Published in final edited form as:

Curr Addict Rep. 2021 September ; 8(3): 440–451. doi:10.1007/s40429-021-00382-8.

Lost in Translation: the Gap Between Neurobiological Mechanisms and Psychosocial Treatment Research for Substance Use Disorders

Elizabeth D. Reese[1], **Louisa F. Kane**[1], **Catherine E. Paquette**[1], **Flavio Frohlich**[1], **Stacey B. Daughters**[1]

[1]Department of Psychology and Neuroscience, University of North Carolina, 253 Davie Hall, 235 E. Cameron Ave, Chapel Hill, NC, USA

Abstract

Purpose of Review: To provide an overview of the state of translational substance use disorder (SUD) research by evaluating the extent to which psychosocial interventions target neurobiological processes known to contribute to the maintenance of SUD.

Recent Findings: A limited number of studies have investigated neurobiological mechanisms of action for commonly utilized SUD treatment approaches. Restrictive samples, post-treatment-only designs, and failure to include substance use outcomes significantly limit the interpretation of these findings.

Summary: Much work is needed to bridge the translational gap between neuroscience and psychosocial treatment research for SUD. Despite existing gaps, addiction neuroscience is highly relevant to SUD assessment, case conceptualization, and treatment. Implications are discussed in addition to suggestions for future research.

Keywords

Substance use disorder; Addiction; Neuroscience; Psychosocial treatment; Translational research; Treatment mechanisms

Introduction

Neuroscientific advances in substance use research have significantly improved our understanding of biologically based processes involved in the development and maintenance of substance use disorders (SUDs) [1]. This work has resulted in the much-needed transition from outdated conceptualizations of substance use disorder (SUD) as a moral failing [2] to the contemporary view of this complex disorder as an array of physical, behavioral, and emotion-related changes that occur via the effects of substances on the brain as substance use progresses from nonproblematic to disordered use [3]. Despite technological advances in addiction science and our continually evolving understanding of the biological basis of SUD, the effectiveness of current psychosocial SUD treatment approaches is modest

✉Elizabeth D. Reese, elizabeth.reese@unc.edu.

at best. Approximately half of the individuals receiving SUD treatment relapse to use within 1 year of treatment completion [4, 5], with the majority doing so within the first 90 days [6]. Moreover, it is estimated that approximately one third of individuals receiving SUD treatment re-engage in services within 6 months of discharge [7]. As such, it is important to evaluate the extent to which psychosocial interventions for SUD are targeting neurobiological processes known to contribute to SUD and relapse to substance use. To this end, we provide a brief overview of current neurobiological conceptualizations of SUD followed by a review of evidence-based psychosocial interventions, with particular attention to research evaluating neurobiological mechanisms of treatment efficacy among adults. We conclude this review with recommendations for future research and implications for clinical practice.

Neurobiology of SUD

Integrating theoretical perspectives from experimental and social psychology, behavioral neuroscience, and psychiatry, addiction has been conceptualized as a cyclical stage-based process consisting of substance use anticipation and craving, bingeing, and withdrawal [8]. This cycle results in continued and repetitive use despite negative consequences and reductions in the rewarding effects of the substance over time. A wealth of research conducted on animal and human models reveals important neuroadaptive changes that occur via chronic substance administration; these maintain and exacerbate continued substance use and contribute to high rates of relapse [9•, 10]. Considering these findings, researchers have utilized a stage-based heuristic of the cycle of addiction to depict the neurobiological mechanisms involved in SUD.

Binge/Intoxication Stage

Substance use activates reward neurocircuitry including the ventral tegmental area (VTA) and ventral striatum via the release of specific neurotransmitters such as dopamine, serotonin, and opioid peptides [9•, 10]. This neurotransmitter release in mesocorticolimbic regions is associated with positive, hedonic, and rewarding subjective experiences particularly characteristic of early substance use [11], which reinforce the substance use experience and precipitate future binge episodes. In addition, neutral stimuli repeatedly paired with the rewarding effects of substance use can over time become cues that motivate compulsive drug seeking and taking through a process known as incentive salience. This occurs via substance-induced sensitization of neurotransmitter systems throughout mesocorticolimbic regions, particularly the extended amygdala [12, 13]. Both motivations for the rewarding effects of substances and activation of neural reward responses during exposure to conditioned stimuli are implicated in this stage of the addiction cycle, leading to compulsive drug seeking and taking.

Withdrawal/Negative Affect Stage

In response to reward system activation, several compensatory biological processes act to maintain homeostasis including hypothalamic–pituitary–adrenal axis and corticotropin releasing factor (CRF) release within the extended amygdala [12]. Over time, chronic activation of the reward system via binge/intoxication leads to compensatory allostatic

changes in neurocircuitry including desensitization of the reward system response, particularly to nondrug rewards, and hypersensitivity of the biological stress response system. Indeed, acute withdrawal from substance use is associated with decreases in striatal dopamine and serotonin transmission coupled with elevations in stress-related hormone release in the extended amygdala. These biochemical changes result in chronic negative mood states including irritability, dysphoria, and anxiety that are characteristic of substance withdrawal and are evident even into protracted abstinence [9•]. Alleviation of these negative affective experiences motivates continued drug seeking and taking through a negative reinforcement process as repeated use transitions to SUD. Moreover, activation of the stress response system in response to stressful life experiences can precipitate a return to substance use even after long-term abstinence has been achieved [12].

Preoccupation/Anticipation Stage

In addition to allostatic changes in both the reward and stress response systems, individuals with SUD exhibit deficits in working memory, attention, and delayed discounting via acute and persistent substance-induced changes in prefrontal cortical regions including the orbitofrontal, dorsolateral, and ventromedial cortices [14, 15]. These cognitive functions are necessary for continued engagement in goal-directed behavior (e.g., maintaining abstinence). Exposure to drug-related stimuli activates the biological craving system, namely, prefrontal and anterior cingulate neural regions, and dopamine release in the prefrontal cortex, striatum, and amygdala. Inhibitory control over cue-induced craving is necessary to facilitate abstinence from substance use, yet disruptions in GABAergic activity in prefrontal neurocircuitry results in self-regulatory deficits and excessive attentional allocation to salient drug cues, leading to the reinstatement of drug seeking and taking [9•].

Integrating Basic Science and Addiction Treatment Research Findings

The binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation stages capture important addiction-related changes in neurocircuitry and elucidate the complex, chronically relapsing nature of SUD whereby individuals become “stuck” in a vicious cycle of substance use binges, psychological and physiological withdrawal-related states, and subsequent craving and drug-seeking behavior. Moreover, the long-lasting neurobiological changes that occur in the context of this multiphase, cyclical process can increase the likelihood of relapse despite long-term abstinence [9•]. It follows that successful SUD treatment is associated with neurobiological changes that disrupt the cyclic nature of SUD. However, there is a clear disconnect between neurobiological conceptualizations of addiction and SUD treatment research and clinical practice. Indeed, commentary within the field of psychological research has highlighted the implementation of psychosocial treatment prior to the rigorous scientific investigation as a costly practice, thwarting the establishment of construct validity, mechanisms of behavior change, and situational or individual difference factors affecting when, how, and for whom such treatment may be effective [16]. This is especially true of treatment for SUD [17].

In an effort to provide a translational bridge between SUD basic science and psychological treatment research, we draw from this stage-based model of addiction as a framework to evaluate the extent to which psychosocial interventions for SUD target hypothesized neurobiological mechanisms both within and across stages of the addiction cycle. A summary of evidence-based psychosocial interventions for adults with SUD is described in the following sections, followed by a critique of the empirical evidence for treatment-related neurobiological mechanisms of action. Psychological and neurobiological evidence for additional mechanisms is then reviewed to generate hypotheses and propose the next steps for addiction research.

Psychosocial Treatments and Neurobiological Mechanisms

Motivational Interviewing (MI)

MI is a client-centered approach to therapy that aims to increase motivation for behavior change [18]. Therapists utilize open-ended questions, nonjudgmental and affirming language, and reflection and summarization to help clients explore and resolve ambivalence. MI is a well-supported intervention, particularly for alcohol and tobacco use [19], associated with increased rates of treatment entry and engagement and reductions in substance use and substance-related problems among adults [20–22]. Theoretical conceptualizations of MI posit multiple active ingredients including relational (therapist–client centered) and technical (therapist behavior) components influencing a central mechanism of action: client change talk [23, 24]. Increased evocation of client-generated statements in favor of change (i.e., change talk) as opposed to client speech consistent with maintaining status quo (i.e., sustain talk) is associated with positive substance use outcomes including overall consumption and negative substance-related consequences [25].

Researchers have posited a testable, translational model through which MI-related change talk predicts improvements in post-treatment substance use via alterations within and between interconnected neural networks involved in relational reasoning, emotional learning and memory, incentive reward, and executive control [26•]. The few empirical studies that have examined neurobiological mechanisms of MI partially support this model. Relevant findings include increased neural activation in prefrontal and temporal regions associated with executive control, self-reflection, and interoception during change talk and following alcohol cue exposure among those who received MI [27, 28], and decreased activation in reward-related regions during alcohol cue exposure following change-talk when compared to counterchange talk [26•]. These findings support the idea that MI change talk enhances clients' ability to integrate ideas of behavior change with decision-making processes about personally relevant behaviors (e.g., substance use), while decreasing the incentive salience of substance cues via inhibitory control of substance-related reward responses. However, limitations of these studies include small sample sizes, inclusion of only individuals with alcohol use problems, and post-treatment-only methodological designs, significantly constraining interpretation of these findings and generalizability to other SUDs. It remains unclear which neurobiological processes are most relevant to substance use outcomes in MI. Thus, neurobiological studies utilizing pre-/post-treatment designs, larger and more diverse samples, and those which test associations to post-treatment substance use are needed to

substantiate proposed translational models of MI for SUD (e.g., in the previous studies [26•, 29]).

Contingency Management (CM)

CM is an evidence-based SUD treatment that utilizes external reinforcers (e.g., prizes or vouchers) to incentivize meeting treatment goals, typically negative urine drug screens [30, 31]. CM has robust evidence of effectiveness for increasing treatment retention and post-treatment abstinence [32]; overall, it demonstrates the largest effect sizes among psychosocial SUD treatments [33]. CM is theorized to target reward-related processes, including delayed discounting deficits, in which individuals with chronic substance use demonstrate heightened bias in favor of immediate (versus delayed) rewards [34, 35]. By offering proximal nondrug rewards for behaviors typically associated with delayed reward (e.g., accomplishing treatment goals such as abstinence), CM may counteract cognitive biases which favor the immediate rewards of drug use. Indeed, there is some evidence that CM is associated with reduced delayed discounting in SUD and smoking samples [36, 37], though findings in this area are mixed [38]. Alternatively, CM has been posited to engage deliberative decision-making processes by offering concrete and immediate reinforcers rather than requiring individuals with SUD to draw on abstract and long-term goals when making short-term decisions regarding substance use. Thus, CM may improve the ability of individuals with SUD to attend to and choose nondrug rewards by promoting careful, deliberative decision-making while interrupting habitual and automatic drug selection behaviors [39].

Neurobiological studies are needed to substantiate the CM's mechanisms of action, but to date, no published empirical studies have examined neural mechanisms of effectiveness in CM among those with SUD. Given this gap, hypotheses regarding neurobiological mechanisms of CM must be drawn from basic science research. The delayed discounting literature supports the idea that individuals with SUD demonstrate increased activity among neural networks involved in decision making, attentional resource allocation, self-reflection, and reward valuation when making choices for large delayed versus small immediate rewards. This pattern of activity may reflect the increased effort needed to choose delayed over immediately available rewards for individuals with SUD, particularly in terms of weighing reward value, flexible attention switching between external stimuli and self-referential processing, and inhibiting impulsive motor responses for more proximal rewards [40]. Thus, CM may reduce the cognitive effort involved in drug refusal via functional improvements among and between neural networks involved in relevant aspects of delayed discounting. Given the extensive research base supporting the effectiveness of CM on SUD, there is a clear need to test the neurobiological basis of this treatment approach to understand its mechanisms of action.

Cognitive Behavioral Therapy (CBT) Treatments for Substance Use (CBT-SUD)

CBT-SUD is brief, structured psychotherapy empirically supported to increase short-term abstinence across SUD populations and treatment settings [33, 41, 42], including among individuals with comorbid psychopathology [43–45] and when administered in web-based formats [46, 47]. CBT-SUD aims to facilitate the reduction in substance use via

identification of substance use triggers, self-monitoring thoughts and behaviors related to substance use (e.g., functional analysis), planning substance-free activities, and coping skills training to manage withdrawal symptoms and craving [48]. Given the various treatment components comprising CBT-SUD, it is difficult to identify general mechanisms and active ingredients of treatment response. Moreover, several CBT-SUD components such as coping skills training (CST) and relapse prevention (RP) have been repackaged and evaluated as stand-alone treatments, while adaptations to current treatment components have also been developed and tested (e.g., mindfulness-based relapse prevention). As such, neural mechanisms of "full-package" CBT-SUD will first be discussed, followed by an individual review of each stand-alone treatment component given the substantial and/or growing empirical base for these treatments as individual psychosocial interventions with potential for unique neural mechanisms of action.

Mechanisms of full-package CBT-SUD are thought to include a dynamic interplay of the various treatment components, namely, the combination of increased cognitive control over cue-induced craving and decreased attentional bias toward and reward valuation of drug-related stimuli. As such, CBT-SUD is thought to restore aberrant functioning between top-down prefrontal and bottom-up subcortical neural circuits [49–51]. However, few studies have empirically tested the effect of full-package CBT on these neurobiological mechanisms. While 2 months of CBT-SUD for tobacco use is associated with decreased resting-state metabolism in the default mode network (DMN), a set of neural regions whose activity is generally diminished during goal-oriented tasks, the specific treatment components associated with that change were not tested [52]. Given the role of the DMN in self-awareness and processing of internal stimuli, it has been posited that heightened DMN activity in SUD could be indicative of increased sensitivity to internal states such as stress and negative affect, leading to ongoing substance use [53]. Thus, a test of the extent to which decreases in DMN via CBT-SUD reflect increased engagement in goal-directed behavior or decreased attentional processing of negative internal states is needed. Alternatively, an integrative treatment study testing the combination of CBT-SUD with contingency management (CM) among individuals with cocaine use disorder reported that increased engagement (i.e., higher treatment attendance) with CBT-SUD versus CM was associated with activation reductions in neural regions associated with cognitive flexibility and decision making (precentral gyrus, inferior parietal lobule, and middle/medial gyrus) during a cognitive control task [54•]. Such findings suggest that, in contrast to CM targeting reward-based processes such as delay discounting, CBT-SUD may have the unique effect of increasing cognitive control by decreasing the cognitive effort needed to guide decision making. Given the limited empirical research regarding neurobiological mechanisms of CBT-SUD, additional studies, particularly those assessing the effect of treatment components on neurobiological processes pre- and post-treatment, including SUD treatment response, are needed to clarify specific mechanisms of action and replicate current findings.

Coping Skills Training (CST): The CST component of CBT-SUD has been investigated as a stand-alone intervention [55] supported by research that identified this component as the primary mediator of SUD treatment outcomes among those receiving CBT-SUD [56]. CST

is associated with reductions in relapse rates, fewer substance use days, and shorter duration of binge episodes [57–59] and includes skills training across domains including enhancing social communication, adaptively responding to substance use urges, managing cognition and mood, and preventing relapse following treatment completion [48, 58].

CST is thought to enhance an individual's ability to cope with craving and high-risk situations thereby decreasing relapse likelihood [50, 55]. Given that no studies to date have investigated the neurobiological basis of these mechanisms of CST, hypotheses must be drawn from empirical work outside of the treatment context. Studies on neural indices of cognitive control over cue-induced craving and affective distress among those with SUD reveal increased activation in prefrontal and medial neural regions associated with emotion regulation, decision making, and attentional control, concurrent with decreased activation in visual- and motor-related regions and subcortical reward and limbic regions [60–64]. Given aberrant activation within and between such regions and related reductions in dopamine receptor function among individuals with SUD [65], it may be that cognitive and emotional coping strategies taught through CST improve neural functioning through increasing prefrontal top-down inhibition of subcortical neural function associated with maladaptive, learned behavioral responses (e.g., substance use) to stress- and substance-related cues. Moreover, decreased activation in subcortical affective-processing regions during cognitive regulation may reflect diminished attention toward the processing of negative affect/withdrawal states, thus increasing an individuals' ability to engage in alternative, substance-free coping strategies. However, empirical studies are needed to test the effect of CST on these specific neurobiological processes and delineate specific mechanisms of action. Additionally, given the overlap in the hypothesized neural mechanisms for CST and full-package CBT, it will be important to evaluate the extent to which various components of CBT-SUD, above and beyond CST, elicit additional treatment-related improvements in neurobiological function and treatment response.

Relapse Prevention (RP): RP is a widely used treatment approach that integrates CST and cognitive therapy including assessment of potentially high-risk situations (e.g., internal experiences of negative affect, substance withdrawal, environmental stressors) [66–68], challenging substance use expectations and providing psychoeducation about substance use relapse to increase individuals' self-efficacy to adaptively respond to risky situations [69]. RP has been widely studied and implemented [70, 71] and is effective at decreasing the probability of relapse while increasing psychosocial functioning post-treatment across substances, treatment modalities, and settings relative to no-treatment control conditions [72–76].

RP is hypothesized to loosen tightly formed associations between stimulus (e.g., negative affect) and response (e.g., substance use), driving reinforcement processes of substance use relapse [71] by challenging outcome expectancies around substance use that precipitate relapse (i.e., "This drug will make me feel better") and increasing self-efficacy in navigating high-risk situations such as experiencing negative affective states [70]. Such hypotheses are supported by empirical work demonstrating outcome expectancies as a mediator of the relationship between negative affect and substance use [77] and a negative association between self-efficacy and negative affective states [78]. To date, no study has examined

the neurobiological changes associated with RP among individuals with SUD. One avenue for future work is to examine the neural correlates of outcome expectancies in the context of RP. Given that cognitive restructuring techniques target substance use outcome expectancies, RP may be modulating function within and among prefrontal neural regions involved in higher order executive control processes that promote cognitive flexibility, inhibition, and working memory updating needed to engage in cognitive restructuring [79, 80]. Alterations in outcome expectancies associated with substance use may also capture changes in anticipatory reward processing associated with RP treatment and facilitated by neurobiological changes in reward-related neurocircuitry in response to substance-related cues. Task-based measurement of neural response to RP is one avenue to test such hypotheses.

Mindfulness-Based Relapse Prevention (MBRP)

MBRP combines formal meditation practices with standard RP to target an individual's ability to respond adaptively to negative affect [81–83]. MBRP aims to identify and grow an individual's awareness of internal and external substance use triggers and practice exposure to aversive affective experiences while resisting the urge to escape or avoid the experience [83]. Individuals learn to experience uncomfortable triggers with detachment from their thoughts and feelings without negative judgment (i.e., guilt, shame) or reaction (i.e., substance use) [81]. MBRP is effective in reducing days of substance use [84–86], relapse frequency [87], craving [84, 88], negative affect [88, 89], and perceived stress [85]. MBRP has additionally been tested across SUD sample populations [81, 86, 87, 89–92], treatment modalities [81, 90, 91], and with various target outcomes [82, 90, 93].

Posited mechanisms of MBRP include the skill of mindfulness itself, which in the context of MBRP is defined as awareness and acceptance of thoughts and feelings, without judgment, as a coping strategy during high-risk relapse situations. Mindfulness is thought to create space between a stimulus (e.g., experiencing difficult emotions) and a response (e.g., substance use), allowing individuals to react adaptively rather than impulsively, thereby decreasing relapse likelihood [82, 94, 95•]. Indeed, MBRP has been shown to reduce craving and reactivity to substance cues (see Bowen et al. [81] for review) and weaken the relationship between self-reported depression and self-reported craving [96].

While neurobiological mechanisms underlying MBRP have not been tested directly, related work provides insight regarding possible mechanisms. Mindfulness training, a key component of MBRP, has been shown to significantly attenuate neural activity in regions implicated in negative affect processing and salience detection during stress exposure [97] and has been linked to increased resting-state connectivity among self-control-related prefrontal cortical regions [98] among individuals with nicotine dependence. In turn, these neural indices predict significant reductions in post-intervention substance use [97, 98]. Thus, mindfulness components of MBRP may target subjective reactivity to stress and substance-related cues by allocating attentional resources toward top-down regulation of internally relevant stimuli and away from the midline and limbic regions involved in the processing of stressful stimuli. This dual process in the face of negative affective states may reduce the likelihood of substance use to alleviate distress. However, what remains

untested is the degree to which mindfulness components both increase prefrontal functioning and decrease limbic reactivity to stress/negative affect. Moreover, expanding empirical work beyond adult smokers, including the effect of MBRP on hypothesized mechanisms (e.g., cue reactivity), and in comparison to standard RP, will enable further isolation of the neurobiological changes specific to MBRP.

Cognitive Bias Modification (CBM)

Cognitive bias modification (CBM) aims to reduce biases in attention and actions toward activities related to substance use through repeated computerized training on cognitive tasks. Typically, CBM involves training to approach a nondrug cue and avoid a drug cue with a motor response such as the movement of a joystick. Given the role of top-down neural circuits involved in inhibitory control of behavioral urges [99], targeting these circuits by cognitive training or remediation is a mechanism-based approach to the treatment of SUDs. However, findings regarding the efficacy of CBM are inconclusive, with a recent meta-analysis of individuals with alcohol and/or nicotine use disorders demonstrating a moderate effect of CBM on the cognitive bias but no effect on substance use or craving [100].

Given this seemingly limited link between the intervention and desired outcome, querying the underlying neurobiological substrate or “target” of such interventions may shed light on how such treatments can be improved to gain clinical efficacy. Relatively few studies of this nature are reported in the literature [101•], though preliminary work demonstrates reductions in prefrontal cortical activation associated with alcohol approach bias [102] and decreased cue-evoked limbic activation among individuals with alcohol use disorder receiving CBM compared to control conditions [103]. These neural regions represent the primary nodes of a network involved in the detection and processing of relevant internal and external stimuli, the salience network. A systematic review of task-related neuroimaging studies found increased activation of the salience network for drug cues versus decreased activation of this same network for nondrug cues among individuals with SUD [104]. Thus, targeting this network during drug-cue exposure via CBM could represent the substrate for the desired reduction in approach bias toward drug cues. Indeed, both studies (data from the same trial) report an association between the effect of CBM on the neural target and substance use craving [102]. Yet, it remains unclear if these task-driven activation signatures associated with CBM map onto reduced substance use.

Future Directions

A lack of empirical evidence investigating the neurobiological basis of treatment mechanisms across common psychosocial interventions for SUD highlights the large translational gap that remains between basic addiction science and psychosocial intervention research. Neurobiological mechanisms have been investigated in a limited number of studies for only three of the commonly utilized interventions for SUD included in this review (MI, CBT-SUD, and CBM). However, significant limitations impair the interpretation and generalizability of empirical findings, including small and restrictive sample sizes, post-

treatment-only methodological designs, and failure to assess relationships between neural indices and treatment response.

Empirical evaluation of treatment-related neurobiological mechanisms has thus far been limited to only a fraction of the neurobiological mechanisms known to underlie SUD. Indeed, research regarding MI and CBM investigated neurobiological indices of cognitive control in the context of substance cue exposure [26•, 28], while an executive function task was utilized to investigate cognitive control mechanisms associated with CBT-SUD [54•]. Together, these three treatments appear to target prefrontal inhibitory control processes relevant to the preoccupation/anticipation stage of SUD. As such, it remains unclear the extent to which evidence-based treatments for SUD target equally important aspects of this disorder relevant to other stages of the addiction cycle, namely, those relevant to withdrawal-induced relapse to substance use (i.e., withdrawal/negative affect) and reward-related drug-seeking behavior (e.g., binge/intoxication). We hope that the inclusion of our own hypotheses will provide a starting point for empirical investigations in future research, as this work is needed to improve the specificity and effectiveness of common treatments for SUD.

Equally important is the need to develop and test mechanism-specific interventions for SUD that target aspects of this disorder that are not adequately attended to by today's SUD treatment approaches. Such work is ongoing for several interventions that are not yet widely utilized in standard SUD treatment but are worth discussing given their strong empirical and theoretical support among SUD populations. For example, behavioral activation for substance use (BA-SUD) is an efficacious behavioral treatment [105–107] that targets the reward deficits and loss of drug-free positive reinforcement characteristic of SUD by helping patients re-engage in naturally rewarding activities, thus substituting drug-related reinforcement with substance-free environmental reinforcement [108]. Accordingly, BA-SUD is hypothesized to reverse neuroadaptations in the reward circuitry that result from repeated drug use while increasing the incentive salience of nondrug rewards [109–112]. Such hypotheses are supported by neurobiological treatment studies of BA among individuals with depressive symptoms, which find that BA helps strengthen anticipation of rewards via normalization of neural functioning in reward-related regions following treatment (as demonstrated by functional changes in reward-associated brain regions) [113] and increases tolerance for negative emotional experiences via increased activation in neural regions supporting cognitive control in affective contexts [114, 115]. BA also disrupts the coupling of neural regions involved in attention, internally focused processing, and rumination, facilitating improved attention to positive reinforcers in the external environment [116]. Given reward deficits observed in both depression and SUD [117], BA-SUD likely works to repair incentive salience of nondrug rewards in a similar fashion. Answers to these questions will be provided by data from a recently completed trial that compared the effect of BA-SUD to treatment as usual during intensive outpatient substance use treatment on neural indicators of reward response and post-treatment substance use (NCT02707887).

Another SUD mechanism prompting targeted intervention is impaired distress tolerance (DT), or the inability to persist in goal-directed action while experiencing affective distress,

which has been associated with poorer rates of substance use treatment retention and post-treatment substance use (e.g., in the previous studies [118–121]). Neurobiological research on DT among individuals with SUD reveals stress-induced activation in and connectivity among neural regions associated with inhibitory control, emotional salience detection, and goal-directed decision making predict higher DT among individuals with SUD [122]. Moreover, decreased resting-state connectivity within prefrontal executive control regions and increased connectivity between regions associated with the processing of internally relevant stimuli (e.g., withdrawal symptoms) predict impairments in DT [123]. Such work highlights impairments in neural network function that may underlie deficits in DT in SUD and provide a clear treatment target relevant to the withdrawal/negative affect stage of addiction (i.e., stress-induced relapse). While interventions have been developed to target low DT in SUD [124–126], empirical studies are needed to test the association between DT treatment efficacy and neurobiological mechanisms of action.

Recommendations for Clinical Practice

Although translational research of psychosocial interventions for SUD is in its infancy, addiction neuroscience research has far-reaching implications for clinical practice in the here and now. SUD treatment recommendations have increasingly moved toward a personalized or individualized approach, which rests on the assumption that patients' individual differences matter in the selection of and response to treatment, supporting the practice of providers tailoring treatments to patient needs based on sound case conceptualization [127, 128]. Given the complexity of SUDs, we emphasize the need for a thorough assessment of underlying factors that maintain SUD and contribute relapse risk to each patient's clinical presentation prior to treatment implementation. Sound assessment practices will increase the likelihood that the interventions utilized are appropriately targeting processes considered to be most relevant for each individual patient. For example, after a pre-treatment assessment, a provider may discern that CBT-SUD or MBRP may be most appropriate for a patient whose difficulty abstaining from substance use is largely in response to daily life stress, while determining that CM may be clinically indicated for a patient with deficits in delayed discounting of substance-free rewards. This shift from one-size-fits-all treatment to personalized medicine will be a key factor in improving treatment outcomes for individuals with SUD [129].

Combined Treatment Approaches

Medication and/or Psychosocial Interventions: Neurobiological evidence supports the combining or integrating of multiple, empirically supported interventions for SUD. Indeed, a recent meta-analytic review reported that best practices for SUDs include combined pharmacotherapy and psychosocial interventions (namely, CBT, CM, and motivational enhancement therapy) instead of either pharmacotherapy or psychosocial treatment alone [130]. For example, pharmacotherapy treatments (e.g., methadone maintenance) for opioid use disorder (OUD) are often paired with psychosocial interventions in a combination known as medication-assessed therapy (MAT) in order to interrupt psychological and physiological symptoms of substance withdrawal and thus both increase an individual's ability to engage (and remain) in treatment while decreasing the

likelihood of substance use relapse [131]. Moreover, combining psychosocial interventions such as CBT and CM demonstrates higher effect sizes for treatment outcomes than either treatment alone [33].

Brain Stimulation: There is a surge in research on the therapeutic potential of noninvasive brain stimulation (NIBS) strategies to target neural network mechanisms underlying psychological disorders. For example, targeting of alpha oscillations, brain network oscillations implicated in the controlled inactivation of cortical areas [132], with transcranial alternating current stimulation (tACS), decreased perseverative errors upon change reward contingencies in a stimulus–response paradigm as a function of the duration of SUD [133] and improved inhibitory control among individuals in a community-based SUD treatment program [134]. Moreover, integration of NIBS with existing SUD treatments is a promising area of current research [135, 136], supported by the argument for a synergistic effect of integrated NIBS and psychosocial interventions on complex SUD symptom profiles [137]. However, not all integrative treatments will be effective: a recent study tested MBRP in combination with tDCS, yet tDCS yielded no additive effects of enhancing MBRP [138]. Taken together, the conditions necessary for such integrative treatments to produce the best treatment outcomes remain unclear (i.e., stimulation frequency, dose, timing). For those that are found effective, it is critical that researchers identify the precise mechanisms at play between the integrated treatment approaches and neurobiological processes conceptualized to be highly relevant to relapse risk for a given individual.

SMART Designs for Individualized Treatment: Adaptive treatments respond to patient characteristics and outcomes (i.e., patient response, adherence) collected during the course of treatment that then inform decision points and recommendations from the clinician along the way, providing a systematic approach to meeting patients where they are in the treatment process [139, 140]. The sequential multiple assignment randomized trial (SMART) design is a research methodology aimed at developing and refining existing treatments in order to develop effective adaptive treatments [140]. At multiple selected critical decision points, patients' treatment response is evaluated, and patients are then re-randomized to an adapted version of their original condition (e.g., type of primary treatment, dose of treatment, secondary treatment with primary) to identify effective treatment courses [140, 141]. Research has begun to use SMART designs to advance treatment for cocaine use disorder [142] and heavy drinking and related problems in college students [143]. SMART designs could be particularly useful for identifying adaptive treatments across the addiction cycle. Given the various psychological and physiological processes posited to change as individuals progress through the stages of addiction, SMART designs could provide the nuance and sophistication needed to test how adaptations impact neural and behavioral treatment responses.

Conclusion

Despite the many known neurobiological processes underlying substance use disorder, there is a dearth of research on such mechanisms of action for commonly utilized, evidence-based psychosocial interventions. Thus, there is much work needed to bridge the translational gap between neuroscience and treatment research for SUD, in hopes

of improving today's unsatisfactory treatment outcomes for SUD. Despite translational gaps, addiction neuroscience has highly relevant implications for SUD treatment, including providing support for the use of individualized treatment protocols based on sound assessment and case conceptualization, the usefulness of integrated treatment approaches given relevant neurobiological processes at play for a given individual, and the need for adaptive intervention techniques that target dynamically shifting processes across the stages of the addiction cycle.

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