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Neuroscience-Informed Classification of Prevention Interventions in Substance Use Disorders: An RDoC-based Approach

Running Title: Addiction Prevention Interventions

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Conflict of Interest

The authors have reported no conflict of interest.

Abstract:

Neuroscience has contributed to uncover the mechanisms underpinning substance use disorders (SUD). The next frontier is to leverage these mechanisms as active ingredients to create more effective interventions for SUD. Recent large-scale cohort studies are generating multiple levels of neuroscience-based information with potential to inform the development and refinement of future preventive strategies. However, there is still no available well-recognized frameworks to guide the integration of these complex datasets into prevention trial protocols. The Research Domain Criteria (RDoC) provides a neuroscience-based multi-system framework that is well suited to facilitate translation of neurobiological mechanisms into behavioural domains amenable to preventative interventions. We propose a novel RDoC-based framework for prevention science that organizes and advances the integration of technologies and findings from neuroscience into the refinement of current and construction of future preventive and early interventions. This neuroscience-informed framework categorizes addiction risk factors within the dysfunction of the five major RDoC domains (*Negative Valence Systems, Positive Valence Systems, Cognitive Systems, Arousal and Regulatory Systems, and Social Processes*). We adapted the framework for the existing preventive interventions and categorized their components using RDoC domains. From a systematic review of randomized controlled trials using a person-centered drug/alcohol preventive approach for adolescents (13-18 years), we identified 101 trials on 22 unique preventive interventions. We categorized them within this framework based on their potential target(s). By using this neuroscience-informed framework, distinct neurocognitive trajectories which have been recognized as precursors or risk factors for SUDs, can be targeted, and more importantly, the change processes can be evaluated to inform causal hypotheses. This framework can also inform individualized assessment, intervention development and outcome measurement in preventive interventions.

Keywords: Substance use disorders, Research Domain Criteria, Prevention, Neuroscience, Adolescence, Interventions

INTRODUCTION

Substance use disorder (SUD) is multifactorial in etiology and numerous risk factors have been implicated in its formation and progression, particularly during adolescence. At the level of prevention, several approaches have been proposed to target some of these factors through educational and socio-emotional skills training programs, starting from early childhood (e.g., Promoting Alternative Thinking Strategies; PATHS) (Riggs et al., 2006). Programs that are largely focused on adolescents in school settings tend to harness social and behavioral theoretical models such as the social influence model, the social learning theory, and the theory of planned behavior (Kempf et al, 2017).

These programs are mainly embedded within the educational structure and include content to increase adolescents' awareness of substance use related harms and various social influences, to correct inaccurate adolescents' perception regarding the prevalence and popularity of SUD, and to teach life skills (e.g., problem-solving, decision-making skills) (Griffin & Botvin, 2010). Building from these models, programs such as PREVENTURE (Conrad, 2016), CLIMATE schools (now called OurFutures) (Slade et al., 2021), Life Skills Training (LST) (Botvin et al., 1990), and

Unplugged (Faggiano et al., 2010) have been developed, implemented and found to have an acceptable degree of efficacy (Tremblay et al., 2020).

Over the past few decades, however, our understanding of SUD has been reshaped by the evidence from neuroscience suggesting SUD can be characterized by certain functional indicators that transcend traditional diagnostic boundaries and act as pre-diagnostic markers that could be targeted through preventive approaches (Debenham et al., 2021; Fishbein et al., 2016). Developmental neuroscience informs us that during adolescence, the development of different brain structures occurs at various rates. The structures (i.e., limbic regions) that are implicated in emotional processes undergo early maturation, while those involved in executive control (i.e., prefrontal cortex) have protracted maturation (Rezapour et al., 2021). This neuroscience-informed understanding introduces adolescence as a distinct developmental stage which offers multiple opportunities to intervene on the early precursors of substance use behaviors. For example, a new prevention approach has emerged from the neuroscience literature which involves prophylactically intervening around psychological risk factors for early onset psychopathology and substance use and has been shown to have beneficial effects on a broader set of outcomes compared to traditional social learning-based prevention programs (Newton et al., 2021).

Additionally, numerous studies have found that variation in several neuropsychological functions plays a role in different stages of SUD. Current neuroscience-based models (Koob & Volkow, 2016; Yücel et al., 2019) conceptualize SUD as neuroadaptive / neurodevelopmental processes that happen at two different time scales: (1) a recurring cycle of binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation (craving) stages; and (2), a protracted “allostasis” that progressively alters neurotransmitter and stress responses, resulting in neuroplastic changes in brain reward, stress, and executive function systems. Identifying the neurocognitive domains implicated in each stage has considerable potential to help practitioners and clinicians improve their insight into SUD and apply that knowledge to more effectively treat and/or prevent SUD (Ekhtiari et al., 2021; Meredith et al., 2021; Debenham et al., 2020). Additional conceptualizations of SUD have focused on neurodevelopmental processes (Rose et al., 2019; Conrod and Nikolaou, 2016) to highlight the importance of individual differences and contextual factors such as trauma (Laroque et al., 2022), in moderating the above processes in formation of SUD (Morin et al., 2018; Afzali et al., 2017; 2021). However, a comprehensive neuroscience-based conceptual framework that could inform underlying neurobiological mechanisms in SUD development is still lacking to guide effective design of preventive interventions.

In 2010, the National Institute on Mental Health (NIMH) launched the Research Domain Criteria (RDoC) as part of its strategic plan to provide a research framework for studying psychiatric disorders, including SUDs (Insel et al., 2010). Grounded in neuroscience, the RDoC covers five domains: Negative Valence Systems, Positive Valence Systems, Cognitive Systems, Systems for Social Processes, and Arousal and Regulatory Systems. This framework was subsequently mapped into the clinical context and multiple variants have been adapted (Figure 1a). For example, the National Institute on Alcohol Abuse and Alcoholism (NIAAA) proposed the *Alcohol and Addiction Research Domain Criteria (AARDoC)*, indexing three research domains relevant to SUD: Negative Emotionality (mapping on NIMH’s negative valence system), Incentive Salience (mapping on NIMH’s positive valence system), and Executive Function (mapping on NIMH’s

cognitive system) (Witkiewitz et al., 2019) (Figure 1b). Subsequently, the *Addictions Neuroclinical Assessment (ANA)* framework was proposed to probe these domains by combining clinical, personality, genetic, neurocognitive, and neuroimaging approaches (Kwako et al., 2016). The three ANA domains are: (1) *Executive Function (including planning, working memory, attention, response inhibition, decision-making, set-shifting, and cognitive flexibility)*, associated with reduced prefrontal cortex (PFC)-mediated top-down impulse control, characterizing the preoccupation/anticipation (‘craving’) stage of the addiction cycle; (2) *Incentive Salience*, associated with phasic dopaminergic activation in the basal ganglia and the binge-intoxication stage; and (3) *Negative Emotionality (including dysphoria, anhedonia, alexithymia, and anxiety)*, associated with the engagement of brain stress systems and the withdrawal/negative affect stage of addiction. NIDA recently expanded these ANA domains by adding two additional domains relevant to SUD (Keyser-Marcus et al., 2021; Ramey & Regier, 2019): *social cognition* (metacognition, theory of mind) and *precognition* (interoception, implicit processes, sleep), which map on NIMH’s RDoC domains of Social Processes and Arousal and Regulatory Systems, respectively (Figure 1c,d). The original RDoC framework has been studied more extensively than its variants and a recent Delphi study conducted by a group of addiction experts revealed a high degree of consensus on the most important components for SUD, identifying two RDoC domains (Positive Valence System and Cognitive System) and one expert-initiated construct (Compulsivity) as primary (Yücel et al., 2019).

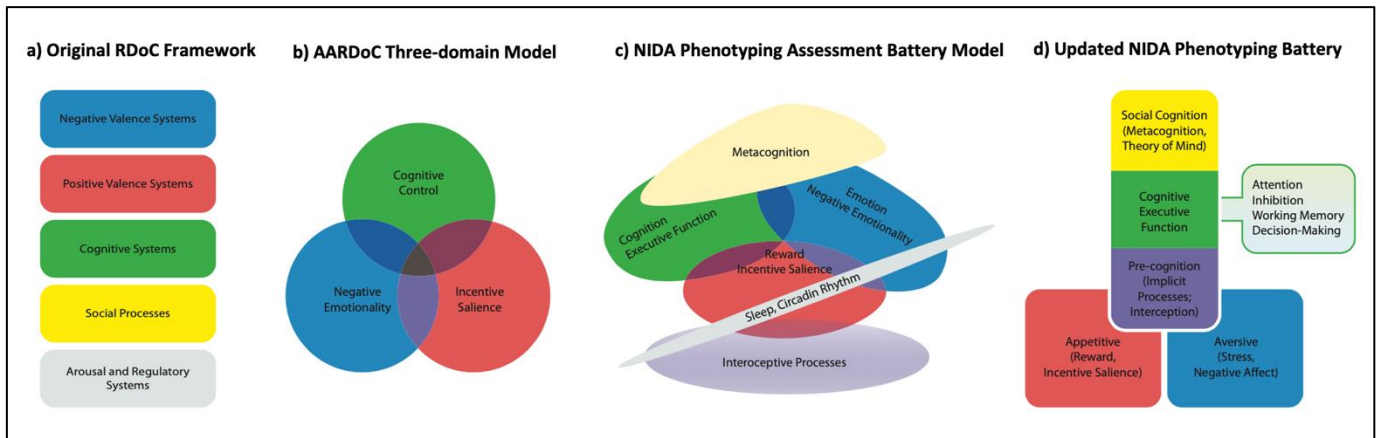


Figure 1 – Addiction-related neurofunctional domains a) The original RDoC framework includes five domains of Negative Valence System, Positive Valence System, Cognitive System, Social Processes, and Arousal and Regulatory Systems. b) The Alcohol and Addiction RDoC (AARDoC) model and the Addictions Neuroclinical Assessments (ANA) battery to assess the three-domain model, where neurofunctional abnormalities in SUDs are indexed by the three domains of Negative Emotionality, Incentive Salience, and Executive Function. c) The NIDA Phenotyping Assessment Battery (PhAB) that is designed to be administered as a set of tools to characterize “core” addiction-relevant domains in a harmonized way, for instance, across NIDA clinical trials. Interoception, Metacognition, and Sleep/circadian rhythm domains have been added to the three-domain model using a Delphi method. d) The updated NIDA Phenotyping battery is a three transdiagnostic research domains with relevance for addiction: Appetitive motivational states (including the RDoC domain of incentive salience), Aversive motivational states (including the RDoC domain of negative emotionality), and the RDoC domain of Cognitive Executive function.

Thus far, the interest in using neuroscience-informed models has been mainly in the context of diagnosis and targeted treatment of SUD, while there is no published framework based on the RDoC for SUD prevention. To address this gap, the goal of this paper is to introduce an RDoC-based framework for SUD prevention. We propose a neuroscience-based model that provides a framework to identify potential precursors or risk factors for SUD and delineate mechanisms that underlie effects of preventive interventions designed to target these factors. Based on this

framework, we conducted a systematic review of school-based SUD prevention trials to identify available evidence-based interventions. The neuroscience-informed RDoC approach is then used to classify these SUD preventive interventions and their components based on their targeted RDoC domains. Such classification would increase understanding about the key elements and neural mediators of different prevention programs and may enable their further refinement and optimization by identifying their most potent components. This approach, in turn, may indicate a potential for interfacing them with other intervention modalities targeting same domains and personalizing them to individual or subtype needs. Therefore, by using RDoC framework, preventive interventions could be developed not only to benefit the general population (universal prevention), but also to affect adolescents who are at risk in each domain of RDoC (selective prevention).

RISK FACTORS FOR SUBSTANCE USE DISORDERS THROUGH THE LENSE OF RDoC

In this section, we describe the main RDoC domains that are potentially involved in SUD development and discuss how their dysfunction could increase SUD vulnerability, especially in adolescents. Figure 2 displays a model that illustrates how these domains could be considered as precursors to or risk factors for SUD development due to their non-adaptive functions in response to various stressors (a), and vice versa how they could be adjusted to protect adolescents against these stressors (b).

Although each domain seems to be independent of the others, the previous studies reveal functional interactions between them through highly integrated neural mechanisms (Ford et al., 2014). For example, affective valence (including negative and positive) could interact with cognitive control from the domain of the cognitive system or interoceptive signals from the domain of arousal and regulatory systems (Hadley et al., 2019).

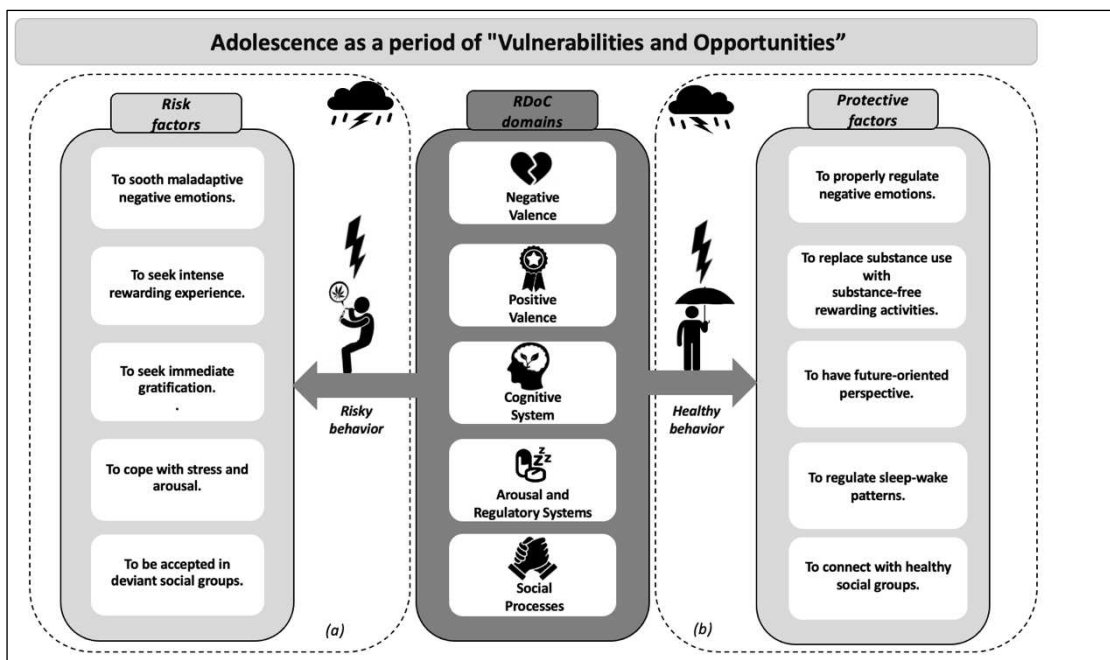


Figure 2: The five major RDoC domains could act as, (a) risk factors, or (b) protective factors for substance use disorders during adolescence.

Negative Valence Systems (NVS)

NVS is expressed in negative emotional responses (including fear, anxiety, avoidance, frustrative non-reward, deprivation of motivationally significant possession) to a particular environmental event (acute threat, ambiguous harm, prolonged threat, withdrawal of reward, loss) (Watson et al., 2017) and the brain regions that have most consistently been associated with these mental processes are the amygdala and anterior insular cortex (Büchel, 2000; Wu et al., 2014). The link between NVS and the development of SUD could be explained by the ability to regulate negative emotion in terms of both intensity and valence (Guinle & Sinha, 2020; Ohannessian & Hesselbrock, 2008).

Subjective distress can be observed as negative emotions in response to potentially aversive stimuli which then place an individual at risk for substance-seeking behaviors and craving (Zambrano-Vazquez et al., 2017). In fact, individuals who engage in substance misuse commonly exhibit maladaptive coping strategies for distress (e.g., anxiety) and often seek out the rewarding properties of abusable substances to reduce negative affect (Brooks et al., 2017).

Increased risk of SUD during adolescence is likely due to in part to vulnerability for various emotionally laden challenges (e.g., romantic break-up, academic pressure, peer rejection) that increase emotional reactivity (Houck, Barker, et al., 2016; Thatcher & Clark, 2008). Limited capacity to regulate negative emotions during adolescence as a function of less connectivity between the PFC and affective limbic structures than in adulthood may result in maladaptive external regulatory strategies that place adolescents at heightened risk for SUD (Tottenham & Galvan, 2016).

Positive Valence Systems (PVS)

The PVS include processes involved in the valuation, responding, maintaining, and learning of rewarding experiences (Swope et al., 2020). This domain is divided into several constructs, including approach motivation (motivation to obtain reward), initial reward responsiveness (hedonic responses during consummation of rewards), sustained reward responsiveness (duration of hedonic response following obtaining rewards), reward learning (linking between information about stimulus and hedonic response), and habit formation (Olino, 2016). These constructs engage a common set of brain regions in the dopaminergic system that are related to SUDs, including the ventral striatum (nucleus accumbens), orbitofrontal cortex (OFC), and anterior cingulate cortex (ACC) (Richards et al., 2013). Additional regions such as the thalamus, amygdala, insula, and inferior frontal gyrus (IFG) have also been implicated in reward processing, which often contributes to substance-seeking behaviors attributed to altered reward sensitivities (Balodis & Potenza, 2015; Silverman et al., 2015).

A potential link between PVS and SUD development in adolescents has been suggested in terms of altered sensitivity to rewarding, novel, and exciting stimuli that affects decision making (Balogh et al., 2013; Walker et al., 2017). Across development, and specifically during adolescence, increased reward-seeking behaviors, either as a result of hypo- (based on the reward deficiency hypothesis) (Cservenka et al., 2013) or hyper-responsivity of the reward system, increase the likelihood of SUD (Galván, 2010; Hardin & Ernst, 2009). Based on such explanations, adolescents place a higher value on substance use and so expect greater pleasure derived from substance use

(Peeters et al., 2017). Inability to regulate responsiveness to rewards and positive emotions is a potential link between PVS and SUD initiation (Castellanos-Ryan et al., 2014; 2016).

Cognitive System (CS)

The domain of CS encompasses a broad range of cognitive processes, including perception, attention, working memory, declarative memory, cognitive control, and language, to select, recognize, and process information to be used in goal-directed actions and future decision-making (Glenn et al., 2018). Adolescence is characterized by asynchronous development of frontostriatal circuitry, with an impulsive striatal and affective amygdala system maturing early and being disproportionately active relative to later-maturing top-down cognitive control systems mediated by the prefrontal cortex (PFC) (Blakemore & Robbins, 2012; Casey et al., 2005; Galvan, 2010). The temporal variation of CS maturation enhance the influence of reward and emotional systems and contributes to impulsive and disinhibited behaviors, including substance use (Rose et al., 2019; Wetherill & Tapert, 2013). Several studies on adolescents indicate a link between poor executive function (i.e., inhibition, working memory) and early initiation of alcohol and other substance use (Gray & Squeglia, 2018), in line with theories such as the Reinforcer Pathology Theory (RPT) (Bickel & Athamneh, 2020). The RPT states that the value of immediate, intense, and certain addictive reinforcers (i.e., substance) would increase, whereas the value of the delayed negative outcomes and prosocial reinforcers (which are less intense and reliable) would decrease as a result of one's short temporal window (the temporal distance over which future outcomes are considered and incorporated into present decisions and behaviors). Although such cognitive weaknesses are mainly attributed to the delayed maturation of cognitive control brain structures in adolescence, some studies support the role of family history of SUD in alcohol and early onset substance use initiation in offspring due to weaker neural connectivity (Squeglia & Cservenka, 2017; Morin et al., 2018). Overall, poor performance of the CS reduces the regulatory capacity to control socioemotional functioning and increases SUD vulnerability.

Arousal and Regulatory Systems (ARS)

The ARS construct reflects responsiveness to internal and external stimuli, and is associated with arousal, circadian rhythms, and sleep-wakefulness (Koudys et al., 2019). The ARS also plays an important role in maintaining bodily homeostasis by using body-related information (interoceptive signals) to predict future body states and select proper approach or avoidance action (Victor et al., 2018). The hypothalamic-thalamic circuitry mainly corresponds to the regulatory systems. Also, neurocircuits related to sleep and arousal have reciprocal connections from the amygdala to other limbic structures such as the thalamus and hypothalamus, as well as to cortical structures (Henje Blom et al., 2014).

In the early course of adolescence, dysregulated stress responses (resulting from biased cognitive processes, a history of trauma, or genetic factors), combined with altered hypothalamic-pituitary-adrenal axis (HPA) axis and sympathetic nervous system responses, increases the risk of SUD development (al'Absi, 2018; Chaplin et al., 2018), particularly the misuse of substances with arousal and fear-reducing properties (Stewart, et al., 2021). In addition to the role of sleep deprivation as a stressor that triggers stress reactivity, there are several studies supporting the relationship between sleep and circadian changes and substance use in adolescents (Logan et al., 2018). Sleep problems, including circadian misalignment, sleep disturbance, and sleep loss, could affect reward systems in a way that young people are more prone toward sensation-seeking and

impulsive behaviors, and thus increase the risk of substance use and risky behaviors (Spear, 2011). The negative effect of sleep problems on self-regulatory functions has been previously reported in both laboratory and field studies in adolescents (Baum et al., 2014; Louca & Short, 2014).

Social Processes (SP)

Broadly defined, SP comprises processes and knowledge that mediate the perception and understanding of the self and others, as well as the responses that are generated within a social context (reception and production of facial and non-facial communication) (Koudys et al., 2019). A recent meta-analysis used the activation likelihood estimate method and reported that the medial prefrontal cortex (mPFC), anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), temporoparietal junction (TPJ), bilateral insula, amygdala, fusiform gyrus, precuneus, and thalamus are the neural underpinnings of the SP domain (Lobo et al., 2022).

To explain how this system contributes to SUD development during adolescence, we refer to the role of metacognition (self-knowledge) in the context of within-person characteristics (e.g., inaccurate emotional awareness, self-efficacy) and the role of affiliation and attachment in the context of between-person interactions (e.g., normative misperceptions) (dos Santos Kawata et al., 2021; Shadur & Hussong, 2014; Uljarević et al., 2021). It is conceivable that the low level of metacognitive ability in adolescents (dos Santos Kawata et al., 2021) could lead to poor self-esteem as well as inaccurate confidence over one's actions and decisions (i.e., continued substance use) regardless of previous negative outcomes (Hauser et al., 2017). Furthermore, the friendship network and the quality of relations between peers could increase the risk of SUD through inducing negative affect (i.e., bullying relationships) or encouraging substance use as a norm and value of the group (Shadur & Hussong, 2014). Family relationship variables (e.g., having deviant sibling, parent warmth) are another group of risk factors that potentially affect adolescents' substance use initiation (Neiderhiser et al., 2013, Slesnick et al., 2002). Based on these findings, we may postulate that social factors in terms of social stress and social learning process, could act differently across individuals due to their differences in brain structures, that make some adolescents more prone to SUDs. Therefore, low levels of self and social awareness could affect the ability to regulate one's behavior within a social context.

These findings suggest how RDoC domains/constructs could potentially contribute to emergence of SUD in adolescents, and in turn may respond to prevention interventions in terms of neural and behavioral alterations. In the following section, we provide a summary of possible approaches that could possibly target these domains/constructs in order to reduce the risk of SUD.

CLASSIFICATION OF THE PREVENTIVE APPROACHES BASED ON THE RDoC DOMAINS

A caveat is worth noting prior to our discussion of ways in which RDoC domains may be applied to prevention of SUD. The interventions cited below, for the most part, were not conceived on the basis of their putative neurobiological mechanisms. Moreover, although their intrinsic targets are undergirded by neurobiological mechanisms, they were not explicitly tested; we argue for the inclusion of such measures in modeling given their heightened sensitivity and specificity and, thus, ability to reveal whether or not these programs are truly moving the mechanistic needle. Interventions can then be refined to more potently affect these targets in individuals or subtypes

on the basis of who/what is affected, potentially improving outcomes. The overarching goal of this “neuroprevention” framework is to produce more effect compared to what we have achieved thus far (Fishbein et al., 2016). Below, we map possible preventive approaches to the RDoC framework according to readily observable changes, such as perceptions, emotional state, orientation to the environment, learned responses, and ultimate outcomes. Each measurable construct, however, is known to be underpinned by neural systems categorized by the RDoC.

Interventions targeting Negative Valence Systems (NVS)

This group of interventions broadly includes a set of educational and practical techniques termed as “*Emotion Regulation (ER)*”, which are applied to manage negative emotions and their expression in the face of emotional situations, specifically when decision making is required (Hadley et al., 2019). ER encompasses a broad range of skills delivered through emotion education (e.g., identifying triggers, recognizing and labeling feelings) and strategy teaching, including distraction, self-expression, physical exercise, and cognitive reappraisal (Houck, Hadley, et al., 2016). It is worth noting that affective valences are critically associated with somatic cues. Most of the developed ER programs affect the ARS and SP domains as well (e.g., mind–body practices), through increasing individuals’ awareness about their interoceptive signals and emotional states in the face of arousal-eliciting situations.

Interventions targeting Positive Valence Systems (PVS)

Interventions in this group are largely intended to interfere with an individual’s preference toward immediate rewards (e.g., substance use) and enhance the valuation of delayed rewards (e.g., college graduation). Therefore, preventive interventions which target delay discounting and reward sensitivity through expanding adolescents’ temporal window could potentially reduce drinking alcohol or using substances (Dennhardt et al., 2015).

Moreover, some interventions such as “*Behavioral activation*” could be implemented to increase the rewarding properties of substance-free activities and encourage individuals to engage in these activities on a daily basis (Reynolds et al., 2011). During the course of behavioral activation, individuals are asked to identify their life goals/values and track the enjoyable activities they do in line with these goals/values (Reynolds et al., 2011). The PAX Good Behavior Game is a sample of approach which have been developed to encourage prosocial behaviors (e.g., reducing drinking alcohol) through creating a shared relational network of prosocial behaviors, assigning positive value to them and reinforcing one’s engagement (Johansson et al., 2020).

Another group of interventions that is likely to adjust the PVS are educational programs developed with the aims of leveraging individuals’ knowledge about substances and providing them with a perspective on the harms and costs of using substances as well as emphasizing the importance of health as a life value to accomplish long-term goals (Debenham et al., 2020, Sussman et al., 2002). Therefore, the gained knowledge may be able to interfere with reward valuation and expectancy regarding substance use. It is noteworthy that the traditional addiction preventive education programs have recently undergone subtle changes in their content and structure. As a result of this transition, a new concept of “Neuroscience-based Psychoeducation” has emerged, which has been used to convey harm-minimization information to adolescents (Debenham et al., 2020; Ekhtiari et al., 2017). The Illicit Project and the Just Say Know programs are samples of the pioneers in this field developed to improve adolescents’ neuroscience based substance literacy level (Meredith et al., 2021; Debenham et al., 2020).

Interventions targeting Cognitive System (CS)

This group of interventions includes all those approaches that tend to promote forethoughtful, and goal-oriented behaviors in which a person could mentally reflect on the consequences of their potential choices. This category mainly relies on a set of processes from basic to more complex cognitive functions activated through using cognitive training and knowledge development. Cognitive training is among the most common components of these interventions, traditionally provided in terms of cognitive games. For example, some studies examined the efficacy of such games (including Lumosity, City Builder game, Fling game) targeting executive functions (e.g., working memory, response inhibition) within a training context (Boendermaker et al., 2017, 2018; Mewton et al., 2020).

Interestingly, the CS could also be targeted by multi-component interventions such as Life Skills Training (Griffin et al., 2006a), RealTeen (Schwinn et al., 2016), and Preventure (Conrad, 2016) which enhance personal competence in terms of complex cognitive skills (e.g., goal setting, planning, decision-making, self-monitoring, problem solving) to motivate and facilitate behavioral change and resist against risky situations. It is note-worthy that some techniques could target multiple interacting domains; for example, self-monitoring technique that could be used to increase both self-awareness (SP) as well as self-management skills (CS).

Interventions targeting Arousal and Regulatory Systems (ARS)

Interventions in this group mainly include approaches to resolve sleep problems and adjust circadian rhythms. Sleep problems are multi-cause conditions, which tend to benefit from multi-component interventions. Broadly speaking, sleep education (e.g., teaching sleep hygiene), sleep monitoring (e.g., recording sleep diary and identifying sleep problems), cognitive strategies (e.g., changing sleep-disruptive thoughts), stress management and relaxation techniques (e.g., diaphragmatic breathing) are among the most common ingredients of sleep interventions used as substance use prevention efforts for adolescents (Dong et al., 2020; Fucito et al., 2017, 2021; Miller et al., 2020; Werner-Seidler et al., 2019). Examples of such multi-component interventions is mind-body practices (including yoga and meditations) developed and applied for at-risk adolescents (Butzer et al., 2017). Although all these interventions are focused on sleep and circadian rhythms, they may also alleviate negative emotions and improve mood and cognitive control.

Interventions targeting Social Processes (SP)

Interventions in this group are divided into two categories, including interventions that target self-awareness and those that enhance social processing. The former category includes interventions that improve self-knowledge and self-esteem (e.g., resistance skills) and those that work on internal attention to calm the mind, body, and behavior and self-awareness (e.g., mindfulness programs)(Waedel et al., 2020); and educational programs which provide scientific knowledge about the effects of different substances on the brain. These educational interventions, such as the Just Say Know (Meredith et al., 2021), translate neuroscience into understandable content, explaining how substances may change brain structures and function and lead to risky behaviors and SUDs. These informative programs increase individuals' self-knowledge and insight and provide scientific evidence for why adolescents are more vulnerable to initiate substance use to reinforce self-agency to regulate their own behaviors.

Another group of interventions targeting self-awareness provides feedback and normative information which indicates deviation of one's behavior (i.e., amount of drinking and cannabis

use) from the peer norms (Geisner et al., 2007; Larimer & Cronce, 2002; Pischke et al., 2021b; Riggs et al., 2018). The second category encompasses interventions that teach social skills (e.g., communication skills, developing healthy relationships (Griffin et al., 2006a). Life Skills Training (Griffin et al., 2006b), Unplugged (Faggiano et al., 2010), the Climate Schools program (Newton et al, 2022; Newton et al; 2020) are some well-known examples of preventive programs developed based on social theoretical models and focus on social competence in adolescents.

Using the aforementioned categories of preventive approaches, in the next section we classified the existing evidence-based school-based addiction prevention programs selected through a systematic review. The rationale behind selecting schools is that they are ideal site to offer preventive interventions, since they have a high access to an engaged group of adolescents from diverse backgrounds, which could reduce the affordability and accessibility barriers.

A SYSTEMATIC REVIEW OF SCHOOL-BASED ADDICTION PREVENTION PROGRAMS FOR ADOLESCENTS

Search Methods

The systematic review was conducted using the PRISMA framework (Moher et al., 2015). Search terms were selected based on past reviews. PubMed databases was searched using the following search syntax: ("Adolescents" OR "Adolescence" OR "Teens" OR "Teen" OR "College" OR "School" OR "Youth" OR "Youths" OR "Young" OR "Teenager" OR "Teenagers" OR "School" OR "College" [tiab]) AND ("Substance Related Disorder" OR "Drug Use Disorders" OR "Drug Use" OR "Substance Abuse" OR "Substance Dependence" OR "Substance Addiction" OR "Addiction" OR "Drug Dependence" OR "Substance Use Disorder" OR "Drug Consumption" OR "Alcohol Related Disorders" OR "Alcohol Problem" OR "Alcohol Dependence" OR "Alcohol Addiction" OR "Alcohol Abuse" OR "Alcohol Use Disorder" OR "Risky Drinking" OR "Heavy Drinking" OR "Alcohol Use" [tiab]) AND ("Prevent" OR "Preventive" OR "Prevention" OR "Intervene" OR "Program" OR "Intervention"). The search period covered studies published from 1996 to August 2022.

Eligibility Criteria

In this review, we selected the studies if they met the following conditions:

- Study design: Randomized control trials, written in English and available in full text were included if they also met the below mentioned inclusion criteria:
- Participants: Preventive intervention studies for adolescent students aged 13–18 years were included. Studies of interventions involved families/teachers of students were excluded because these programs have specific components focusing on parent/teacher's skills and attitude towards adolescents' addiction, which could not be embedded within the RDoC framework. Moreover, we excluded those studies with college students or students who were clinically diagnosed with a disorder (e.g., attention deficit hyperactivity disorder, depression) and were not considered as regular substance users, or those with alcohol/substance use disorders. Because interventions for these groups have substantial differences.
- Intervention: The intervention had to be introduced as a school-based drug/alcohol preventive approach delivered via face-to-face training or technology (e.g., app, web). Community-based

interventions or those conducted in the clinical context (e.g., emergency department) were excluded.

- Outcomes measures. Studies that assessed or were planned to assess (e.g., protocol studies) variables related to drug and alcohol (e.g., knowledge, attitude, intention) were included. Studies were excluded if they concerned with other negative behaviors (e.g., violence, gambling)

Data Collection and Analysis

Two independent reviewers (TR, PR) screened each title and abstract per inclusion/exclusion criteria. The selected interventions were coded and reviewed in full text by both reviewers. Using the aforementioned criteria, a total of 24 [unique] interventions out of 101 eligible prevention trials (Table 1, See Figure 3) were extracted and analyzed in terms of the type of intervention developed or applied (the specific term coined for the interventional program) as well as their content explained by their authors (Table 2). We also reviewed [Blueprint](#) for the evidence-based programs aimed to prevent substance use in adolescents. The protocol of this systematic review was registered on the Open Science Framework (OSF) on October 9, 2022: <https://osf.io/z4v5m/>

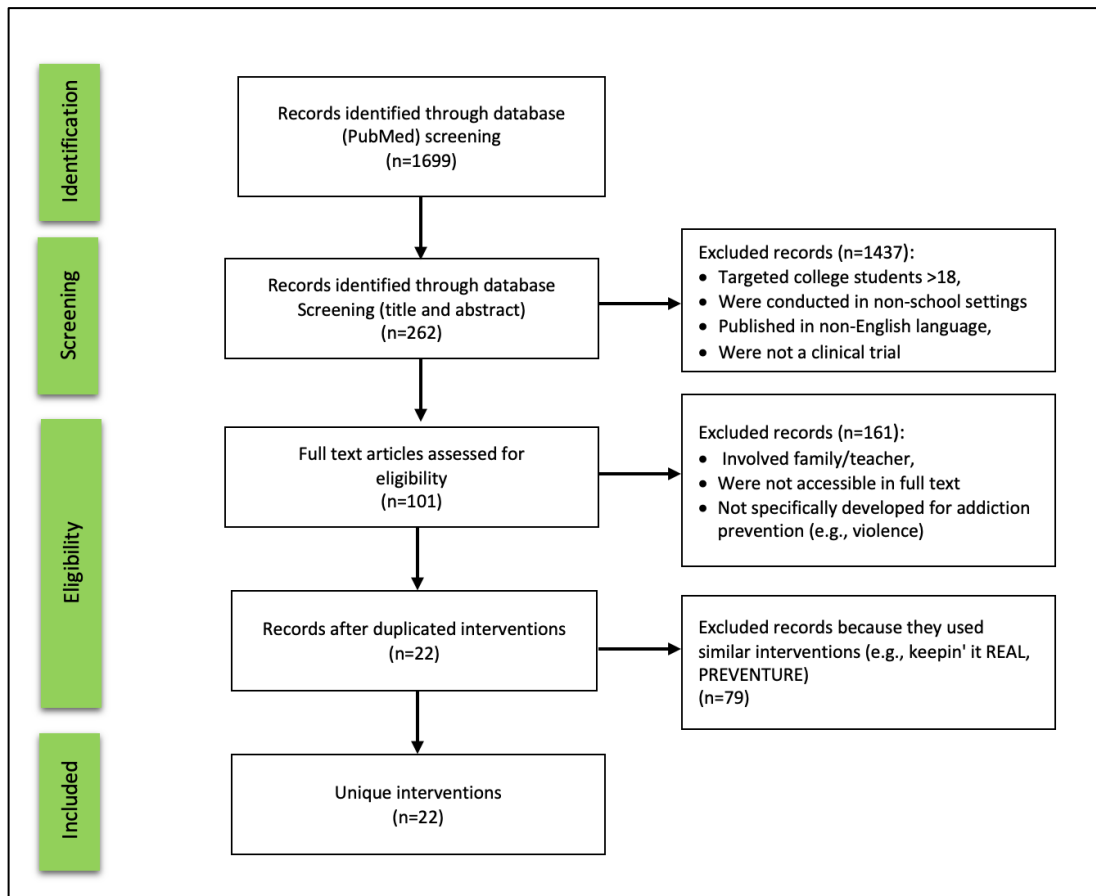


Figure 3: PRISMA summary of identified studies/ interventions included in the review

Table 2. Selected substance use disorder preventive interventions (n=22) and the provided details about their components

Name of program	Detailed components
Ready4life (Haug et al., 2021)	Substance-related knowledge and attitudes, normative expectations, and skills for resisting media and peer influences to use, personal self-management (decision-making and problem-solving ability, skills for identifying, analyzing, interpreting, and resisting media influences, skills for coping with anxiety, anger, and frustration, basic principles of personal behavior change and self-improvement (e.g., goal-setting, self-monitoring, and self-reinforcement) and social skills (communication, initiating social interactions, conversation, complimenting, skills related to male-female relationships, and verbal and nonverbal assertive skills)
eCHECKUP TO GO (Doumas et al., 2020)	Personalized normative feedback on peer drinking, positive alcohol beliefs, and positive alcohol expectancies, as perceptions of peer drinking and cognitions about alcohol, protective behavioral strategies (e.g., social activities instead of partying)
ALERT, Alerta Alcohol program (Martinez-Montilla et al.,2020)	Change students' beliefs about drug norms and the social, emotional, and physical consequences of using drugs; help them identify and resist pro-drug pressures from parents, peers, the media, and others; build resistance self-efficacy, the belief that one can successfully resist pro-drug influences
Kripalu Yoga in the Schools (KYIS) curriculum (Butzer et al.,2017)	Stress management, emotion regulation, self-appreciation, confidence, and strong peer relationships
The GOOD life (Stock et al.,2016)	Social Norms Intervention (social norm and attitude)
Brief alcohol intervention (Giles et al., 2016)	Personalized feedback about the individual student's drinking behaviour and attitude, behaviour change counselling, advice about the health and social consequences of continued risky alcohol consumption
Preventure (Barrett et al., 2015)	Psycho-education (personality profile), behavioral and cognitive coping skills (e.g., goal setting, cognitive restructuring), motivational interviewing
MobileCoach Alcohol (Haug et al., 2014)	Social norm interventions, outcome expectations, self-efficacy, planning processes
Saluda program (Hernández-Serrano et al., 2013)	Information on alcohol and illicit drugs, and their effects; information on causal factors (motivations) for drinking and taking pills among adolescents; advertising analysis; social skills and assertiveness skills; information on healthy leisure offers existing in the city; abilities in problem solving and decision making; public commitment to non-abuse of alcohol and synthetic drugs
Motivational interviewing-oriented brief alcohol interventions (Gmel et al., 2012)	Knowledge, attitude, motivation
Brief intervention for poly-drug use (Arnaud et al., 2012)	Personalized feedback on their substance consumption patterns including the associated risks (related to health and other consequences) and comparisons to a normative reference group. Interactive MI-based exercises that have been proven effective in prompting readiness to change by encouraging the participant to consider the costs and benefits of their current substance use and actual change. Practical advice concerning alternative behavior in tempting situations, with a focus on peer resistance skills to raise self-efficacy beliefs and implementation intentions.
Drug education program (Midford et al.,2012)	Knowledge, change of thinking, drug-free activities, norms, analyzing, media and social pressure, risk reduction, personal confidence (e.g., positive self-talk, refusal skills, peer negotiation), decision making, assertion skills
Project Toward No Drug Abuse (Sussman et al., 2011)	Active listening and communication skills, Stereotyping and social norms, chemical dependency and consequences of drug use, coping with stress, self-control, being assertive, positive/negative thought and behavior loop, attitude, decision-making
IPSY (Spaeth et al.,2010)	Intrapersonal and interpersonal Life Skills (e.g., self-awareness, coping strategies, assertiveness, or communication skills), instruction on substance-specific skills (e.g., resistance to peers offering substances). Knowledge concerning alcohol and tobacco use (e.g., prevalence rates, short-term effects, advertising strategies)
Cognition-Motivation-Emotional Intelligence-Resistance Skills (CMER) (Guo et al., 2010)	Knowledge about psychoactive substances, the adverse consequences of these substances, anti-drug attitudes and social norms. Motivational intervention to change intrinsic motivation for addictive behavior, coping skills to enhance overall personal competence and to decrease vulnerability to social influences of drug use.
RealTeen (Schwinn et al., 2010)	Goal setting, decision making, coping (particularly with stress, puberty, and bodily changes), self-esteem, assertion, communication, media influences, peer pressure, and drug facts.
Climate Schools (now known as OurFutures) (Vogl et al., 2009)	Information regarding social, psychological, physical, and legal consequences of drug use, social pressure, media influences, alcohol-free social activities, normative education, resistance-skills training
Take Charge of Your Life (TCYL) (Sloboda et al., 2009)	Personal, social, and legal risks and consequences involved in the use of substances including tobacco, alcohol, and illicit drugs and those beliefs that "everybody does it" are not congruent with reported usage data from national studies. Life skills such as communication, decision-making, assertiveness and refusal skills. Students learn to make sense of experiences, ideas and values about the health, social, and legal risks and consequences of substance use by comparing them with their existing understandings and beliefs.
keepin' it REAL (Kulis et al., 2007)	Knowledge, anti-drug norms and attitudes and to facilitate the development of students' risk assessment, decision-making, and ability to refuse drugs, manage stress, interact effectively.
Reconnecting Youth (Hallfors et al., 2006)	Self-esteem, decision making, personal control, and interpersonal communication
Life skills training (LST) (Seal, 2006)	Information and skills specifically related to drug and tobacco use, such as the effects of drugs, self-awareness skills, decision-making and problem-solving skills, stress and coping skills, and refusal skills.
Alcohol Misuse Prevention Study (AMPS) (Shope et al.,2001)	Awareness of the short-term effects of alcohol, risks of alcohol misuse, situations and social pressures to misuse alcohol. Skills for resisting against social pressures, self-agency,

Table 3. Substance use disorder preventive interventions (n=22) based on the targeted RDoC domain (s)

Name of program	NVS	PVS			SP								CS			ARS
	Skills for coping with negative affects	Motivation to change behavior (e.g., self-reinforcement)	Drug-free activities	Substance-related knowledge (e.g., consequences)	Substance-related knowledge (e.g., consequences)	Attitude towards substance use	Social norms (popularity and prevalence)	Social pressure resisting skills (e.g., awareness, refusal skills)	Social skills (e.g., communication skills, assertiveness)	Self-related awareness (e.g., personality) and self-efficacy skills	Cognitive Restructuring (way of thinking)	Self-monitoring	Self-management skills (e.g., decision-making, problem solving, analyzing)	Behavior changes and self-improvement skills (e.g., self-monitoring, goal-setting, implementation intentions)	Self-control skills and protective behaviors	Stress management
Ready4life	+	+		+	+	+	+	+	+			+	+	+		
eCHECKUP TO GO				+	+	+	+								+	
ALERT, Alerta Alcohol program				+	+		+	+		+						
Kripalu Yoga in the Schools (KYIS)	+									+	+					+
The GOOD life										+				+		
Brief alcohol intervention		+		+	+	+	+									
Preventure		+								+	+			+		
MobileCoach Alcohol										+				+		
Saluda program			+	+	+			+	+				+			
Motivational interviewing-oriented brief alcohol interventions		+		+	+	+										
Brief intervention for poly-drug use		+		+	+			+	+					+		
Drug education program			+	+	+			+	+	+	+		+			
Project Toward No Drug Abuse (TND)		+		+	+	+	+		+		+		+		+	+
IPSY	+			+	+	+	+	+	+	+			+			+
Cognition-Motivation-Emotional Intelligence-Resistance Skills (CMER)		+		+	+	+	+	+								
RealTeen				+	+			+	+	+			+	+		+
Climate Schools (now known as OurFutures)			+	+	+			+	+							
Take Charge of Your Life (TCYL)				+	+	+	+	+	+	+			+			+
keepin' it REAL				+	+	+	+	+	+				+			+
Reconnecting Youth									+	+			+		+	
Life skills training (LST)	+			+	+	+		+	+	+			+			+
Alcohol Misuse Prevention Study (AMPS)				+	+			+		+						

Interestingly, most of preventive interventions were multi-component programs having more than one target for intervention and addressing a few risk factors for SUD, thereby targeting more than one RDoC domain. For example, one of the best-established prevention programs is the *PreVenture* Program which selectively targets four personality risk factors for SUDs: hopelessness, anxiety sensitivity, impulsivity, and sensation seeking (Conrod, 2016). The traits comprise hopelessness, anxiety sensitivity, impulsivity, and sensation seeking, which are all embedded in this interventional program. Each of the intervention components in *Preventure* program links to a distinct RDoC domain and has been shown to be associated with risk for specific substance use behaviours and concurrent mental health concerns (Conrod, 2016; Stewart, et al., 2021). For example, sensation seeking, is closely related to PVS domain of the RDoC, and is targeted using psychoeducation, motivational enhancement therapy, and cognitive behavioral therapy techniques specifically focused on reward sensitivity. The impulsivity component of the intervention is relevant to CS and focuses on building motivation and cognitive behavioural skills to help young people manage an impulsive personality style and has been shown to reduce substance misuse as well as risk for conduct disorder symptoms (O’Leary-Barrett et al., 2013). The hopelessness and anxiety sensitivity components are relevant to the NVS domain of the RDoC (although hopelessness might be etiologic related to low PVS and lack of inhibition on NVS). Experimental designs have shown that cognitive-behavioural strategies that differentially target these risk factors show some specificity in reducing risk for substance misuse and clinically significant levels of anxiety disorders and major depression (O’Leary-Barrett et al., 2013). The other example of multi-dimensional program is life skill programs (LSPs) which target intra- and interpersonal skills (e.g., communication skills, empathy, assertiveness, problem solving and decision-making skills, coping with emotions and stress), as well as training substance-related skills (e.g., resistance skills), changing attitude, and improving substance related knowledge (e.g., norms) (Wenzel et al., 2009).

Therefore, addiction prevention programs such as *LSPs* and *Preventure* could have an integrated approach that targets multiple domains of RDoC for a potentially broader target of intervention.

DISCUSSION

In this paper, we described the major RDoC domains involved in SUD and proposed an RDoC-based framework to classify prevention approaches based on their potential functional targets.

Overall, there are several reasons why the classification, development and application of SUD preventive interventions would benefit from the RDoC framework (Insel et al., 2010). First, the RDoC have delineated the major underlying constructs (negative, positive, cognitive, arousal, social) involved in SUD development that could be measured using different levels of analysis, which include molecular, cellular, neural, behavioral, and self-report assessments. At the macro level, researchers within a shared RDoC framework could contribute to increase harmonisation and reduce methodological heterogeneity across studies by using a common set of reliable measures, and thus make their results more comparable and compatible with each other. At the micro level, clinical researchers who tend to identify and screen vulnerable individuals, could benefit from these measures to assess the type and the intensity of dysfunction in each domain, and in turn develop tailored interventions tapping these systems. Referencing this individualized approach to pinpoint the motive(s) for substance use, could result in more phenotypically matched interventions that may increase the likelihood of long-term success.

There are a few pieces of evidence showing great potentials in using specific personal characteristics that moderate SUD vulnerability to predict the responsiveness to the prevention interventions. For example, in a study on a sample of adolescents with and without conduct disorder, the participants with lower neurocognitive skills (i.e., risk taking) achieved less benefits from the component of intervention targeting impulse control, verbal negotiations, problem solving, and cautious decision making (Fishbein et al., 2006). In another study, participants with impulsivity trait responded better to the inhibitory control interventions, while those with sensation seeking trait were more responsive to the interventions that target positive valence system (Conrod, 2016). These moderating effects reminisce of the compensation and magnification hypotheses that account for degree of benefit that people may gain from cognitive stimulation therapy depending on their baseline characteristics (i.e., pre-training level of cognitive alteration) (Carbone et al., 2022). There is still no published study have applied the RDoC framework to identify high-risk adolescents and examined their responsiveness to an addiction prevention intervention grounded in RDoC-framework.

Second, the RDoC framework provides a set of standardized paradigms which could be efficiently applied for intervention development. The RDoC framework aims to translate the neuroscience-based findings (i.e., precise developmental trajectory) from big datasets such as Adolescent Brain Cognitive Development (ABCD) and HEALthy Brain and Child Development (HBCD) projects to develop preventive interventions and measure their efficacy with proxy neural outcomes (MacNeill et al., 2021; Nelson et al., 2022). Although, cohort studies must begin to incorporate newer designs (e.g., embedded randomized trials, O’Leary-Barrett et al., 2017; Bourque et al., 2016) in order to increase the pace of discovery around promising intervention strategies (Conrod, 2022).

Third, several of the interventions included in this overview (and possible future interventions) have an impact on a broader spectrum of outcome variables (e.g., suicidal ideation, depression, externalizing symptoms) and can be considered as transdiagnostic interventions (Lynch et al., 2021). The RDoC framework allows for a more systematic exploration of the interrelation between these outcome domains and their specific impact on the pathway leading to substance use. In this respect, integration of the RDoC with other empirically model such as the Hierarchical Taxonomy of Psychopathology (HiTOP) that study psychopathological conditions by their signs, symptoms, maladaptive behaviors and traits, may be more efficient for targeting common mechanisms across varied conditions (Michelini et al.,2021).

Additionally, the RDoC framework offers an opportunity to provide drug-related education and trainings from the lens of neuroscience that is more engaging, non-judgmental, and favorable for the potential end users that would be preventologists, adolescents and their parents.

By using the standardized guidelines derived from such robust findings, modular preventive interventions could be developed using a holistic approach that could be customized to meet the specific needs of individuals, in line with the precision medicine approach (Collins et al, 2007). For example, for adolescents who have experienced various types of childhood trauma (e.g., loss of loved ones, sexual abuse), interventions which emphasize the negative valence (e.g., emotion regulation), regulatory systems (e.g., relaxation) and social processes (e.g., communicating with

supportive therapists through conjoint sessions) could be more effective. Finally, by using an RDoC framework, researchers could measure the efficacy of their interventions by using measures which correspond to specific intervention components.

CONCLUSION

Overall, we suggest that focusing on the broadness and multi-dimensionality of addiction prevention programs targeting multiple RDoC domains hold promise for the development of a novel neuroscience-informed approach with extensive positive impacts. The RDoC framework has a vast potential for informing SUD prevention, particularly in terms of developing comprehensive preventive interventions and measuring their target engagement and efficacy. Although discussing the effectiveness of these interventions is not within the scope of this paper, the proposed conceptual framework provides an insight into how we can develop holistic prevention programs for adolescents by integrating multiple evidence-based paradigms aimed at multiple mechanistic targets. There are several steps ahead for reaching this overarching aim. First, the proposed RDoC domains should receive approval from the global community of addiction prevention experts and achieve their consensus in a Delphi study. This survey can also assess the agreement on the importance of the proposed domains and sub domains to be included in the preventive interventions or if some domains/sub-domains should be prioritized based on multiple factors such as developmental milestones and vulnerabilities. Secondly, the established model should be mapped onto the existing well-established interventions as well as implemented into universal and selective prevention programs to be applied and examined in terms of feasibility and acceptability among adolescents. For the final step, randomized clinical and mechanistic studies should be designed to explore the efficacy of the intervention and its long-term effects in terms of engaging different units of analysis in the RDoC domains including and most importantly delaying the onset of substance use and reducing the harms. Surely, the active collaboration of the National Institute on Alcohol Abuse and Alcoholism (NIAAA) and the National Institute on Drug Abuse (NIDA) in the US and their counterparts in other countries through allocating funded grants within this framework would be highly effective in taking steps forward and reaching these overarching aims.

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