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

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Abstract:
The neuroscience of substance use disorder (SUD) has substantially extended our knowledge about mechanisms underlying its etiology—mechanisms that provide clues as to how interventions might exert their impacts and whether they may serve as novel targets for more effective prevention and intervention strategies. 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) framework was originally developed for similar purposes relative to a variety of mental health disorders and may be very useful in considering neurobiological mechanisms that may drive intervention effects. 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 constructs *(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 functional components using RDoC constructs. From a systematic review of randomized controlled trials using a person-centered drug/alcohol preventive approach for adolescents (13-18 years), we identified 98 trials on 37 preventive interventions. We categorized them within this framework based on their potential functional 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.

1. 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 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 attempts (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; 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).
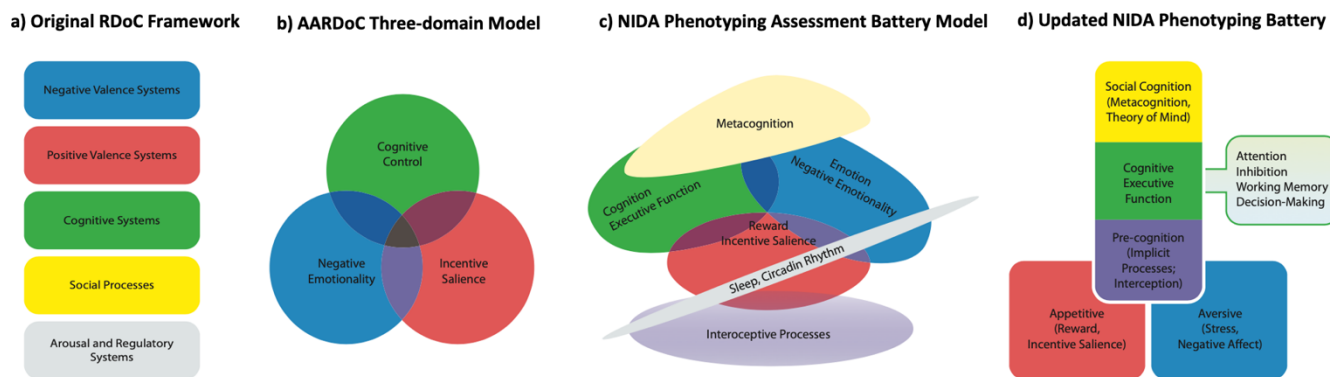

Figure 1 – Addiction-related neurofunctional domains a) The original RDoC framework includes five domains of Negative Valence System, Positive Valence System, Cognitive System, Social Processes, and Arousal and Regulatory Systems. b) The Alcohol and Addiction RDoC (AARDoC) model and the Addictions Neuroclinical 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 frame of reference 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 modules 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).

2. Risk Factors for Substance Use Disorders through the Lens 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 frame demonstrating 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).
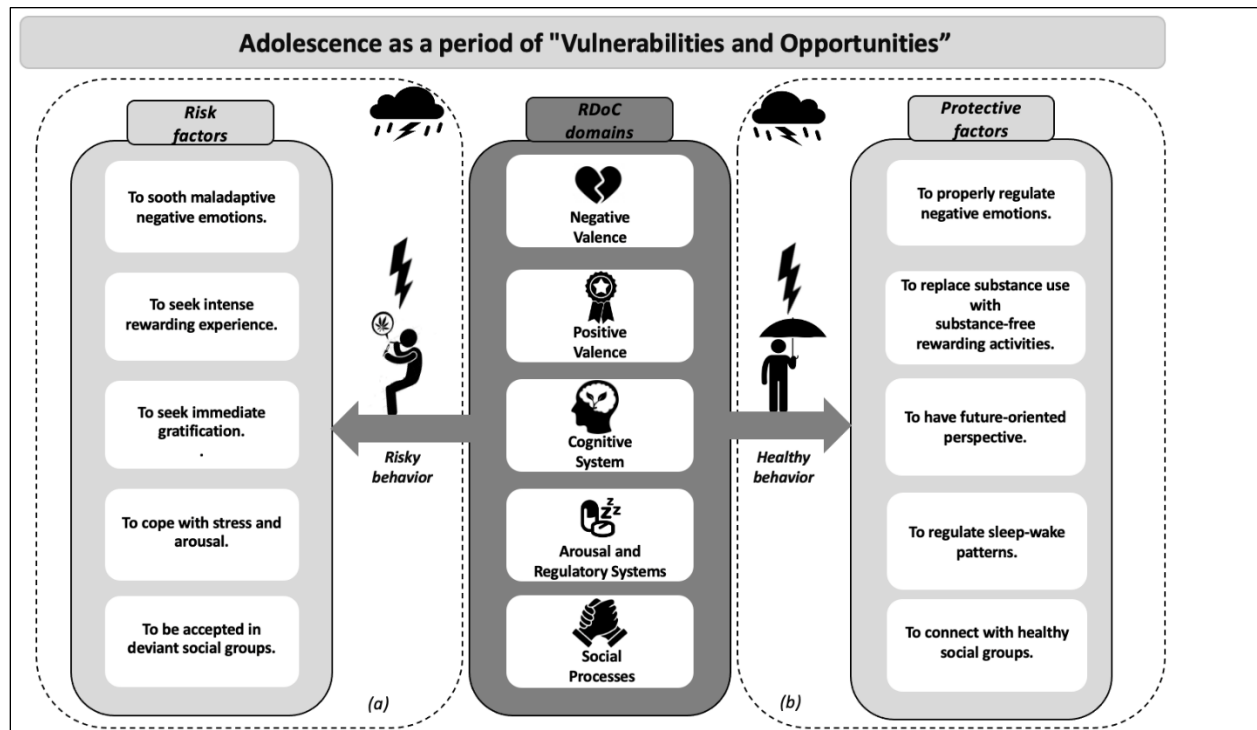

Figure 2: The five major RDoC domains could act as, (a) risk factors, or (b) protective factors for substance use disorders during adolescence.

2.1. *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 insular cortex (Büchel, 2000). 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).

Adolescence is a particularly high risk period for development of SUD (Thatcher & Clark, 2008) likely due 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). 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).

2.2. *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).

2.3. *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 (Pihl et al., 1990; Squeglia & Cservenka, 2017; Morin et al., 2018). There is also evidence highlighting the promising effects of cognitive training interventions such as working memory training or episodic future thinking for improving impulse control and self-regulation (goal-directed behaviors) in substance users (Bickel et al., 2014; 2016; Brooks et al. 2017; Rudner et al., 2021). More generally, cognitive training programs have shown promising effects in reducing substance-related salience via prefrontal cortex-amygdala brain circuitry (Verdejo-Garcia, 2016; Baker et al., 2017). Overall, poor performance of the CS reduces the regulatory capacity to control socioemotional functioning and increases SUD vulnerability.

2.4. *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).

2.5. 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 interoceptive awareness) 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 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 knowledge could affect the ability to regulate one's behavior within a social context.

These findings suggest how RDoC domains/constructs could potentially contribute to SUD formation 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 these interventions that meet the eligibility criteria to be included in our systematic review of school-based addiction prevention studies. 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.

3. A systematic review of school-based addiction prevention programs for adolescents

To identify the relevant studies, we employed 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") via PubMed database. In this review, we selected those randomized control trials studies having the person-centered (not involving parents and family) drug/alcohol preventive approach, published between start of 1996 and August 2022, written in English, and conducted as a school-based program for adolescents (13-18 years) who were not 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. Two independent reviewers (TR, PR) screened each title and abstract per inclusion/exclusion criteria. Using the aforementioned criteria, a total of 37 interventions out of 98 eligible prevention trials (Table 1, See Figure 1) 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 underlying conceptual theories and foci (Table 2).

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

Table 1: The list of 98 articles included in the systematic review (n=98)

No	Study	Intervention	No	Study	Intervention
1	The 7-Year Effectiveness of School-Based Alcohol Use Prevention.From Adolescence to Early Adulthood: A Randomized Controlled Trial of Universal, Selective, and Combined Interventions	Climate, PREVENTURE	20	Effectiveness of Fresh Start: A Randomized Study of a School-Based Program to Retain a Negative Attitude Toward Substance Use in Secondary School Freshmen	Fresh Start
2	A national effectiveness trial of an eHealth program to prevent alcohol and cannabis misuse: responding to the replication crisis	Climate	21	Assessment of the Efficacy of a Mobile Phone-Delivered Just-in-Time Planning Intervention to Reduce Alcohol Use in Adolescents: Randomized Controlled Crossover Trial	MobileCoach Alcohol
3	Effects of the "Unplugged" school-based substance use prevention program in Nigeria: A cluster randomized controlled trial	Unplugged	22	The #Tamojunto Drug Prevention Program in Brazilian Schools: a Randomized Controlled Trial	#Tamojunto
4	A Mobile Phone-Based Life-Skills Training Program for Substance Use Prevention Among Adolescents: Cluster-Randomized Controlled Trial	SmartCoach	23	A cluster-randomized controlled trial evaluating the effects of delaying onset of adolescent substance abuse on cognitive development and addiction following a selective, personality-targeted intervention programme: the Co-Venture trial	PREVENTURE
5	A cluster randomized controlled trial evaluating the effectiveness of the school-based drug prevention program #Tamojunto2.0	Tamojunto2.0 (Brazilian Portuguese translated version of Unplugged)	24	A Randomized Controlled Trial Testing the Efficacy of a Brief Online Alcohol Intervention for High School Seniors	eCHECKUP TO GO (e-CHUG)
6	The efficacy of a targeted PREVENTION programme for addictive behaviour (PREVENTURE) among vulnerable Adolescents in France - study protocol	PREVENTURE	25	Combined universal and selective prevention for adolescent alcohol use: a cluster randomized controlled trial	Climate, PREVENTURE
7	The long-term effectiveness of universal, selective and combined prevention for alcohol use during adolescence: 36-month outcomes from a cluster randomized controlled trial	Climate, PREVENTURE	26	Evaluation of Yoga for Preventing Adolescent Substance Use Risk Factors in a Middle School Setting: A Preliminary Group-Randomized Controlled Trial	Yoga
8	Efficacy of the eCHECKUP TO GO for High School Seniors: Sex Differences in Risk Factors, Protective Behavioral Strategies, and Alcohol Use	eCHECKUP TO GO (e-CHUG)	27	Efficacy of a web- and text messaging-based intervention to reduce problem drinking in adolescents: Results of a cluster-randomized controlled trial	MobileCoach Alcohol
9	Evaluating the differential effectiveness of social influence and personality-targeted alcohol prevention on mental health outcomes among high-risk youth: A novel cluster randomised controlled factorial design trial	Climate, PREVENTURE	28	The eCHECKUP TO GO for High School: Impact on risk factors and protective behavioral strategies for alcohol use	eCHECKUP TO GO (e-CHUG)
10	A Web-Based, Computer-Tailored Intervention to Reduce Alcohol Consumption and Binge Drinking Among Spanish Adolescents: Cluster Randomized Controlled Trial	Alerta Alcohol	29	Efficacy evaluation of the school program Unplugged for drug use prevention among Brazilian adolescents	Unplugged
11	Decision-making skills as a mediator of the #Tamojunto school-based prevention program: Indirect effects for drug use and school violence of a cluster-randomized trial	Tamojunto2.0	30	The long-term effectiveness of a selective, personality-targeted prevention program in reducing alcohol use and related harms: a cluster randomized controlled trial	PREVENTURE
12	The Effect of Contextual Risk Factors on the Effectiveness of Brief Personality-Targeted Interventions for Adolescent Alcohol Use and Misuse: A Cluster-Randomized Trial	PREVENTURE	31	Effectiveness of a Web-Based Screening and Fully Automated Brief Motivational Intervention for Adolescent Substance Use: A Randomized Controlled Trial	WISEteens
13	Additive Effectiveness of Mindfulness Meditation to a School-Based Brief Cognitive-Behavioral Alcohol Intervention for Adolescents	Cognitive behavior therapy plus Mindfulness meditation	32	Mechanisms of personality-targeted intervention effects on adolescent alcohol misuse, internalizing and externalizing symptoms	PREVENTURE
14	The role of normative beliefs in the mediation of a school-based drug prevention program: A secondary analysis of the #Tamojunto cluster-randomized trial	Tamojunto2.0	33	Can cannabis use be prevented by targeting personality risk in schools? Twenty-four-month outcome of the adventure trial on cannabis use: a cluster-randomized controlled trial	PREVENTURE
15	Screening and brief intervention with adolescents with risky alcohol use in school-based health centers: A randomized clinical trial of the Check Yourself tool	Check Yourself tool	34	Effectiveness of a selective intervention program targeting personality risk factors for alcohol misuse among young adolescents: results of a cluster randomized controlled trial	PREVENTURE
16	Effectiveness evaluation of the school-based drug prevention program #Tamojunto in Brazil: 21-month follow-up of a randomized controlled trial	Tamojunto2.0	35	Prevention of illicit drug use through a school-based program: results of a longitudinal, cluster-randomized controlled trial	Drug use prevention program (general name)
17	Universal cannabis outcomes from the Climate and Preventure (CAP) study: a cluster randomised controlled trial	Climate, PREVENTURE	36	Substance use outcomes in the Healthy School and Drugs program: results from a latent growth curve approach	Healthy School and Drugs
18	Differential intervention effectiveness of a universal school-based resilience intervention in reducing adolescent substance use within student subgroups: exploratory assessment within a cluster-randomised controlled trial	Resilience intervention	37	Effectiveness of the 'Healthy School and Drugs' prevention programme on adolescents' substance use: a randomized clustered trial	Healthy School and Drugs
19	A latent transition analysis of a cluster randomized controlled trial for drug use prevention	Tamojunto2.0	38	Short-term mediating factors of a school-based intervention to prevent youth substance use in Europe	Unplugged

No	Study	Intervention	No	Study	Intervention
39	A test of the efficacy of a brief, web-based personalized feedback intervention to reduce drinking among 9th grade students	eCHECKUP TO GO (e-CHUG)	62	he effectiveness of a school-based substance abuse prevention program: 18-month follow-up of the EU-Dap cluster randomized controlled trial	Unplugged
40	Effectiveness of a selective, personality-targeted prevention program for adolescent alcohol use and misuse: a cluster randomized controlled trial	PREVENTURE	63	The Project Towards No Drug Abuse (TND) dissemination trial: implementation fidelity and immediate outcomes	Towards No Drug Abuse (TND)
41	A quasi-randomized group trial of a brief alcohol intervention on risky single occasion drinking among secondary school students	Brief alcohol interventions	64	Preventing drug abuse among adolescent girls: outcome data from an internet-based intervention	RealTeen
42	Preventing Alcohol Use with a Voluntary After School Program for Middle School Students: Results from a Cluster Randomized Controlled Trial of Project CHOICE	CHOICE	65	Brief, personality-targeted coping skills interventions and survival as a non-drug user over a 2-year period during adolescence	PREVENTURE
43	Integrating life skills into a theory-based drug-use prevention program: effectiveness among junior high students in Taiwan	Drug use prevention program (general name)	66	Is universal prevention against youths' substance misuse really universal? Gender-specific effects in the EU-Dap school-based prevention trial	Unplugged
44	"Unplugged": a school-based randomized control trial to prevent and reduce adolescent substance use in the Czech Republic	Unplugged	67	The Adolescent Substance Abuse Prevention Study: A randomized field trial of a universal substance abuse prevention program	Take Charge of Your Life (TCYL)
45	One-year outcomes of a drug abuse prevention program for older teens and emerging adults: Evaluating a motivational interviewing booster component	Towards No Drug Abuse (TND)	68	A computerized harm minimization prevention program for alcohol misuse and related harms: randomized controlled trial	Climate
46	Boosting a teen substance use prevention program with motivational interviewing	Towards No Drug Abuse (TND)	69	CLIMATE Schools: alcohol module: cross-validation of a school-based prevention programme for alcohol misuse	Climate
47	An evaluation of immediate outcomes and fidelity of a drug abuse prevention program in continuation high schools: project towards no drug abuse (TND)	Towards No Drug Abuse (TND)	70	The effectiveness of a school-based substance abuse prevention program: EU-Dap cluster randomised controlled trial	Unplugged
48	Long-term effects of a personality-targeted intervention to reduce alcohol use in adolescents	PREVENTURE	71	Brief multiple behavior health interventions for older adolescents	Brief multiple behavior health interventions
49	The influence of socioeconomic environment on the effectiveness of alcohol prevention among European students: a cluster randomized controlled trial	Unplugged	72	One-year follow-up evaluation of Project Towards No Drug Abuse (TND-4)	Towards No Drug Abuse (TND)
50	Cluster randomised trial of the effectiveness of motivational interviewing for universal prevention	Motivational Interviewing	73	Personality-targeted interventions delay the growth of adolescent drinking and binge drinking	PREVENTURE
51	Are substance use prevention programs more effective in schools making adequate yearly progress? A study of Project ALERT	Project ALERT	74	School-based drug prevention among at-risk adolescents: effects of ALERT plus.	Project ALERT
52	Effects of a school-based prevention program on European adolescents' patterns of alcohol use	Unplugged	75	Peer acceleration: effects of a social network tailored substance abuse prevention program among high-risk adolescents	Towards No Drug Abuse (TND)
53	Effectiveness of a web-based brief alcohol intervention and added value of normative feedback in reducing underage drinking: a randomized controlled trial	Brief alcohol intervention with normative feedback	76	A cluster randomized controlled trial of school-based prevention of tobacco, alcohol and drug use: the EU-Dap design and study population	Unplugged
54	Short-term impact of cognition-motivation-emotional intelligence-resistance skills program on drug use prevention for school students in Wuhan, China	Cognition-Motivation-Emotional Intelligence-Resistance Skills (CMER)	77	Promoting reduced and discontinued substance use among adolescent substance users: effectiveness of a universal prevention program	keepin' it R.E.A.L.
55	Personality-targeted interventions delay uptake of drinking and decrease risk of alcohol-related problems when delivered by teachers	PREVENTURE	78	Neighborhood effects on the efficacy of a program to prevent youth alcohol use	keepin' it R.E.A.L.
56	One-year follow-up evaluation of the Project Towards No Drug Abuse (TND) dissemination trial	Towards No Drug Abuse (TND)	79	Efficacy of cognitive-behavioral interventions targeting personality risk factors for youth alcohol misuse	PREVENTURE
57	Preventing alcohol use among late adolescent urban youth: 6-year results from a computer-based intervention	CD-ROM intervention	80	Efficacy vs effectiveness trial results of an indicated "model" substance abuse program: implications for public health	Reconnecting Youth
58	Examining the differential effectiveness of a life skills program (IPSY) on alcohol use trajectories in early adolescence	Life skills program (IPSY)	81	Preventing tobacco and drug use among Thai high school students through life skills training	Life Skills Training (LST)
59	The effects of Project ALERT one year past curriculum completion	Project ALERT	82	Project Towards No Drug Abuse: long-term substance use outcomes evaluation.	Towards No Drug Abuse (TND)
60	Longitudinal outcomes of an alcohol abuse prevention program for urban adolescents	CD-ROM prevention program	83	A multihealth behavior intervention integrating physical activity and substance use prevention for adolescents	Sport Consultation and Alcohol Preventive Consultation
61	Internet-based prevention for alcohol and cannabis use: final results of the Climate Schools course	Climate	84	Gender-Specific Computer-Based Intervention for Preventing Drug Abuse Among Girls	Girls and Stress

| No	Study	Intervention	No	Study	Intervention
85	Modifying pro-drug risk factors in adolescents: results from project ALERT	Project ALERT	92	Project Towards No Drug Abuse: generalizability to a general high school sample.	Towards No Drug Abuse (TND)
86	A sport-based intervention for preventing alcohol use and promoting physical activity among adolescents	Sport Consultation and Alcohol Preventive Consultation	93	Outcomes of a brief alcohol abuse prevention program for Israeli high school students	Life Skills Training (LST)
87	Culturally grounded substance use prevention: an evaluation of the keepin' it R.E.A.L. curriculum	keepin' it REAL	94	Long-term follow-up of a high school alcohol misuse prevention program's effect on students' subsequent driving	Alcohol Misuse Prevention Study (AMPS)
88	New inroads in preventing adolescent drug use: results from a large-scale trial of project ALERT in middle schools	Project ALERT	95	Preventing illicit drug use in adolescents: long-term follow-up data from a randomized control trial of a school population	Life Skills Training (LST)
89	Project Towards No Drug Abuse: two-year outcomes of a trial that compares health educator delivery to self-instruction	Towards No Drug Abuse (TND)	96	One-year outcomes of Project Towards No Drug Abuse	Towards No Drug Abuse (TND)
90	Effectiveness of a universal drug abuse prevention approach for youth at high risk for substance use initiation	Life Skills Training (LST)	97	Effectiveness of a High School Alcohol Misuse Prevention Program	Alcohol Misuse Prevention Study (AMPS)
91	Preventing binge drinking during early adolescence: one- and two-year follow-up of a school-based preventive intervention	Life Skills Training (LST)	98	Effectiveness of a school-based substance abuse prevention program	Michigan Model for Comprehensive School Health Education
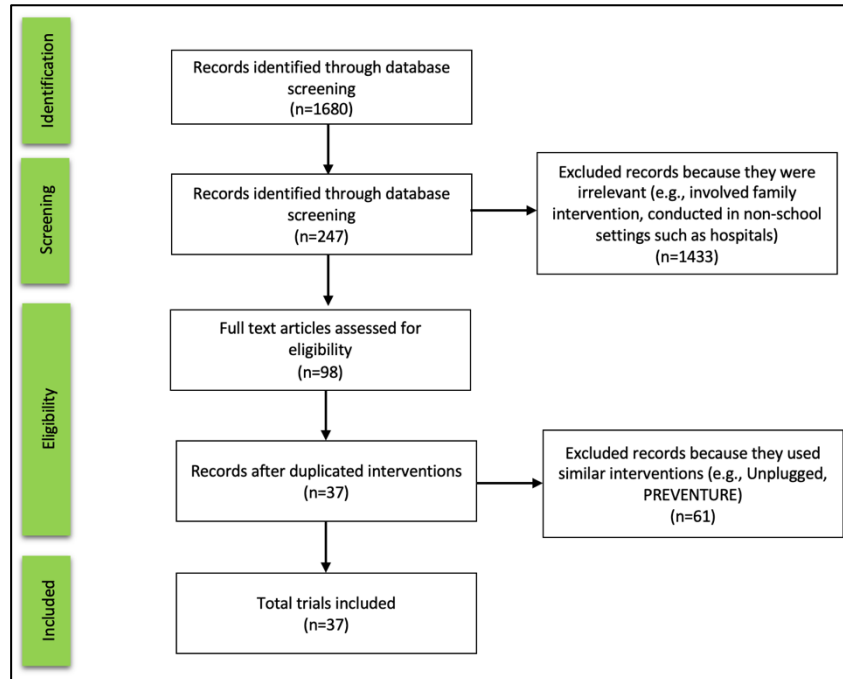
Figure 1: PRISMA summary of identified studies included in the review

Table 2. Substance use disorder preventive interventions (n=37) based on their theoretical models and the targeted RDoC domain (s)

Author, year	Name of program	Theoretical models and foci	RDoC domain(s)
(Bernstein & Woodall, 1987)	Alcohol and Substance Abuse Prevention Program (ASAP)	Social learning theory, Life skills training, Social competencies, Coping strategies	NVS, PVS, SP
(Botvin et al., 1990)	Life Skills Training (LST)	Cognitive-behavioral substance abuse prevention approach	NV, PV, CS, SP
(Shope, Copeland, Maharg, et al., 1996)	Alcohol Misuse Prevention Study (AMPS)	Social learning theory	SP, PVS
(Clayton et al., 1996)	Drug Abuse Resistance Education (Project DARE)	Informational, affective, and social influence approaches	PVS, CS, SP
(Shope, Copeland, Marcoux, et al., 1996)	Michigan Model for Comprehensive School Health Education	Social pressures resistance training	SP
(Palmer et al., 1998)	Normative education (NORM)	Social pressure resistance training, Normative education	SP
(Chou et al., 1998)	The Midwestern Prevention Project	Social influence model	SP
(Harrington et al., 2001)	All Stars	Social learning theory, Education	SP
(Cuijpers et al., 2002)	The Healthy School and Drugs (HSD)	Attitude, Refusal skills	SP
(Hecht et al., 2003)	keepin' it R.E.A.L. Curriculum	Ecological risk, Resiliency theory, Communication competence theory, Narrative theory	CS, SP
(Eisen et al., 2003)	Lions–Quest Skills for Adolescence (SFA)	Social influence, Social cognitive approaches	SP
(Werch et al., 2003)	Sport Consultation and Alcohol Preventive Consultation	Social Cognitive Theory	SP, ARS
(Bond et al., 2004)	The Gatehouse Project	Emotional and behavioral well-being	PVS, SP
(Hallfors et al., 2006)	Reconnecting Youth	Improving academic achievement and mood management, preventing illegal substance use	CS, SP
(Valente et al., 2007)	Towards No Drug Abuse (TND)	Motivational and behavioral skills, Decision making, Social environment	SP
(Bühler et al., 2008)	Allgemeine Lebenskompetenzen und Fertigkeiten	General life skills training, Substance use-related issues	NVS, CS, SP
(LaBrie et al., 2008)	Adaptations of Motivational interviewing (AMIs)	Motivational interviewing	CS, SP
(Turrisi et al., 2009)	Brief Alcohol Screening and Intervention for College Students (BASICS)	Personalized feedback, Norms, Expectancies, Negative consequences, Behavioral strategies	PVS, SP
(Newton et al., 2009)	Climate Schools (now known as OurFutures)	Social influence approach	CS, PS
(Sloboda et al., 2009)	Take Charge of Your Life substance prevention program	Theory of Planned Behavior, Normative belief, Refusal skills	CS, SP
(Hustad et al., 2010)	AlcoholEdu and e-Chug	Personalized normative feedback	SP
(Schinke et al., 2010)	CD-ROM prevention program	Social learning theory	CS, SP
(Guo et al., 2010)	Cognition-Motivation-Emotional Intelligence Resistance Skills (CMER)	Drug-related knowledge, Attitudes, Motivation, Coping skills	NVS, PVS, SP
(Conrod et al., 2010)	Preventure; Personality-targeted coping skills interventions	Psychoeducation, Motivation, Cognitive behavioral therapy	NVS, PVS, CS
(Schwinn et al., 2010)	RealTeen	Skills-based prevention personal and social skills and assertiveness	NVS, PVS, SP
(Paschall et al., 2011)	AlcoholEdu	Normative education, Goal setting, Information about alcohol problems, Skill Training	PVS, CS, SP
(Caria et al., 2011)	Unplugged program	Comprehensive Social Influence Model	CS, SP
(Hernández-Serrano et al., 2013)	Saluda	Social learning theory, Social-skills and problem-solving training	PVS, CS, SP
(Lubman et al., 2016)	MAKINGtheLINK	Information-Motivation-Behavioral Skills Model, Theory of Planned Behavior	SP
(Mewton et al., 2017)	The Brain Games	Personality risk factors	CS
(Martinez-Montilla et al., 2020)	Alerta Alcohol	I--Change Model	CS, SP
((Debenham et al., 2020)	The Illicit Project	Neuroscience-informed psychoeducation about brain and substance use	NVS, PVS, CS, SP
(Teesson et al., 2020)	Health4Life	Social influence, Social cognitive &Self-determination theories, Two-process model of sleep	SP, ARS
(Cordova et al., 2020)	Storytelling 4 Empowerment (S4E)	Eco-developmental and empowerment theories	SP
(Kvillemo et al., 2020)	WISEteens	Motivational Interviewing, Social influence	CS, SP
(Pischke et al., 2021a)	Social Norm	Changing misperceptions about peer substance use	SP
(Meredith et al., 2021)	Just Say Know Prevention Program	Neuroscience-informed psychoeducation about brain and substance use	NVS, PVS, CS, SP

NVS: Negative Valence Systems; PVS: Positive Valence Systems; SP: Social Processes; CS: Cognitive Systems; ARS: Arousal and Regulatory Systems

4. Classification of the preventive interventions 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 neural targets. 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 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.

4.1 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 (i.e., identifying triggers, recognizing and labeling feelings) and strategy teaching, including distraction, self-expression, physical exercise, and cognitive reappraisal (Houck, Hadley, et al., 2016). For example, one study applied expressive writing to alleviate negative emotions triggered by traumatic events (Young et al., 2013). Expressive writing is an emotional disclosure technique that is tied to both ER and cognitive processes, shown to be associated with lower drinking intention in adolescents who were asked to write about their negative drinking experiences. Another study (Barnett et al., 2015) found decreased alcohol use as a result of subjective evaluation of the negative consequence of drinking. This type of intervention is based on the theory of behavioral learning which posits that positive or negative reinforcement could increase or decrease the likelihood of any given behavior. 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, through increasing individuals' awareness about their interoceptive signals and emotional states in the face of arousal-eliciting situations.

4.2. *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). Previous research has shown that using behavioral economic intervention (Dennhardt et al., 2015) and episodic future thinking (Voss et al., 2021) result in decreased substance use. Both interventions highlight the values of future goals (e.g., academic, career goals) planned by adolescents, and encourage them to rethink the value of substance-related goals (Rafei et al., 2021). 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 the other example of preventive approach which have been developed to encourage prosocial behaviors (i.e., 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 cost of using substances (Debenham et al., 2020). 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 is one of the pioneers in this field developed to improve adolescents' neuroscience based substance literacy level (Debenham et al., 2020).

4.3. *Interventions targeting Cognitive System (CS)*
This group of interventions includes all those approaches that tend to promote planned, forethoughtful, and goal-oriented behaviors in which a person could mentally reflect on the consequences of their behavior. 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 used 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 brief image-based multiple behavior intervention ((Chad) Werch et al., 2008), Health4Life app (Thornton et al., 2021), Life Skills Training (Griffin et al., 2006a), RealTeen (Schwinn et al., 2016), and Preventure (Conrad, 2016) which enhance personal competence in terms of goal setting, planning, self-monitoring, decision-making and problem solving to motivate and facilitate behavioral change and improve resilience.

4.4. *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), 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 are "Call it a Night®" (CIAN) (Fucito et al., 2017) and Transdiagnostic Sleep and Circadian Intervention (TranS-C) (Dong et al., 2020) as well as 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.

4.5. *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 such as mindfulness programs working on internal attention to calm the mind, body, and behavior and improve self-awareness (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; Lee et al., 2010; 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 Rational Addiction Prevention Program (RAPP) (López-Ramírez et al., 2021), 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.

5. 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 limit the 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.

6. 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 survey. 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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