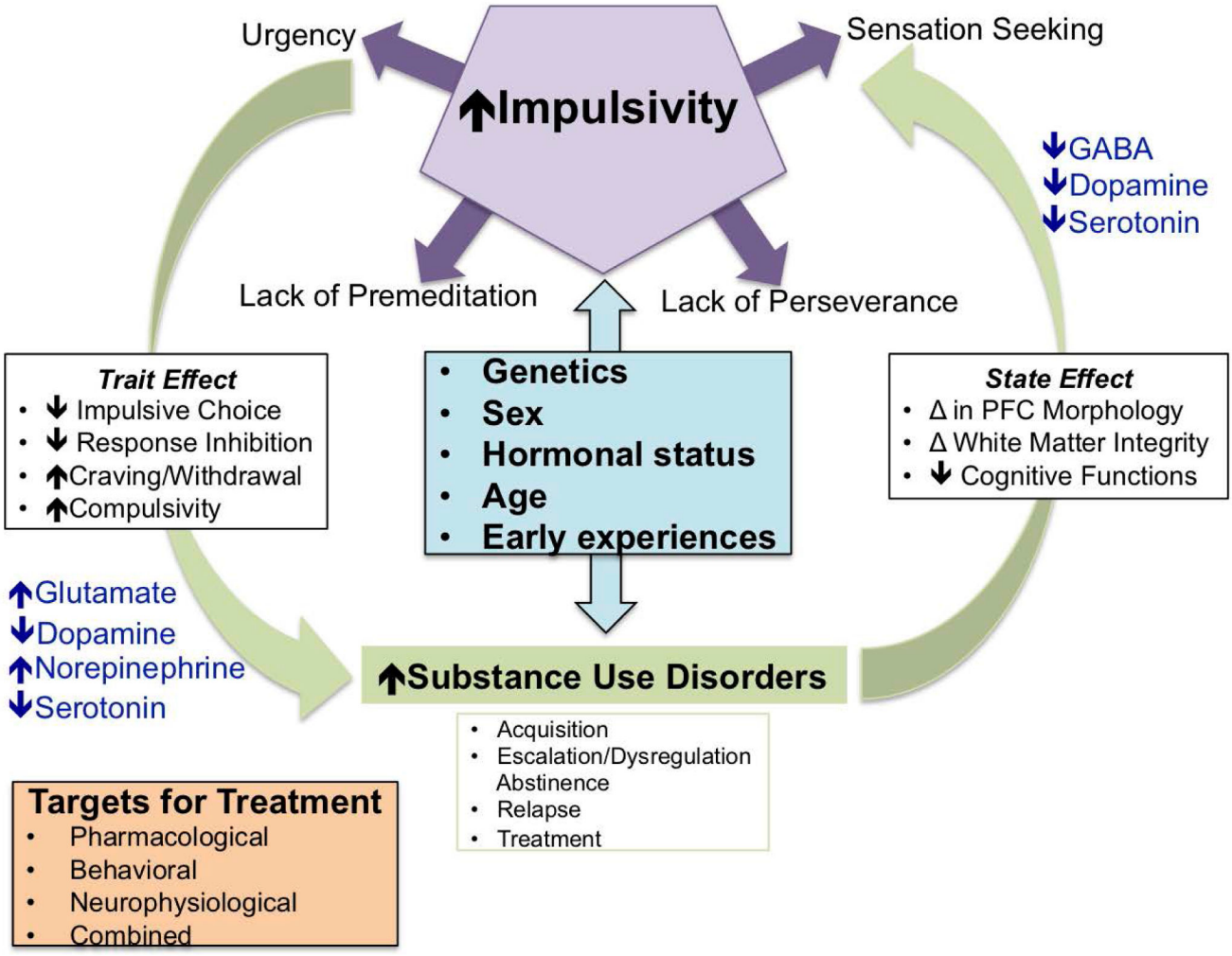

Figure 2.

Transdiagnostic model for addiction risk and targets for treatments. The interrelationship between trait effects, state effects and other environmental and genetic factors, as well as implicated neurotransmitter levels, influencing the initiation and progression of impulsivity and substance use disorders.

Table 1.

Summary of various subjective and objective measures of impulsivity.

Tasks	Purpose	Impulsive dimension/ component
Subjective: self-report tasks		
The Barratt impulsiveness scale (BIS-11)[38]	A 30-item questionnaire assessing three separable dispositions: attentional, motor, and non-planning impulsiveness	Impulsive trait: inhibitory control; accounts for lack of premeditation and perseverance impulsivity dimensions[55]
The Eysenck impulsiveness questionnaire (I_7)[215]	To assess personality traits of impulsivity, venturesomeness, and empathy	Impulsive trait
The temperament and character inventory (TCI)[216]	An inventory of personality traits based on four temperaments: novelty seeking, harm avoidance, reward dependence, and persistence	Impulsive trait
The multidimensional personality questionnaire (MPQ)[217]	A comprehensive assessment of personality traits (control versus impulsivity) encompassed of mostly 276 true-false items	Impulsive trait
The UPPS impulsive behavior scale (IBS)[41]	59-item scale measuring different aspects of impulsive personality encompassing four traits: negative urgency, premeditation, lack of perseverance, and sensation seeking	Impulsive trait
Objective: behavioral tasks		
The Kirby delay-discounting task (KDDT)[134]	A 27-item questionnaire measuring temporal discounting, using small immediate monetary rewards versus larger delayed rewards	Impulsive state/choice: delay discounting
The Iowa gambling task (IGT)[218]	Task assessing decision making under risk and uncertainty using four virtual decks of cards on a computer screen, with contingencies are discovered by trial and error	Impulsive state/choice: impulsive decision making
The Cambridge gambling task (CGT)[219]	Rodent version of IGT, signaling the odds of winning	Impulsive state/choice: impulsive decision making
The experiential discounting task (EDT)[220]	Computerized task requiring participants experience choice consequences during a measurement period assessing motivation to earn or prevent loss of monetary reward	Impulsive state/choice: delay discounting
The go/no-go task[37]	Test of response inhibition with participants trained over multiple trials to make a particular response to a “go” signal, with some trials of “stop” signal presented prior to or simultaneously	Impulsive state/action: motor disinhibition
The stop-signal reaction-time (SSRT) task[36]	Test of behavioral inhibition/discrimination with a “stop” signal presented after the “go” signal	Impulsive state/action: motor disinhibition
The balloon analogue risk task (BART)[221]	Task designed to assess the risk propensity with balloon presentations on a computer screen that can be incrementally inflated while accumulating reward, with a constant probability of popping (loss of reward)	Impulsive state: impulsive choice: impulsive-decision making
The oddball task[87]	Analyzing a positive event-related potential (ERP), P300 mitigated through the presentations of sequences of repetitive stimuli infrequently disrupted by deviant stimulus	Impulsive state: inhibitory control
The Stroop color and word test (SCWT)[222]	Information processing approach to assess emotions examining response time of naming colors of negative emotional words	Impulsive state/action: cognitive disinhibition

Table 2.

Pharmacological treatments for impulsivity and SUD.

Reference	Sample	Drug	Design	Impulsivity measures	Impulsivity dimension	Treatment		Outcome
157	Adults (n = 165)	Tobacco	RCT	Personality profile: novelty seeking/ hyperactive	Sensation seeking	**1** **2**	Standard treatment (nicotine patch OR gum + behavioral intervention) Modified treatment for hyperactivity (nicotine patch + gum, buproprion, impulse control addiction treatment modules, daily routine structure, and conflict resolution)	No differential effects between treatment groups based on personality profile
158	Adolescents (n = 115)	Cannabis	RCT	BIS-11	Lack of premeditation Lack of perseverance	**1** **2**	CM + placebo CM + N-Acetylcysteine	No effect of treatment group on substance use outcomes in highly impulsive individuals
162	Adult males (n = 160)	Alcohol	RCT	TPQ Novelty seeking subscale	Sensation seeking	**1** **2** **3**	Six months of lithium Six months of buspirone Six months of Placebo	Novelty seeking higher among dropouts. No differential effects between treatment groups based on novelty seeking
163	Adult males (n = 51)	Alcohol	Open-label study	BIS-11, IMT, and SKIP	Lack of premeditation Lack of perseverance	**1** **2** **3**	Naltrexone-treated Naltrexone- Healthy controls	Naltrexone had no effect on alcohol use outcomes based on impulsivity
166	Adult males (n = 63)	Alcohol	RCT	CPT, SST, and DRLR	Urgency (behavioral inhibition)	**1** **2**	TP Placebo	TP group improved alcohol use outcomes which was associated with performance on behavioral inhibition paradigm, CPT. TP group had higher improvement rates on CPT and stop-signal task.
164	n = 83	Alcohol	RCT	BIS-11, State Impulsivity Questionnaire, SST, and DDT	Lack of premeditation Lack of perseverance	**1** **2**	Modafinil Placebo	Modafinil improved measures of state impulsivity but had no effect on behavioral measures of impulsivity Modafinil prolonged time to relapse, increased abstinent days in participants with poor response inhibition at baseline, and reduced in participants with good response inhibition at baseline
165	n = 99	Alcohol	RCT	BIS-11	Lack of premeditation Lack of perseverance	**1** **2**	Aripiprazole Placebo	Apriprazole increased latency to consume drinks in individuals with high impulsivity

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Reference	Sample	Drug	Design	Impulsivity measures	Impulsivity dimension	Treatment	Outcome
174	Adults (n = 75)	Cocaine	RCT	BIS-11 and IGT	Lack of premeditation Lack of perseverance	**1** Citalopram + CBT + CM **2** Placebo + CBT + CM	No difference between treatment groups or impulsivity at baseline CBT + CT effective for highly impulsive cocaine dependent patients
175	Adults (n = 65)	Crack cocaine	RCT	BIS-11, SWCT, and SST	Lack of premeditation Lack of perseverance	**1** Modafinil + CBT **2** CBT	Modafinil did not appear to reduce measures of impulsivity in this population
176	Adults (n = 34)	Cocaine	Open-label trial	BIS-11, IMPSS, Immediate/Delayed Memory Task, Go/Stop task, DD	Lack of premeditation Lack of perseverance	1. D-amphetamine	D-amphetamine did not reduce impulsivity
181	n = 38	Problem gamblers	RCT	EIQ Impulsiveness subscale	Sensation seeking	**1** Paroxetine **2** Control	Improvement in gambling severity by paroxetine was associated with changes in impulsiveness scores

BIS-11, Barratt impulsiveness scale-11; BT, behavioral therapy; CBT, cognitive behavioral therapy; CM, contingency management; CPT, continuous performance pest; DD, delay discounting task; DRLR, differential reinforcement for low-rate responding; EIQ, Eysenck impulsiveness questionnaire; IGT, Iowa gambling task; IMPSS, Zuckerman's Impulsive Sensation Seeking subscale; IMT, immediate memory task; RCT, randomized control trial; SKIP, single-key impulsivity paradigm; SST, stop-signal task; SCWT, Stroop color and word test; TP, topiramate; TPQ, tridimensional personality questionnaire.

Table 3.

Behavioral treatments for impulsivity and SUD.

Reference	Sample	Drug investigated	Design	Impulsivity measures	Impulsivity dimension	Treatment	Outcome
182	Adolescents (n = 81)	Tobacco	RCT	IMPSS	Sensation Seeking	**1** MET 1 session **2** Tobacco education control	High impulsivity/sensation-seeking group showed greater reduction in cigarettes with the tobacco educational control condition Low impulsivity/sensation-seeking group showed greater reduction in MET condition
183	Adolescents (n = 64)	Tobacco	RCT	BIS-11	Lack of premeditation Lack of perseverance	**1** CBT **2** CBT + CM	CM was more effective at increasing abstinence for individuals high in impulsivity compared to CBT alone
184	Adults (n = 127)	Cannabis	RCT	EDT	Lack of premeditation	**1** CBT **2** CBT + CM for attendance **3** CM for abstinence **4** CBT + CM for abstinence	Pretreatment discount not associated with cannabis treatment outcomes Individuals in CM condition did not change discounting over time whereas those that did not receive CM increased their discounting
185	Adolescents (n = 2904)	Cannabis	ClusterRCT	Reckless Behavior Questionnaire	Sensation Seeking	Personality-targeted interventions based on high-risk profile (anxiety sensitivity, hopelessness, impulsivity, and sensation seeking)	Impulsivity-targeted intervention did not reduce cannabis use outcomes Delayed onset of cannabis use in sensation-seeking targeted intervention
186	Young adults (n = 67)	Alcohol	RCT	TPQ and IMPSS novelty-seeking subscale	Sensation Seeking	**1** MET 1 session **2** Alcohol education control	High novelty-seeking group showed greater improvement in alcohol outcomes with the alcohol educational control condition Low novelty-seeking group showed greater improvements in MET condition
187	Young adults (n = 207)	Alcohol	RCT	UPPS	Urgency	**1** Mindfulness intervention **2** Relaxation intervention **3** Control	Negative urgency was positively associated with urge to drink in mindfulness intervention
188	Adults (n = 90)	Cocaine and Alcohol	RCT	Monetary Choice Questionnaire	Lack of premeditation	**1** ATM **2** Control	ATM intervention associated with less delay discounting and less cocaine use relative to control condition. Increases in delay discounting associated with decreased cocaine abstinence

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Reference	Sample	Drug investigated	Design	Impulsivity measures	Impulsivity dimension	Treatment	Outcome
189	Adults (n = 36)	Cocaine	Prospective	DD	Lack of premeditation	**1** CM with low magnitude voucher condition **2** CM with high magnitude voucher condition	Delay discounting unrelated to abstinence in high-magnitude condition, decreased abstinence in low-magnitude condition
144	Adults (n = 50)	Methamphetamine	RCT	BSI-11	Lack of premeditation Lack of perseverance	**1** WM CT **2** Treatment as usual **3** Healthy controls	Impulsivity scores improved in CT group
190	Adults (n = 68)	Heroin and Cocaine	RCT	TPQ Novelty-seeking subscale	Sensation Seeking	**1** Buprenorphine + BT + voucher based reinforcement therapy **2** Buprenorphine + BT + reduced value voucher reinforcement therapy **3** Buprenorphine + BT + non-contingent voucher reinforcement therapy	No differences found between contingency treatment groups
192	Adults (n = 38) adults	Methadone Maintenance/ Opioids and Cocaine	Pilot study	BIS-11	Lack of premeditation Lack of perseverance	**1** Spiritual Self Schema (3-S^{+}) therapy **2** Standard care control	3-S^{+} therapy group demonstrated reduced impulsivity and substance use
191	n=159	Opioid	Second analysis	DD	Lack of premeditation	Buprenorphine + variations of voucher CM or standard counselling	All treatments equally promoted decreases in delay discounting

ATM, advisor-teller monetary manager; BIS-11, Barratt impulsiveness scale-11; BT, behavioral therapy; CBT, cognitive behavioral therapy; CM, contingency management; CT, cognitive training; DD, delay-discounting task; EDT; experiential discounting task; IMPSS, Zuckerman's Impulsive Sensation Seeking subscale; RCT, randomized control trial; WM, working memory; UPPS, urgency premeditation perseverance sensation-seeking positive impulsivity scale.