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ADHD AND AFFECTIVITY MODULATE THE ASSOCIATION BETWEEN REINFORCEMENT SENSITIVITY AND ADOLESCENT SUBSTANCE USE

PhD thesis

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LIST OF ABBREVIATIONS

Abbreviation	Concept
ADHD	attention-deficit/hyperactivity disorder
ARS-5	ADHD Rating Scale-5
AUD	alcohol use disorder
AUDIT	Alcohol Use Disorders Identification Test
BAS	behavioral approach system
BIS	behavioral inhibition system
BLADS	Budapest Longitudinal Study of ADHD and Externalizing Disorders
CD	conduct disorder
CN	caudate nucleus
CN/PU	region spanning the caudate nucleus and putamen
DBD-RS	Disruptive Behavior Disorders-Rating Scale
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition, revised
ERP	event-related potential
ESPAD	European School Survey Project on Alcohol and Other Drugs
FDR	False Discovery Rate
FFFS	fight-flight-freeze system
fMRI	functional magnetic resonance imaging
FWHM	full width at half maximum
mPFC	medial prefrontal cortex

NA	negative affectivity
NAcc	nucleus accumbens
ODD	oppositional defiant disorder
PA	positive affectivity
PANAS	Positive and Negative Affectivity Schedule
PU	putamen
RewP	reward positivity
SBQ	Smoking Behavior Questionnaire
SFG	superior frontal gyrus
SPM	Statistical Parametric Mapping
WFU	Wake Forest University School of Medicine
YSR	Youth Self-Report
PRI	perceptual reasoning index
VCI	verbal comprehension index
VS	ventral striatum

1. INTRODUCTION

This dissertation focuses on the association between substance use and reinforcement sensitivity; specifically, on the boundary conditions and mechanisms of the relation between adolescent substance use and neural and self-reported reinforcement sensitivity. Adolescent substance use has deleterious individual and societal outcomes. However, available interventions, especially preventions, are generally ineffective. Enhancing the available knowledge by further specifying which characteristics explain and/ or modulate risk for adolescent substance use may inform the development or enhancement of interventions. In the following literature review, I will: first, review basic descriptive information on adolescent substance use; second, review evidence indicating reinforcement sensitivity may be a relevant characteristic in explaining and modulating risk for adolescent substance use; and third, review evidence indicating attention-deficit/hyperactivity disorder (ADHD) and affectivity may also be relevant characteristics in explaining and modulating risk for such use.

1.1. Adolescent substance use

Substance use is the use of specific substances, including but not limited to alcohol, drugs, inhalants, and tobacco products, that can be consumed, inhaled, injected, or absorbed into the body and may cause dependence and other effects that are harmful (1).

Adolescence is a developmental period of interest with regard to substance use. Adolescent developmental processes affect brain circuitry (2,3), neurotransmitter receptor systems (4,5) and the endocrine system (6,7) and contribute to difficulties with inhibition (8,9) and enhanced reward sensitivity (10). Furthermore, adolescence is characterized by asynchronous maturation of affect- and motivation-generating and affect- and motivation regulatory systems such that the former completes development earlier whereas the latter matures later (11). As a result, relative to adults and children, adolescents exhibit greater reward but lower punishment sensitivity, reward sensitivity peaks in adolescence (12), and adolescents are more likely (than adults or children) to engage in risk taking, including substance use (2). My focus hereafter is on alcohol, cannabis, and nicotine, as these are the substances most likely to be used by adolescents.

Adolescents frequently engage in substance use. For example, 35% of European adolescents have used alcohol, nine percent has been drunk at least twice, and 13% have smoked a cigarette in their lifetime (13). Twelve percent have used cannabis in their lifetime (13). Twenty percent of European adolescents have used alcohol, seven percent has been drunk at least twice, and 15% of Hungarian adolescents have smoked an e-cigarette in the past 30 days (13). Five to ten percent of Hungarian adolescents have used cannabis in the past 30 days (13).

Adolescence is a vulnerable developmental period with regard to negative outcomes related to substance use. *First*, relative to adults, adolescents are more vulnerable to the harmful effects of chemical substances (14), including alcohol (11), cannabis (15), and nicotine (16), and less sensitive to deterring effects but more susceptible to the reinforcing effects of substances (17). *Second*, adolescent substance use has both short- and long-term negative consequences. For example, in adolescents, repeated exposure to alcohol is associated with neuroinflammation (18–20) and repeated exposure to substances has neurotoxic effects (21–26). Evidence also indicates cognitive effects including deficits in executive functioning (27) and learning (28) as well as in academic achievement (27,29,30). As a final example, adolescent substance use is one of the strongest predictors of addiction in adulthood and is associated with enhanced likelihood of psychiatric disorders in adulthood (31) (cf: (32)).

Despite availability of evidence-based interventions (e.g., cognitive-behavioral therapy, ecological family-based treatment, motivational interviewing/motivational enhancement therapy) (33) for substance use, there is room for improvement, as abstinence rates are relatively low (34–36). Such relatively low abstinence rates may be a result of characteristics implicated in substance use that remain unaddressed or of inadequate personalization in these interventions. Accordingly, better understanding or identification of predisposing factors, mechanisms and maintaining characteristics of adolescent substance use (2) may be needed to improve effectiveness of early identification and of prevention.

1.2. Reinforcement sensitivity as a characteristic relevant to adolescent substance use

A characteristic that may be implicated in adolescent substance use is reinforcement sensitivity. In this dissertation, I adopt the conceptualization of the revised

reinforcement sensitivity-theory of personality (37). The theory posits that individual differences in personality characteristics relevant to reinforcement sensitivity are governed by the underlying sensitivity of three brain-behavioral systems, the behavioral approach system (BAS), the fight-flight-freeze system (FFFS), and the behavioral inhibition system (BIS). The BAS is activated by reward stimuli and relevant behavioral responses manifest as active approach behavior toward a goal (causing pleasure). The FFFS is activated by stimuli indicating danger and FFFS activation manifests in *active avoidance* aim are removing the organism from danger, via "fight", "flight" or "freeze". The BIS is activated by punishment stimuli and relevant behavioral responses manifest as *passive avoidance* allowing for conflict (between competing drives, e.g. approach-avoidance) detection, monitoring and resolution.

Individual differences in reinforcement sensitivity are associated with substance use. For example, in adolescents, BAS sensitivity is positively associated with likelihood of drug use (38), and predicts earlier initiation and greater quantity of use (39–41). Findings on the association of BIS sensitivity with drug use are mixed; in one research, BIS sensitivity was not associated with severity and initiation of substance use (39), whereas in another study, BIS sensitivity was associated with substance use (42). Differences in neural reinforcement sensitivity are also associated with substance use (e.g., (43)). For example, attenuated fMRI-measured mPFC response to reward anticipation and receipt are associated with greater substance misuse (44) and enhanced VS response to reward receipt is associated with greater misuse (44). In an ERP study, differential ERP response to alcohol rewards compared to non-drug rewards is linked to a higher risk of alcohol misuse and problems (45).

1.3. Affectivity and ADHD as modulators of the association between reinforcement sensitivity and adolescent substance use

Knowledge on the mechanisms and modulators of the association between reinforcement sensitivity and adolescent substance use is limited (cf. (38,39)). Prior studies have examined only a few mediating or moderating variables, including inhibition (39), social variables such as parental characteristics, parenting, and peer relationships (38,42), and sex (38,42).

Given the complexity of substance use as a behavioral pattern, reinforcement sensitivity may not be directly linked with substance use, but indirectly through more

proximal traits as mechanisms (38). Affectivity may be a mechanism of the association of reinforcement sensitivity with substance use (37,41,46,47). ADHD may also modulate that association (48–51). Accordingly, my focus in this dissertation is on affectivity and ADHD as characteristics relevant to the association between reinforcement sensitivity and substance use.

1.3.1. Affectivity as a mechanism of the association between reinforcement sensitivity and adolescent substance use

Affectivity is a domain of temperament (52,53), and is a trait-like tendency that characterizes how an individual experiences certain types of emotions (i.e., positive and negative) (54). Individual variations in BAS, BIS and FFFS sensitivity constitute the neural foundation of temperament (52,55–58) and early temperament creates a foundation for adult personality (52). Temperament also determines how individuals behaviorally and emotionally respond to environmental and internal stimuli (59).

Data indicate affectivity is associated both with reinforcement sensitivity and with substance use and, as such, may be a mechanism of the association between reinforcement sensitivity and adolescent substance use, though this has not been examined. Greater BAS sensitivity is associated with greater PA (60) (and extraversion as a relevant personality dimension (37)), whereas greater BIS (60) and FFFS sensitivity are associated with greater NA (56,57) (and neuroticism as a relevant personality dimension (60)). Similarly, neural response to reward (e.g., RewP, to both monetary gain and loss) are associated with self-report affectivity and emotion dysregulation (61). Accordingly, affectivity is a promising but scarcely investigated variable that may explain heterogeneity in outcomes in youth (62).

Regarding affectivity and substance use, NA is associated with substance use (63–65), forms the core of disorders of substance use (64), and enhances risk for initiation of substance use (66,67). Considering PA, current empirical evidence is mixed. Findings of a longitudinal study show that PA is negatively associated with substance use (i.e., a composite variable of tobacco, cannabis and alcohol use) in an adolescent community sample (47). In another study, PA was positively associated with cannabis use in community samples (68,69). Further, traits that are related to PA, such as sensation-seeking and extraversion are positively associated with alcohol use in adolescents and young adults (70–72).

1.3.2. ADHD and comorbidities as modulators of the association between reinforcement sensitivity and adolescent substance use

Attention-deficit/hyperactivity disorder is characterized by developmentally inappropriate symptoms of inattention and hyperactivity/impulsivity and functional impairment (73). ADHD is associated with reinforcement sensitivity and with substance use.

On the group level, individuals with ADHD exhibit atypical reinforcement sensitivity but the association between ADHD and reinforcement sensitivity is complex. For example, behavioral findings show individuals with ADHD exhibit temporal discounting (74) and delay aversion (75). fMRI studies suggest ADHD is characterized by enhanced prefrontal and striatal response to receipt of reward (76) and attenuated parietal response to, along with lower levels of VS signaling in reward learning (77). Differences in hyperactivity-impulsivity may be more relevant to reinforcement sensitivity than inattention (78,79), as hyperactivity-impulsivity (but not inattention) has been linked to temporal discounting (74) and to attenuated VS response to reward (79,80).

Findings suggest ADHD is associated with substance use. Children and adolescents with ADHD are at a higher risk of alcohol, cannabis, and nicotine use (81) and of developing substance use disorders during adolescence and adulthood (82,83). Specifically, childhood ADHD predicts alcohol disorders and problematic use (84). In ADHD, current and lifetime prevalence of cannabis misuse are high, 36% and 51%, respectively (85). In clinical and high-risk samples, ADHD has been identified as an independent risk factor for nicotine use (86). Further, ADHD is associated with faster progression from initial to heavy levels of substance use in adolescence (87). Genetic liability for ADHD is also associated with genetic liability for (88,89) and likelihood of (90) substance use.

ADHD is thus associated with both reinforcement sensitivity and substance use. ADHD may also modulate the association between reinforcement sensitivity and adolescent substance use. Specifically, the association between certain correlates of ADHD – e.g. behavioral and emotional features (49), electrophysiological features (50,51), and genetic polymorphisms (48) – with outcomes differs in direction or magnitude, depending on ADHD status. There is reason to believe that the association

between neural response to reward and substance use also varies depending on ADHD status, though this remains to be explored (91).

Summary

Adolescent substance use is a key and leading public health problem: it is common, and on the rise (92–96) and is associated with consequences that are serious, including at the level of the individual and society. Available approaches to early identification and prevention are apparently inadequate or insufficient to tackle frequency and severity of adolescent substance use, indicating there is need to improve our understanding of hypothesized predisposing and maintaining mechanisms so that those can be better incorporated into screening and intervention. Reinforcement sensitivity is a relevant target as adolescence is characterized by developmental processes that affect reinforcement sensitivity and differences in substance use are associated with differences in reinforcement sensitivity. Yet, gaps in knowledge remain about specifics of the association between reinforcement sensitivity and adolescent substance use, including regarding mechanisms and modulators. Affectivity and ADHD are two characteristics that may be implicated in the association between reinforcement sensitivity and adolescent substance use and in the research that is presented in this dissertation, it was my aim to empirically examine the extent to which and the way in which affectivity and ADHD are implicated in the association between reinforcement sensitivity and adolescent substance use.

2. OBJECTIVES

The overarching AIM of my doctoral research was: To examine the boundary conditions and mechanisms of the relation between reinforcement sensitivity and adolescent substance use.

Specific AIM 1 (empirical article): Examine whether affectivity mediates the association between reinforcement sensitivity and adolescent substance use. Specifically, whether self-reported negative and positive affectivity mediate the association between self-reported BAS and BIS sensitivity and self-reported alcohol, cannabis, and nicotine use in adolescents.

Specific AIM 2 (empirical article): Examine whether ADHD risk modulates the association between reinforcement sensitivity and adolescent affective, clinical, and substance use outcomes. Specifically, examine whether (1) the association between neural response to reward and concurrent and prospective measures of affectivity, externalizing and internalizing symptoms, and alcohol use differs across adolescents at-risk for and not at-risk for ADHD and (2) ADHD risk moderates the association between neural response to reward and concurrent and prospective measures of affectivity, externalizing and internalizing symptoms, and alcohol use.

Empirical Article I.: The Association Between Reinforcement Sensitivity and Substance Use is Mediated by Individual Differences in Dispositional Affectivity in Adolescents (62)

Research Questions:

First, are individual differences in reinforcement sensitivity associated with affectivity and with adolescent substance use? If associated, what is the direction and nature (which indices of which characteristic) of the association?

Second, do individual differences in affectivity mediate (statistically) the association between reinforcement sensitivity and adolescent substance use? If so, what is the direction and nature (which indices of which characteristic) of the indirect effect?

Aims were to examine:

(1) associations between reinforcement sensitivity (indexed by BAS and BIS sensitivity), affectivity (indexed by NA and PA) and substance use (i.e., alcohol use and alcohol problems, nicotine and cannabis use)

(2) and whether associations between reinforcement sensitivity and substance use are mediated by NA and PA

Empirical Article II.: Concurrent and Prospective Associations of Reward Response with Affective and Alcohol Problems: ADHD-Related Differential Vulnerability (91)

Research Questions: Does ADHD risk modulate the association between response to reward and relevant outcomes? Specifically, does the association between response to reward and affective, externalizing, internalizing, and substance use outcomes differ in magnitude given ADHD risk (depend on level of ADHD risk) in adolescents?

Aims were to examine whether the association between fMRI-measured neural response to reward attainment (relative to loss) and concurrent and prospective measures of affective, externalizing, internalizing, and substance use outcomes would differ across adolescents at-risk for and not at-risk for ADHD.

3. METHODS

3.1. Procedures (Study I. and Study II.)

Data were collected in the context of a larger longitudinal project, the Budapest Longitudinal Study of ADHD and Externalizing Disorders (BLADS) study (62,91,97–99). Participants were a sample comprised of a community subsample and a clinical subsample (an adolescent sample who showed different levels of ADHD severity). For the larger study, 14–17-year-old adolescents were recruited from clinics and community partners (mainly, public middle, technical and vocational, and high schools) and assessed at three timepoint across 30 months (baseline, T1: 18-month follow-up, and T2: 30-month follow-up). Permission for recruitment was obtained from the principal of each school as well as the class teacher of each 8th, 9th, 10th and 11th grade classroom. Research staff informed students about the larger study, including its general goals and methods.

Exclusionary criteria for the larger study were cognitive ability ≤ the percentile rank corresponding to a full-scale IQ score of 80 across administered indices for adolescents (100) and adults (101); autism spectrum disorder (severity≥2); bipolar, obsessive-compulsive, and psychotic disorder on the Structured Clinical Interview for DSM-5 Disorders - Clinical Version (SCID-5-CV) (102); neurological illness as indicated by self-report; and having visual impairment as defined by impaired vision <50 cm, as indicated by self-report, unless corrected by glasses or contact lenses. For Study II, an additional exclusionary criterion was contraindication to magnetic resonance imaging (i.e., having any ferromagnetic implants such as pacemaker, non-removable braces; having any implants held in place by a magnet (e.g., dental implant); non-removeable piercings; having any metal fragments under the skin; as well as certain health conditions such as aneurysm, epilepsy, Sturge-Weber syndrome, ventricular septal defect). BLADS was approved by the National Institute of Pharmacy and Nutrition (OGYÉI/17089-8/2019) and has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Once parents and participants provided written informed consent (and assent), at baseline, participants underwent a series of tests, including assessment of cognitive functioning, a clinical interview, genetic sampling and questionnaires (first assessment session), electrophysiological measures and further questionnaires (second assessment session) and an fMRI measurement and questionnaires (third assessment session). Parents

also completed a series of questionnaires using the Psytoolkit platform (103) and the Qualtrics software, Version June 2020–September 2022 (Qualtrics, Provo, UT). At T1, all baseline measures were repeated with the exception of assessment of cognitive functioning and the clinical interview and at T2, all baseline measures were repeated with the exception of assessment of cognitive functioning and fMRI measurement.

Assessments took place in laboratories of a research institute and were conducted by master's and doctoral level trainees supervised by a team comprised of a clinical psychologist, a child psychiatrist, and an adult psychiatrist. Assessment sessions lasted roughly three hours and were conducted either before (9:00am–12:00 pm) or after (13:30–17:00 pm) lunch. Data analyzed in Study I were obtained during the first and the second assessment sessions at baseline, whereas data analyzed in Study II were obtained during the first three assessment sessions at baseline, and during the first assessment session at T1.

3.2. Study I.

3.2.1. Participants

Participants were 121 adolescents (M_{age} = 15.67 years; *SD* = 0.94; range: 14–17 years, 51% boys, 100% Caucasian). The average family net income fell in the 300 001–500 000 HUF range[1], and average level of highest primary caregiver education fell between short-term (vocational) training and bachelor's degree[2]. Average cognitive ability was $M_{\sim PRI\ percentile\ rank}$ = 54.58 (*SD* = 25.21) and $M_{\sim VCI\ percentile\ rank}$ = 67.33 (*SD* = 21.44). For additional details on basic sample descriptives including heaviness and history of substance use, see Table 1.

3.2.2. Measures

3.2.2.1. Adolescent self-report measures[3]

Reinforcement sensitivity. The Reinforcement Sensitivity Theory of Personality Questionnaire (RST-PQ; (104)) is a 79-item self-report measure of revised Reinforcement

[1] $M_{monthly\ family\ income}$=6.66, *SD*=1.148 on the following scale: 2: 50 001 – 99 000 Ft; 5: 200 001 – 300 000 Ft; 6: 300 001 – 500 000 Ft; 7: 500 001–700 000 Ft; 8: 700 000 – 800 000 Ft; 9: 800 000 – 1 000 000 Ft.

[2] $M_{highest\ education\ of\ primary\ caregiver}$=6.58, *SD*=1.368 on the following scale: 3: trade school; 4: vocational secondary school; 5: high school; 6: vocational (short term) training courses for adults; 7: Bachelor's degree; 8: Master's degree; 9: PhD degree.

[3] As the assumptions of Cronbach's alpha are not met with the measures used (e.g. tau equivalence), we also assessed McDonald's omega. We present alpha values so that those can be compared with the broader

Sensitivity Theory (rRST) personality dimensions, comprised of three subscales: Behavioral Activation System (BAS; 32 items, e.g., *„I regularly try new activities just to see if I enjoy them."*), Behavioral Inhibition System (BIS; 23 items, e.g., *„ I feel sad when I suffer even minor setbacks."*), and Fight-Flight-Freeze System (FFFS; 10 items, e.g., *„I would be frozen to the spot by the sight of a snake or spider."*), and two additional subscales developed to complement the core RST-PQ: Panic (6 items, e.g., *„My heart starts to pump strongly when I am getting upset."*) and Defensive Fight (8 items, e.g., *„If I feel threatened I will fight back."*). The BAS subscale consists of four further subscales: Reward Interest (7 items, e.g., *„I am a very active person."*), Reward Reactivity (10 items, e.g., *„I am especially sensitive to reward."*), Goal-Drive Persistence (7 items, e.g., *„I put in a big effort to accomplish important goals in my life."*), and Impulsivity (8 items, e.g., *„I'm always buying things on impulse."*). Respondents rate how accurately each item describes them on a four-point Likert-type response format scale (1 – 'not at all' to 4 – 'highly'). Higher scores reflect greater reinforcement sensitivity. Prior findings indicate that the RST-PQ has adequate psychometric properties, as indicated by acceptable internal consistency and convergent and discriminant validity (104–106).

In BLADS, the English version of the RST-PQ was translated into Hungarian applying the following procedures: (1) the English version was translated into Hungarian by three independent translators; (2) these three translations were combined into a single "summary translated" measure by a fourth independent translator, reconciling all discrepancies across the three translations/ors; (3) the "summary" was back-translated into English by two additional independent translators and (4) the two back-translations were combined into a single "summary back-translated" measure by members of the research team, reconciling all discrepancies in a manner that the "summary back-translation" measure best matches the Hungarian "summary translated" measure. This "summary back-translated" questionnaire was sent to the original author(s) who provided the research team with feedback and ultimately approved the translated measure (P. Corr, personal communication, May 29, 2019). ((62), p. 3-4.)

literature but rely on omega values to determine whether the measure exhibited acceptable internal consistency.

In Study I, the BAS subscale exhibited good (ω = 0.829, α = 0.869) and the BIS subscale exhibited excellent (ω = 0.909, α = 0.904) internal consistency. The BAS and BIS subscales were used in analyses.

Positive and negative affectivity. The Positive and Negative Affectivity Schedule (PANAS; (54)) is a 20-item self-report measure of state and/or trait positive and negative affect, comprised of two subscales, the positive affect (PA) subscale, reflecting the extent to which a person feels active, alert and enthusiastic, and the negative affect (NA) subscale, reflecting a general dimension of subjective distress and a variety of aversive mood states such as contempt, anger, fear, guilt, disgust, and nervousness. Respondents rate the extent to which they are experiencing each mood state "during the past two weeks" (i.e., trait version) or "right now" (i.e., state version) on a five-point Likert-type response format scale (1 – 'very slightly or not at all' to 5 – 'very much'). Higher scores on the PA and NA subscales indicate greater positive and negative affect, respectively. Prior findings indicate that the PANAS has adequate psychometric properties, as indicated by good internal consistency and convergent and discriminant validity with other measures (107). Additionally, the Hungarian translation (108) also has adequate psychometric properties, as indicated by good internal consistency (109).

In Study I, the PANAS-trait NA and PA subscales were administered and both exhibited good (ωNA = 0.853, αNA = 0.851; ωPA = 0.823, αPA = 0.821) internal consistency. The NA and PA subscales were used in analyses.

Alcohol problems. The Alcohol Use Disorders Identification Test (AUDIT; (110)) is a 10-item self-report measure of alcohol use, comprising 3 subscales, Harmful Alcohol Use (e.g., *„Have you or someone else been injured because of your drinking?"*), Dependence (e.g., *„How often during the last year have you found that you were not able to stop drinking once you had started?"*), and Hazardous Alcohol Use (e.g., *„How many drinks containing alcohol do you have on a typical day when you are drinking?"*). Items are rated on a five-point scale (0 – 'never' to 4 – 'four or more times a week'), with higher scores indicating greater difficulty with alcohol use. In adolescents, alcohol problems are indicated by a total AUDIT score ≥5 (111). Prior findings indicate the AUDIT has adequate psychometric properties (113), as indicated by acceptable internal consistency and high item-total correlations (110,112). Furthermore, the Hungarian translation also

has adequate psychometric properties, as indicated by internal consistency (114) and construct validity (114–116).

In Study I, the AUDIT total exhibited acceptable **(**$\alpha = 0.717$[4]**)** internal consistency and was used in analyses.

Alcohol use. The master questionnaire of the European School Survey Project on Alcohol and Other Drugs (ESPAD; (117)) is a measure of substance use among 15–16-year-old European adolescents. Items of the master questionnaire assess alcohol consumption, energy drink consumption, drug use, cigarette smoking, internet use and gaming. In Study I, select items were used to assess alcohol use: "*On how many occasions (if any) have you had any alcoholic beverage to drink?*" (response options ranging from 0 to ≥ 40), "*On how many occasions (if any) have you been intoxicated from drinking alcoholic beverages, for example staggered when walking, not being able to speak properly, throwing up or not remembering what happened?*" (response options ranging from 0 to ≥ 40), and "*How many times (if any) have you had five or more drinks on one occasion?*" (response options ranging from none to ≥ 10). For each item, respondents are asked to respond by addressing the question as applied to (a) their lifetime, (b) during the last 12 months, and (c) during the last 30 days. In prior studies (118,119), individual items were used as indices of substance use, with greater scores representing greater use. As the ESPAD survey is administered anonymously, little empirical research has been done on its psychometrics. Available relevant data indicate the ESPAD has adequate psychometric properties, as indicated by high test–retest reliability and internal consistency (120,121) and some evidence of validity, in the form of comparable responses across countries (117).

In Study I, we used a total score of all items across all categories for the sake of parsimony and to therefore reduce the number of models tested. In Study I, the total score of all items exhibited excellent ($\omega = 0.936$, $\alpha = 0.904$) internal consistency.

Cannabis use. The Illicit Drug Use Questionnaire (122) is an 11-item self-report measure of the frequency of use of different substances – i.e., cannabis, nicotine, hallucinogens, inhalants, cocaine, tranquilizers, opiates, methamphetamine, club drugs, ecstasy, and illegal use of prescription drugs – during the past year (e.g., „*In the past 12*

[4] Omega could not be calculated due to low variance on certain items.

months, how often did you use metamphetamine?"). Greater use is indicated by higher scores.

For BLADS, the English version of the Illicit Drug Use Questionnaire was translated into Hungarian following identical steps as for the translation of RST-PQ. The translated measure was approved by the original author (B. T. Wymbs, personal communication, August 16, 2019). In Study I, the marijuana item was used in analyses.

Nicotine use. The Smoking Behavior Questionnaire (SBQ; (123)) is a 13-item self-report measure of actual nicotine use (i.e., tobacco chewing and cigarette smoking) (e.g., *"Have you smoked a cigarette?"*, *"Have you ever tried chewing tobacco?"*, *"During the past month, how many cigarettes have you smoked on an average day?"*) and attitude and environmental influences promoting nicotine use (e.g., *"How do your parents feel about someone your age smoking cigarettes?"*, *"How many of your friends smoke cigarettes on a pretty regular basis?"*, *"Does either of your parents (or step-parents or guardians) smoke cigarettes?"*, *"Do you think smoking can have an effect on the health of young people your age?"*). Of the 13 items, the 8 items applicable to all youth (and not only to those who have smoked or chewed at least a few times as indicated by respective screener items) were used to create a total nicotine use score as our goal was to assess use risk as reflected by actual use and general risk, both of which can be assessed in youth who do not regularly smoke cigarettes or chew tobacco. Greater use risk is indicated by higher scores. Prior findings indicate the SBQ has adequate psychometric properties, as indicated by acceptable internal consistency (123).

For BLADS, the English version of the SBQ was translated into Hungarian following identical steps as for the translation of RST-PQ. The translated measure was approved by the original author (J. Donovan, personal communication, August 2, 2019).

In Study I, the total nicotine use score exhibited acceptable ($\omega = 0.688$, $\alpha = 0.359$) internal consistency and was used in analyses.

3.2.3. Analytic plan

To examine associations among variables, bivariate correlations were computed. To examine whether associations between reinforcement sensitivity and substance use are mediated by NA and PA as parallel mediators, we used PROCESS v4.3 (124) to calculate 95% CIs around the total and indirect effects with 1,000 bootstrap resamples,

implementing a heteroscedasticity-consistent standard error estimator[5]. As is commonly done in – and recommended for – atemporal/ mathematical mediation studies (126–130), to establish unidirectionality of observed effects (i.e., that models are supported in the hypothesized direction, but not the reverse), in case of significant models, we also tested the alternative model with dispositional affectivity as the predictor, reinforcement sensitivity as the mediator, and substance use variables as the outcome.

ESPAD items were added later in BLADS. Accordingly, information regarding alcohol use was accessible – and therefore analyzed – on a subsample (*n*=103).

The importance of adjusting for age and sex in analyses involving substance use and reinforcement sensitivity is highlighted by age and sex differences in substance use (131,132) and in reinforcement sensitivity (133,134). Similarly, adjustment of externalizing and internalizing symptoms is also warranted given association between such symptoms and substance use and reinforcement sensitivity (135).

Consequently, as a follow-up analysis to supported mediational models, we investigated whether age, sex, or comorbid externalizing and internalizing symptoms (defined as a total of all symptoms on all evaluated externalizing, i.e., attention-deficit/ hyperactivity, conduct, and oppositional defiant disorders and internalizing, i.e., persistent depressive disorder, major depressive disorder, generalized and social anxiety disorders, panic disorder, agoraphobia, – measured by the SCID-5-CV (102) –, moderate the mediational models. We tested moderation of the direct and the indirect path of mediation models (one for each supported mediational model with each potential moderator), in which age, sex, internalizing and externalizing symptoms were tested as moderators of the direct path (from reinforcement sensitivity to substance use) and the indirect path (from reinforcement sensitivity to substance use through affectivity) applying PROCESS v4.3 (124), applying 1000 bootstrap resamples and a heteroscedasticity-consistent standard error estimator.

[5] "A post hoc power analysis using Monte Carlo Power Analysis for Indirect Effects (125) indicated that, with sample size and parameter estimates derived from the current dataset, Monte Carlo draws per replications set to 5000, alpha set to 0.1, in case of *alcohol use*, for the BIS>alcohol use model, power was 0.2 (a1b1 path) and 0.8 (a2b2 path and for the BAS>alcohol use model power was 0 (a1b1 path) and 0 (a2b2 path). In case of *alcohol problems*, for the BIS>alcohol problems model, power was 0.2 (a1b1 path) and 0.4 (a2b2 path) and for the BAS>alcohol problems model power was 0.2 (a1b1 path) and 0 (a2b2 path). For *tobacco use*, for the BIS>tobacco use model power was 0.4 (a1b1 path) and 0.6 (a2b2 path) and for the BAS>tobacco use model power was 0.8 (a1b1 path) and 0.2 (a2b2 path). In case of marijuana use, for the BIS>marijuana use model power was 0.2 (a1b1 path) and 0 (a2b2 path) and for the BAS>marijuana use model power was 0.8 (a1b1 path) and 0 (a2b2 path)." ((62), p. 5.)

3.3. Study II.

3.3.1. Participants

Participants included in the current study were 129 adolescents. At baseline, they were between the ages of 14–17 years, n = 50 met criteria for at-risk for ADHD (Entire sample: M_{age} = 15.29 years, SD = 1.00; 62% boys; not at-risk for ADHD subsample: M_{age} = 15.37 years, SD = 0.98; 51.9% boys; at-risk for ADHD subsample: M_{age} = 15.18 years, SD = 1.04; 78% boys). At 18-month follow up (T1), data on variables of interest in the current study were available for 118 adolescents (8.5% attrition) (n = 45 at-risk for ADHD as classified at baseline). At T1, adolescents were between the ages of 15–19 years (M_{age} = 17.20 years, SD = 1.04, 57.8% boys).

At baseline, N = 305 adolescents were enrolled into the BLADS study and n = 256 expressed interest in the MR portion and n = 150 attended the MR portion (structural, resting state, task-based). Of these, n = 144 had Doors fMRI data (see section '3.3.2.1. *fMRI task'* of Study II Methods). (Of the six who attended the MR portion but did not have Doors fMRI data, five did not begin scanning due to claustrophobia (that they did not indicate at the pre-screen) and one began scanning but discontinued after the first Doors run due to a headache. Doors fMRI data from 15 adolescents were excluded because of movement artifacts (n = 10 ≥ 2 mm/°), because the adolescents did not have complete MR portion data (and their measurement was therefore atypical in some regard) (n = 4), or assessment was nonstandard due to autism spectrum disorder (n = 1) (see section '3.3.2.2. *fMRI data acquisition and preprocessing'* of Study II Methods). Doors fMRI data from 129 adolescents were analyzed statistically.

Representative of the Hungarian population based on the official census data, (136), the majority of adolescents (93.6%) identified as Hungarian whereas 5.5% identified as belonging to a Hungarian ethnic minority group (1 as Slavic, 2 as Serb, 2 as Kraut, 1 as Roma and 1 as Transylvanian) (0.8% had missing ethnicity data). Participants were from a slightly above-average socioeconomic background based on data from 74.4% of participants (for whom such data were available) and monthly net household income per person (average net income fell in the 150 001–200 000 HUF/ month range, with the Hungarian average being approximately 147 000 HUF/month in 2020) (137).

3.3.2. Measures

3.3.2.1. fMRI task

During fMRI, adolescents completed the Doors task (138) designed to probe initial response to reward. The task consisted of 80 trials in total, presented in two blocks of 40 trials/condition. Participants were told that on each trial they could either gain 100 or lose 50 (HUF). At the beginning of each trial, a fixation mark (+) appeared for 900 ms. Afterwards, participants were presented with an image of two doors for 3000 ms and asked to choose one door by pressing one of two buttons on a response device (ResponseGrip, NordicNeuroLab AS, Bergen, Norway). Finally, after a short delay of 500 ms, feedback was presented for 1000 ms on the screen. Gain was represented by a green "↑" and loss was represented by a red "↓". The duration of the intertrial interval (ITI) varied from 4500 to 7500 ms (with 1000 ms steps, each ITI used for 5 trials/condition in each block). In a single block, 20 gain and 20 loss trials were presented in random order.

To maximize effectiveness of the experimental paradigm, participants were informed that the virtual money they accrued can be exchanged for snacks (chips, candy, etc., chosen by the participant before the task).

3.3.2.2. fMRI data acquisition and preprocessing

Structural imaging was performed with a magnetization-prepared rapid gradient-echo (MP-RAGE) scan in a Siemens MAGNETOM Prisma 3 T scanner with a standard Siemens 32-channel head coil using the following parameters: repetition time (TR) = 2300 ms, echo time (TE) = 3.03 ms, field of view (FOV) = 256 × 256 mm, flip angle (FA) = 9°, gap = 0.5 mm, slice thickness = 1 mm, voxel size = 1 × 1 × 1 mm.

Functional imaging was performed with blood-oxygen-level-dependent (BOLD) sensitive whole-brain fMRI using the following parameters: TR = 2000 ms, TE = 30 ms, FOV = 210 × 210 mm, FA = 83°, slices = 36, gap = 0.75 mm, slice thickness = 3mm, voxel size = 3 × 3 × 3 mm. Standard preprocessing procedures were performed in SPM12, including slice timing correction, image realignment to correct head movements, normalization to standard 2 × 2 × 2 mm Montreal Neurological Institute space, as well as spatial smoothing with a Gaussian FWHM kernel of 8 mm. All participant data satisfied

criteria for quality with minimal motion correction (average movements across runs were ≤2 degrees rotation and ≤2 mm in any one direction).

First-level single subject SPMs were created from a model, specifying the onset of win (i.e., ↑) and loss (i.e., ↓) cues. The brain regions involved in reward processing were identified by using second-level whole brain analysis for the win vs. loss *t*-test contrast. Using an extent threshold of 10 contiguous voxels, images were thresholded using a family-wise error (FWE) corrected $\alpha = 0.05$.

3.3.2.3. Adolescent self-report measures[6]

Alcohol problems. Details of the Alcohol Use Disorders Identification Test (AUDIT; (110)) are presented above in section *'3.2.2.1. Adolescent self-report measures'* of Study I Methods.

In Study II, the Harmful Alcohol Use ($\omega = 0.344$, $\alpha = 0.222$) and the Dependence ($\omega = 0.225$, $\alpha = 0.343$) subscales exhibited unacceptable whereas the Hazardous Alcohol Use subscale exhibited acceptable ($\omega = 0.799$, $\alpha = 0.794$) internal consistency. As such, in Study II, only the Hazardous Alcohol Use subscale was used in analyses.

Positive and negative affectivity. Details of the Positive and Negative Affectivity Schedule (PANAS; (54)) are presented above in section *'3.2.2.1. Adolescent self-report measures'* of Study I Methods.

In Study II, the PANAS-trait was administered and both subscales exhibited acceptable internal consistency ($\omega NA = 0.834$, $\alpha NA = 0.830$; $\omega PA = 0.831$, $\alpha PA = 0.825$). In Study II, the NA and PA subscales were used in analyses.

Anxiety problems and depressive problems. The Youth Self-Report (YSR; (139)) is a 112-item self-report questionnaire designed for adolescents (ages 11–18) assessing aspects of impaired and adaptive functioning. The YSR measures impaired functioning via *Diagnostic and Statistical Manual of Mental Disorders (DSM)-oriented scales*: depressive problems *(*e.g., *„There is very little that I enjoy."*), anxiety problems *(„I am nervous or tense."*), somatic problems (e.g., *„Physical problems without known medical cause, for example stomachaches"*) attention-deficit/ hyperactivity problems

[6] As the assumptions of Cronbach's alpha are not met with the measures used (e.g. tau equivalence), we also assessed McDonald's omega. We present alpha values so that those can be compared with the broader literature but rely on omega values to determine whether the measure exhibited acceptable internal consistency.

(e.g., *„I have trouble concentrating or paying attention."*) conduct problems (e.g., *„ I am mean to others."*), and oppositional defiant problems (e.g., *„I disobey at school."*); as well as *syndrome scales*: depressed/withdrawn (e.g., *„I would rather be alone than with others."*), anxious/depressed (e.g., *„I am self-conscious or easily embarrassed."*), somatic complaints (e.g., *„I feel dizzy or lightheaded."*), attention problems (e.g., *„I daydream a lot."*), thought problems (e.g., *„Parts of my body twitch or make nervous movements"*), social problems (e.g., *„I feel lonely."*), aggressive behavior (e.g., *„I destroy my own things."*), rule-breaking behavior (e.g., *„I lie or cheat."*), internalizing problems, and externalizing problems, and adaptive functioning through competence scales: activities (e.g., *„Please list your favorite hobbies, activities, and games, other than sports"*), academic performance (e.g., *„Failing/Below Average/Average/Above Average"*), and social competence (e.g., *„About how many close friends do you have?"*). Respondents rate items are rated on a 3-point scale (0 – 'Not True', 1 – 'Somewhat or Sometimes True', 2 – 'Very True or often True'). The cutoff for subclinical problems on the YSR is a T-score of ≥64 (139). Prior findings indicate the YSR has adequate psychometric properties, as indicated by acceptable test-retest reliability and internal consistency (139).

In BLADS, the English version of the YSR was translated into Hungarian following procedures also described in Study I Methods. The "summary back-translated" questionnaire was sent to the publisher who provided the research team with feedback and ultimately approved the translated measure (Achenbach System of Empirically Based Assessment (ASEBA) representative, personal communication, August 26, 2019).

In Study II, the depressive problems subscale exhibited good ($\omega = 0.840$, $\alpha = 0.820$) and the anxiety problems subscale exhibited acceptable ($\omega = 0.781$, $\alpha = 0.760$) internal consistency and were used in analyses.

3.3.2.4. Parent-report measures[7]

ADHD. The ADHD Rating Scale-5 (ARS-5) (140) is a 30-item parent- and teacher-report measure of the past 6-month presence and severity of Diagnostic and

[7] As the assumptions of Cronbach's alpha are not met with the measures used (e.g. tau equivalence), we also assessed McDonald's omega. We present alpha values so that those can be compared with the broader literature but rely on omega values to determine whether the measure exhibited acceptable internal consistency.

Statistical Manual of Mental Disorders, 5th Edition ADHD symptoms (9 inattentive symptom items and 9 hyperactivity/ impulsivity symptom items) and functional impairment across six domains: relationship with peers, relationship with significant others (family members for the home version), behavioral functioning, academic functioning, homework performance and self-esteem (2 × 6 impairment items, with one set corresponding to hyperactivity/impulsivity and one to inattention). The ARS-5 is comprised of two symptoms scales, Inattention (e.g., „*Fails to give close attention to details or makes careless mistakes in schoolwork, at work, or during other activities"*, „*Does not seem to listen when spoken to directly")* and Hyperactivity-Impulsivity (e.g., „*Fidgets with or taps hands or feet or squirms in seat*", „*Talks excessively*") and a Total Scale. The ARS-5 is suitable for ages 5–17 years, with separate forms for children (5–10 years) and adolescents (11–17 years) and age-appropriate and DSM-5 compatible descriptions of symptoms. Parents and teachers rate items on a four-point scale ranging in case of symptoms from 0 (never or rarely) to 3 (very often) and in case of impairment from 0 ("no problem") to 3 ("severe problem"); higher scores reflect more severe symptoms and impairment. The ARS-5 has adequate psychometric properties, as indicated by reliability of the adolescent, home version (e.g., 6-week test-retest reliability and internal consistency) and predictive and concurrent validity as well as clinical utility (140). Data indicate the Hungarian translation also has adequate psychometric properties, as indicated by acceptable construct validity (98) and internal consistency (99).

In BLADS, the English version of the ARS-5 was translated into Hungarian following procedures described in Study I Methods. The original author approved the translated measure (G. DuPaul, personal communication, June 5, 2020).

In Study II the adolescent home (i.e., parent-report) version was used, and the ARS-5 parent-report exhibited excellent internal consistency (ωHI = 0.907, αHI = 0.904; ωIA = 0.946, αIA = 0.944). ADHD classification (at-risk) was determined using parent-report on the ADHD Rating Scale-5 (ARS-5) (140). To be classified as at-risk for ADHD, adolescents had to meet a total of ≥4 of the Diagnostic and Statistical Manual of Mental Disorders (5th ed; DSM-5) ADHD symptoms (from either the inattentive or the hyperactive/ impulsive domain) (141).

Oppositional defiant disorder and conduct disorder. The Disruptive Behavior Disorders-Rating Scale (DBD-RS) (142) is a 45-item parent- and teacher-report measure

of the presence and severity of DSM-III-R ADHD symptoms (9 hyperactivity/ impulsivity symptom items and 9 inattentive symptom items), CD symptoms (15 items, e.g., *„Physically cruel to others."*, *„Often truant from school, even before the age of 13."*), and ODD (8 items, e.g., *„Often actively defies or refuses to comply with adults' requests or rules"*, *„Often angry and resentful of others."*). Parents and teachers rate items on a four-point scale ranging 0 (not at all) to 3 (very much); more severe symptoms are indicated by higher scores. The DBD-RS has adequate psychometric properties as indicated by acceptable internal consistency and factor structure (e.g., (143)).

In BLADS, the English version of the DBD-RS was translated into Hungarian following identical steps as for the ARS-5. Approval from the original author was not requested as item wordings are identical to Diagnostic and Statistical Manual of Mental Disorders item wordings, with a Diagnostic and Statistical Manual of Mental Disorders Hungarian translation available (144).

In Study II, the parent-report form was used, and the CD and ODD items were of interest. As items reflect DSM-III-R symptom wording, those were modified to match DSM-5 symptom wording (73). In Study II, the ODD subscale exhibited excellent (ω = 0.906, α = 0.9), whereas the CD subscale exhibited unacceptable (α = 0.374[8]) internal consistency. As such, in Study II, only the ODD subscale was used in analyses.

3.3.3. Analytic Plan

Consistent with comparable research (e.g., (48)), the following analytic pipeline was employed given that the research question was whether and to what extent the magnitude of the association between X and Y differs between groups rather than whether the relation between X and Y changes as a function of W (i.e., moderation). First, bivariate correlations were computed between neural response to gain (relative to loss) and baseline variables (using data from N = 129 adolescents): internalizing, externalizing, and alcohol use problems; affectivity; as well as age and sex, separately for groups at-risk for and not at-risk for ADHD. Second, partial bivariate correlations were computed between neural response to gain (relative to loss) and 18-month follow-up variables, controlling for corresponding baseline values (using data from n = 118 adolescents): internalizing, externalizing, and alcohol use problems; affectivity, separately for groups

[8] Omega could not be calculated due to low variance on certain items.

at-risk for and not at-risk for ADHD. Third, correlations were chosen for further analysis, when: the correlation was significant at $p \leq 0.05$ in one but not the other group, when the correlation was significant at $p \leq 0.05$ in both groups but the association was in the opposite direction across groups, or the correlation was significant at $p \leq 0.05$ in both groups but the magnitude of the effect was meaningfully different, i.e., a small vs. a medium or a large *r* value or a medium vs. a large *r* value. Selected *r* value-pairs (i.e., in the at-risk vs. not at-risk groups) were transformed into *z*-scores (i.e., Fisher's *r* to *z* transformation) and *z*-scores were compared for statistical significance. Obtained *p* values were Benjamini-Hochberg corrected for FDR.

Assumptions of analyses of correlation were checked; Kolmogorov-Smirnov results indicated normality was violated in case of all variables but indices of fMRI-measured initial response to reward attainment (see section *'4.2.2. fMRI'* of Study II Results), baseline PA and 18-month follow-up PA and NA. Accordingly, analyses involving these variables were conducted assessing Pearson correlations and analyses involving any of the remaining variables were conducted using Spearman's rank order correlations. Across analyses, outcomes were continuous measures of anxiety problems, depressive problems, affectivity, hazardous alcohol use, and ODD symptoms.

Of the $n = 118$ participants who participated in T1 assessments, self-report data were available on the AUDIT for $n = 118$, PANAS (PA and NA) for $n = 116$ (two participants did not complete the entire battery), the YSR for $n = 117$ (one participant did not complete the entire battery), and parent-report data were available on the DBD-RS (ODD) for $n = 91$ participants. (ODD data were thus missing for $n = 27$ participants; either the parent did not complete the questionnaire, or the adolescent turned 18 and ODD was no longer an appropriate characteristic to assess). Analyses involving each of these variables were conducted with the respective sample sizes.

To determine whether follow-up data were missing at random, binary logistic regression analyses were conducted for each dependent variable (ODD symptoms, hazardous alcohol use, PA, NA, depressive problems and anxiety problems) separately. Independent variables were entered simultaneously and included adolescent age, sex, cognitive ability, ADHD risk status, and socioeconomic status (SES). For YSR, only anxiety problems are reported, and for the PANAS, only NA, as no participant had missing follow-up data on only one of the subscales of the anxiety/depression and

affectivity measure). As a fourth of the sample (n = 33) did not report their SES, these analyses were repeated without SES as an independent variable.

Alternate model analyses were conducted as a form of a statistical check/ internal replication to evaluate the robustness of obtained findings. Accordingly, whether ADHD risk status moderates the association between neural response to gain and internalizing/ externalizing and affective outcomes was examined. PROCESS v4.3 (124) was employed to estimate simple moderation models with brain response as the predictor, T1 internalizing/ externalizing and affective symptoms, and alcohol problems as the outcome, ADHD risk status as the moderator, and baseline internalizing/ externalizing and affective symptoms, and alcohol problems as a covariate. These analyses were repeated with baseline age and sex as additional covariates.

4. RESULTS

4.1. Study I.

4.1.1. Mediation analyses with BAS sensitivity

The models with affectivity mediating the link between alcohol use and BAS sensitivity (95%CIs [-0.043; 0.062]) and between alcohol problems and BAS sensitivity (95%CIs [-0.104; 0.173]) were not supported.

Affectivity mediated the association between nicotine use and BAS sensitivity (point estimate = -0.209; *SE* = 0.088; 95%CIs [-0.388; -0.024])[9], with PA driving the mediational effect (point estimate = -0.213; *SE* = 0.087; 95%CIs [-0.395; -0.049]). BAS sensitivity was positively associated with PA and greater PA was negatively associated with nicotine use (the BAS-nicotine use association was positive but nonsignificant, p = .195) (Table 2). In follow-up mediation analyses that only included the actual nicotine use items pooled together, affectivity mediated the association between nicotine use and BAS sensitivity (point estimate = -0.019; *SE* = 0.70; 95%CIs [-0.033; -0.006]) (direction of effects was the same as in the overall model). In follow-up mediation analyses with the environmental/ attitude influences items pooled together, affectivity mediated the association between BAS sensitivity and environmental/ attitude influences promoting nicotine use (point estimate = -0.017; *SE* = 0.01; 95%CIs [-0.031; -0.004]) (direction of effects was the same as in the overall model).

Affectivity mediated the association between cannabis use and BAS sensitivity (point estimate = -0.141; *SE* = 0.071; 95%CIs [-0.295; -0.010]), with PA driving the mediational effect (point estimate = -0.143; *SE* = 0.068; 95%CIs [-0.296; -0.027]). BAS sensitivity was positively associated with PA and PA showed a trend-level negative association with cannabis (the BAS-cannabis use association was positive but nonsignificant, p = .442) (Table 2).

4.1.2. Mediation analyses with BIS sensitivity

Affectivity mediated the association between alcohol use and BIS sensitivity (point estimate = 0.210; *SE* = 0.099; 95%CIs [0.022;0.399]), with NA driving the mediational effect (point estimate = 0.202; *SE* = 0.092; 95%CIs [0.034;0.390]). BIS

[9] Reported data correspond to completely standardized indirect effects of X on Y.

sensitivity was positively associated with NA and NA was also positively associated with alcohol use (the BIS-alcohol use association was negative but nonsignificant, $p = .253$) (Table 2).

Affectivity mediated the association between alcohol problems and BIS sensitivity (point estimate = 0.209; *SE* = 0.065; 95%CIs [0.090;0.337]), with NA driving the mediational effect (point estimate = 0.224; *SE* = 0.062; 95%CIs [0.107;0.359]). BIS sensitivity was positively associated with NA and NA was also positively associated with alcohol problems (the BIS-alcohol problems association was negative but nonsignificant, $p = .253$) (Table 2).

Affectivity mediated the association between nicotine use and BIS sensitivity (point estimate = 0.215; *SE* = 0.083; 95%CIs [0.055;0.382]), with both PA and NA driving the mediational effect (point estimate = 0.038; *SE* = 0.027; 95%CIs [0.004;0.116] and point estimate = 0.177; *SE* = 0.076; 95%CIs [0.023;0.325], respectively). BIS sensitivity was negatively associated with PA but BIS sensitivity was positively associated with NA. NA was positively associated with nicotine use whereas PA was negatively associated with nicotine use. (The BIS-nicotine use association was negative but nonsignificant, $p = .552$) (Table 2). In follow-up mediation analyses that only included the actual nicotine use items pooled together (i.e., items measuring actual nicotine chewing and cigarette smoking compared to environmental/ attitude influences promoting nicotine use), affectivity mediated the association between BIS sensitivity and nicotine use, with NA driving the mediational effect (point estimate = 0.019; *SE* = 0.01; 95%CIs [0.003;0.035]) (direction of effects was the same as in the overall model)). In follow-up mediation analyses with the environmental/ attitude influences items pooled together, affectivity mediated the association between BIS sensitivity and environmental/ attitude influences promoting nicotine use, with PA driving the mediational effect (point estimate = 0.003; *SE* = 0.01; 95%CIs [0.013;0.009]) (direction of effects was the same as in the overall model).

The model with affectivity mediating the association between cannabis use and BIS sensitivity was not supported (95%CIs [-0.175;0.257]).

See Fig. 1. for a visual summary of mediation results.

None of the alternative models (i.e., where the roles of the mediator and independent variables were reversed) were supported (95% CIs: NA > BIS > alcohol

problems [-0.041;0.009]; NA > BIS > alcohol use [- 0.360;0.116]; PA > BAS > nicotine use [-0.001;0.066]; PA > BAS > cannabis use [-0.012;0.051]; NA > BIS > nicotine use [-0.152;0.134]); PA > BIS > nicotine use [- 0.015;0.001]). None of the moderated (age, sex, or comorbid externalizing or internalizing symptoms) mediational models were supported (all highest order interaction 95% CIs contained zero).

Table 1

Descriptive statistics of sample and variables.

	AUDIT total	AUDIT 1	AUDIT 2	AUDIT 3	ESPAD 1			ESPAD 2			ESPAD 3		
					a	b	c	a	b	c	a	b	c
M	1.95	.802	.364	.281	3.394	2.692	1.548	1.731	1.500	1.144	2.163	1.856	1.221
SD	2.549	.691	.753	.551	1.792	1.488	.787	1.108	.788	.380	1.673	1.361	.557
range	0-12	0-2	0-4	0-3	1-7	1-7	1-5	1-5	1-4	1-3	1-6	1-6	1-4

Note. AUDIT = Alcohol Use Disorders Identification Test – AUDIT 1: *How often do you have a drink containing alcohol*? (response options ranging from 0 = Never; 2 = 2-4 times a week; and 4 = 4 or more times a week); AUDIT 2: *How many drinks containing alcohol do you have on a typical day when you are drinking*? (response options ranging from 0 = 1 or 2; 2 = 5 or 6; and 4 = 10 or more); AUDIT 3: *How often do you have six or more drinks on one occasion*? (response options ranging from 0 = Never; 2 = Monthly; and 4 = Daily or almost daily). ESPAD = European School Survey Project on Alcohol and Other Drugs – ESPAD 1: *On how many occasions (if any) have you had any alcoholic beverage to drink? a: in your lifetime, b: in the past 12 months, c: in the past 30 days* (response options ranging from 1 = Never; 2 = 1-2 times; 3 = 3-5 times; 4 = 6-9 times; 5 = 10-19 times; 6 = 20-39 times; 7 = 40 or more); ESPAD 2: *On how many occasions (if any) have you been intoxicated from drinking alcoholic beverages, for example staggered when walking, not being able to speak properly, throwing up or not remembering what happened in your lifetime? a: in your lifetime, b: in the past 12 months, c: in the past 30 days* (response options ranging from1 = Never; 2 = 1-2 times; 3 = 3-5 times; 4 = 6-9 times; 5 = 10-19 times; 6 = 20-39 times; 7 = 40 or more); ESPAD 3: *How many times (if any) have you had five or more drinks on one occasion? (A 'drink' is one glass/bottle of beer [ca. 5 dl], one bottle of cider [ca. 5 dl], one glass of wine [ca. 5 dl] or one glass of concentrated alcohol, such as palinka [5 cl]) a: in your lifetime, b: in the past 12 months, c: in the past 30 days* (response options ranging from 1 = Never; 2 = Once; 3 = Twice; 4 = 3-5 times; 5 = 6-9 times; 6 = 10 or more).

In the current sample, the average sample household income was around but somewhat higher than the 2018 Hungarian regional average https://www.ksh.hu/docs/hun/xstadat/xstadat_eves/i_zhc014c.html. (62)

Table 1 continued

Descriptive statistics of sample and variables.

	Nicotine use total	Nicotine use 1	Nicotine use 2	Nicotine use 3	Cannabis
M	13.116	1.256	14.593	6.111	.215
SD	3.199	.725	1.010	7.526	.933
range	8-25	1-5	13-17	0-16	0-6

Note. Smoking Behavior Questionnaire – Nicotine use 1: *During the past month, how many cigarettes have you smoked on an average day?* (response options ranging from 1 = None at all; or 4 = About half a pack a day; and 7 = About 12 packs or more a day); Nicotine use 2: *How old were you when you first smoked a cigarette?*; Nicotine use 3: *How old were you when you started smoking on a pretty regular basis, like one or two times a week?*. Cannabis – *In the past 12 months, how often did you use marijuana?* (response options ranging from 0 = Not at all; 3 = 8-11 times; 7 = 2-3 times a week; and 11 = Several times a day).

In the current sample, the average sample household income was around but somewhat higher than the 2018 Hungarian regional average https://www.ksh.hu/docs/hun/xstadat/xstadat_eves/i_zhc014c.html. (62)

Table 2

Model coefficients for parallel mediation models testing effects of reinforcement sensitivity through affectivity on substance use.

	Consequent					
	M (PA)		*M* (NA)		*Y* (alcohol use)[a]	
Antecedent	*b*	SE	*b*	SE	*b*	SE
X (BAS)	.313***	.039	.011	.064	.001	.094
M (PA)	-	-	-	-	-.024	.198
M (NA)	-	-	-	-	.231[§]	.122
Constant	6.645[§]	3.576	17.522**	5.812	13.814*	6.623
	R^2=.43, *F*(1,101)=64.064***		R^2=.01, *F*(1,101)=1.198		R^2=.04, *F*(1,99)=1.199	
	Consequent					
	M (PA)		*M* (NA)		*Y* (alcohol use)[a]	
Antecedent	*b*	SE	*b*	SE	*b*	SE
X (BIS)	-.111*	.05	.385***	.04	-.092	.091
M (PA)	-	-	-	-	-.046	.151
M (NA)	-	-	-	-	.353*	.155
Constant	39.973***	2.429	-1.544	1.978	17.170*	7.04
	R^2=.05, *F*(1,101)=4.899*		R^2=.52, *F*(1,101)=93.019***		R^2=.04, *F*(1,99)=1.827	
	Consequent					
	M (PA)		*M* (NA)		*Y* (alcohol problems)	
Antecedent	*b*	SE	*b*	SE	*b*	SE
X (BAS)	.304***	.031	.011	.052	.016	.019
M (PA)	-	-	-	-	.012	.046
M (NA)	-	-	-	-	.086[§]	.044
Constant	7.807***	2.729	17.608***	4.616	-1.399	1.692
	R^2=.45, *F*(1,123)=98.553***		R^2=.01, *F*(1,123)=.045		R^2=.06, *F*(3,121)=2.127	

Table 2 continued.

	Consequent					
	M (PA)		*M* (NA)		*Y* (alcohol problems)	
Antecedent	*b*	SE	*b*	SE	*b*	SE
X (BIS)	-.103*	.046	.376***	.036	-.029	.026
M (PA)	-	-	-	-	.030	.039
M (NA)	-	-	-	-	.128**	.040
Constant	39.358***	2.252	-.821	1.746	.109	1.976
	R^2=.05, *F*(1,123)=5.055*		R^2=.49, *F*(1,123)=108.870***		R^2=.06, *F*(3,121)=3.394*	

	Consequent					
	M (PA)		*M* (NA)		*Y* (nicotine use)	
Antecedent	*b*	SE	*b*	SE	*b*	SE
X (BAS)	.306***	0.033	.020	.053	.067	.042
M (PA)	-	-	-	-	-.193*	.078
M (NA)	-	-	-	-	.085§	.043
Constant	7.616	2.945**	16.717***	4.737	12.313***	2.306
	R^2=.44, *F*(1,123)=87.115***		R^2=.01, *F*(1,123)=.143		R^2=.11, *F*(3,121)=4.872**	

	Consequent					
	M (PA)		*M* (NA)		*Y* (nicotine use)	
Antecedent	*b*	SE	*b*	SE	*b*	SE
X (BIS)	-.093	.048	.373***	.037	-.012	.029
M (PA)	-	-	-	-	-.095*	.048
M (NA)	-	-	-	-	.119§	.060
Constant	38.969***	2.329	-.698	1.795	14.768***	2.206
	R^2=.04, *F*(1,123)=3.769§		R^2=.49, *F*(1,123)=10.756***		R^2=.08, *F*(3,121)=4.209**	

Table 2 continued.

	Consequent					
	M (PA)		*M* (NA)		*Y* (cannabis use)	
Antecedent	*b*	SE	*b*	SE	*b*	SE
X (BAS)	.304***	.031	.011	.052	.009	.012
M (PA)	-	-	-	-	-.034[§]	.020
M (NA)	-	-	-	-	.013	.018
Constant	7.807**	2.729	17.608***	4.616	.361	.371
	R^2=.45, *F*(1,123)=98.553***		R^2=.01, *F*(1,123)=.046		R^2=.04, *F*(3,121)=1.537	
	Consequent					
	M (PA)		*M* (NA)		*Y* (cannabis use)	
Antecedent	*b*	SE	*b*	*b*	SE	*b*
X (BIS)	-.103*	.046	.376***	.036	.008	.008
M (PA)	-	-	-	-	-.109[§]	.011
M (NA)	-	-	-	-	.005	.019
Constant	39.360***	2.252	-.821	1.746	.334	.284
	R^2=.05, *F*(1,123)=5.055 *		R^2=.49, *F*(1,123)=108.870***		R^2=.04, *F*(3,121)=1.055	

Note. ***: $p<.001$; **: $p<.01$; *: $p<.05$; [§]: $.1>p>.05$. [a]: $n=103$. Alcohol use = ESPAD (select items) Total; Alcohol problems = AUDIT Total. (62)

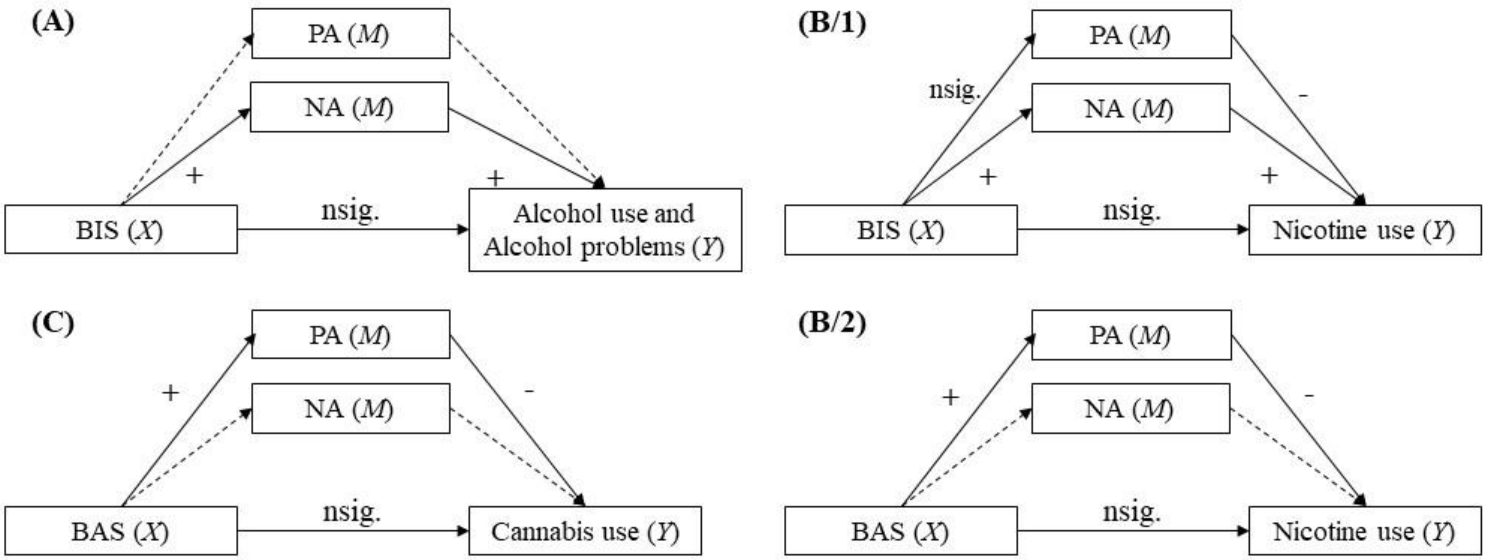

Figure 1. **Visual summary of parallel mediation results:** (A) The association between both BIS and alcohol use and between BIS and alcohol problems was mediated by NA. (B/1) The association between BIS and nicotine use was mediated by positive and negative affectivity. (B/2) The association between BAS and nicotine use was mediated by positive affectivity. (C) The association between BAS and cannabis use was mediated by positive affectivity.

Note. BAS = Behavioral Activation System; BIS = Behavioral Inhibition System; PA = positive affectivity; NA = negative affectivity; + = a positive effect, where greater scores on one variable are associated with greater scores on the other variable; - = a negative effect, where greater scores on one variable are associated with lower scores on the other variable; nsig. = a nonsignificant effect. Solid lines represent supported indirect effects, dashed lines represent non-supported indirect effects. Alcohol use = ESPAD (select items) Total; Alcohol problems = AUDIT Total. (Rádosi et al., 2021)

4.2. Study II

4.2.1. Descriptive statistics and missing data analyses

For descriptive statistics on demographic and clinical and fMRI variables across the entire sample and ADHD at-risk and not at-risk subsamples, see Tables 3, 4. Regarding sample variability, the cutoff for subclinical problems on the YSR is a T-score of ≥64 (139). Seventeen (13%) and twenty adolescents (15%) of the total sample exhibited subclinical anxiety problems and depressive problems at baseline, with comparable proportions across groups (12% for anxiety problems and 15% for depressive problems of the not at-risk group and 14% for anxiety problems and 16% for depressive problems of the at-risk group). Regarding alcohol use, in adolescents, the cutoff for alcohol problems on the Alcohol Use Disorders Identification Test is a total score ≥5 (111). Twenty-one adolescents (16%) of the total sample exhibited alcohol problems at baseline and fourty-five (38.1%) at follow-up, with comparable proportions across groups (18% of the at-risk group and 15% of the not-at-risk group at baseline and 37.7% of the at-risk group and 38.3% of the not-at-risk group at follow-up). 36% of the total sample was at-risk for ODD (defined as exhibiting ≥2 symptoms), with 40% of the at-risk for ADHD subsample and 34% of the not at-risk for ADHD subsample being at-risk for ODD.

Models for missing data analyses were nonsignificant: ODD symptoms $\chi2(5) = 3.638$, $p = 0.603$, hazardous alcohol use $\chi2(5) = 4.265$, $p = 0.512$, anxiety problems $\chi2(5) = 6.912$, $p = 0.227$, and NA $\chi2(5) = 8.415$, $p = 0.135$. Models were also nonsignificant when SES was excluded from the independent variables: ODD symptoms $\chi2(4) = 2.658$, $p = 0.617$, hazardous alcohol use $\chi2(4) = 4.697$, $p = 0.320$, anxiety problems $\chi2(4) = 6.295$, $p = 0.178$, and NA $\chi2(4) = 8.342$, $p = 0.080$.

4.2.2. fMRI

Second-level whole brain analyses revealed cortical activation in the right SFG and subcortical activations right-sided in a region spanning the caudate nucleus and putamen (CN/PU) as well as in the left NAcc and in the right PU (145) (Fig. 2).

SFG, CN/PU, PU and NAcc fMRI activity elicited by the win vs. loss contrast was extracted using WFU Pick-Atlas (146,147) from voxels (with an uncorrected $p <$

0.001) within a 6 mm sphere centered on the coordinates reported in Fig. 2. Statistical analyses were performed on these regional fMRI activations.

4.2.3. Concurrent associations between initial response to reward and outcomes given ADHD risk

Correlations between variables differed across adolescents at-risk for (Table 5) and not at-risk for (Table 6) ADHD. The association of SFG response to gain with depressive problems (z=−2.51, p=0.012) and NA (z=−2.7, p=0.007) differed across groups such that in youth at-risk for ADHD, greater SFG response to gain was associated with both lower depressive problems (medium effect) and lower NA (medium effect). However, these characteristics were not associated in youth not at-risk for ADHD. Correlations did not differ across groups in case of SFG response with anxiety problems and with PA (ps > 0.05).

4.2.4. Prospective associations between initial response to reward and outcomes given ADHD risk

Correlations between variables differed across adolescents at-risk for (Table 7) and not at-risk for (Table 8) ADHD. Controlling for baseline hazardous alcohol use, the association of PU response to gain with 18-month hazardous alcohol use differed (z = 2.88 p = 0.004) across groups such that in youth at-risk for ADHD, greater PU response to gain was associated with greater 18-month hazardous alcohol use (medium effect), whereas in youth not at-risk for ADHD, greater PU response to gain was associated with lower 18-month hazardous alcohol use (small effect). Correlations did not differ across groups in case of SFG response and PA or in case of NAcc response and PA (ps > 0.05).

4.2.5. Alternative model/ internal replication analyses

a) Concurrent associations between initial response to reward and outcomes given ADHD risk

The association between SFG response to gain and baseline depression was moderated by ADHD risk (F(1, 123) = 7.666, ΔR^2 = 0.057, p = 0.006); no main effects were supported (ps > 0.050). The SFG response by ADHD risk interaction (b = −7.722, SE = 2.789, p = 0.006; 95% CI[−13.243,−2.201]) was such that greater SFG response was associated with lower baseline depression in adolescents at-risk for ADHD (b = −7.451,

SE = 2.209, *p* = 0.001; 95% CI[−11.823, −3.080]) but not associated in adolescents not at-risk (*b* = 0.271, *SE* = 1.703, *p* = 0.874; 95% CI[−3.101, 3.642]).

Regarding concurrent associations with baseline age and sex as covariates, the association between SFG response to gain and baseline depression was moderated by ADHD risk ($F(1, 121)=8.183$, $\Delta R^2=0.052$, $p=0.005$); the main effects of ADHD risk (*b*=2.082, *SE*=0.751, *p*=0.006; 95% CI[0.594, 3.569]), sex (*b*=−2.183, *SE*=0.711, *p*=0.003; 95% CI[−3.590, −0.776]), and age (*b*=1.285, *SE*=0.337, *p* < 0.001; 95% CI[0.617; 1.953]) were supported. The SFG response by ADHD risk interaction (*b*=−7.486, *SE*= 2.617, *p*=0.005; 95% CI[−12.666, −2.305]) was such that greater SFG response was associated with lower baseline depression in adolescents at-risk for ADHD (*b*=−6.359, *SE*=2.083, *p*=0.003; 95% CI[−10.482, −2.235]) but not associated in adolescents not at-risk (*b*=1.127, *SE*=1.590, *p*=0.480; 95% CI[−2.021, 4.275]).

b) Prospective associations between initial response to reward and outcomes given ADHD risk

The association between PU response to gain and 18-month hazardous alcohol use was moderated by ADHD risk ($F(1, 113) = 6.572$, $\Delta R^2 = 0.036$, $p = 0.012$); the main effect of baseline hazardous alcohol use (*b* = 0.614, *SE* = 0.082, *p* < 0.001; 95% CI[0.451, 0.777]) was supported. The PU response by ADHD risk interaction (*b* = 4.479, *SE* = 1.747, *p* = 0.012; 95% CI[1.018, 7.941]) was such that greater PU response was associated with greater 18-month hazardous alcohol use in adolescents at-risk for ADHD (*b* = 2.516, *SE* = 1.261, *p* = 0.048; 95% CI[0.017, 5.015]) but not associated in adolescents not at-risk (*b* = −1.963, *SE* = 1.205, *p* = 0.106; 95% CI[−4.349, 0.424]).

The association between SFG response to gain and 18-month ODD was moderated by ADHD risk ($F(1, 86)=5.575$, $\Delta R^2=0.027$, $p=0.020$); the main effect of baseline ODD (*b*=0.560, *SE*=0.077, *p* < 0.001; 95% CI[0.406, 0.713]) was supported. The SFG response by ADHD risk interaction (*b*=6.292, *SE*=2.665, *p*=0.020; 95% CI[0.995, 11.589]) was such that greater SFG response was associated with greater 18-month ODD symptoms in adolescents at-risk for ADHD (*b*=6.169, *SE*=2.232, *p*=0.007; 95% CI[1.733, 10.606]) but not associated in adolescents not at-risk (*b*=−0.123, *SE*=1.523, *p*=0.936; 95% CI[−3.149, 2.904]).

Regarding prospective associations with baseline age and sex as covariates, the association between PU response to gain and 18-month hazardous alcohol use was moderated by ADHD risk ($F(1, 111) = 6.148$, $\Delta R^2 = 0.034$, $p = 0.015$); the main effect of baseline hazardous alcohol use ($b = 0.596$, $SE = 0.084$, $p < 0.001$; 95% CI[0.428, 0.763]) was supported. The PU response by ADHD risk interaction ($b = 4.392$, $SE = 1.771$, $p = 0.015$; 95% CI[0.882, 7.902]) was such that greater PU response was associated with (marginal significance) greater 18-month hazardous alcohol use in adolescents at-risk for ADHD ($b = 2.505$, $SE = 1.269$, $p = 0.051$; 95% CI[−0.009, 5.019]) but not associated in adolescents not at-risk ($b = -1.887$, $SE = 1.222$, $p = 0.125$; 95% CI[−4.308, 0.534]).

The association between SFG response to gain and 18-month ODD was moderated by ADHD risk ($F(1, 84) = 5.530$, $\Delta R^2 = 0.028$, $p = 0.021$); the main effect of baseline ODD ($b = 0.559$, $SE = 0.078$, $p < 0.001$; 95% CI[0.404, 0.715]) was supported. The SFG response by ADHD risk interaction ($b = 6.342$, $SE = 2.697$, $p = 0.021$; 95% CI[0.979, 11.705]) was such that greater SFG response was associated with greater 18-month ODD symptoms in adolescents at-risk for ADHD ($b = 6.270$, $SE = 2.270$, $p = 0.007$; 95% CI[1.756, 10.784]) but not associated in adolescents not at-risk ($b = -0.072$, $SE = 1.540$, $p = 0.963$; 95% CI[−3.134, 2.991]).

Table 3

Descriptive statistics for demographic variables.

	Entire sample (*N*=129)					At-risk for ADHD (*n*=50)					Not at-risk for ADHD (*n*=79)				
	Min	Max	*M*	*SD*	% boys	Min	Max	*M*	*SD*	% boys	Min	Max	*M*	*SD*	% boys
Age	14	17	15.29	1.003	-	14	17	15.18	1.044	-	14	17	15.37	.976	-
Sex	0	1	.62	.487	62	0	1	.78	.418	78	0	1	.52	.503	51.9
PRI	4	98	57.63	24.856	-	4	97	54.58	26.667	-	7	98	59.59	23.591	-
VCI	15	98	68.63	22.437	-	15	98	63.12	23.506	-	22	98	72.15	21.129	-

Note. Age=participant age at baseline visit; PRI=estimated percentile of perceptual reasoning index; VCI=estimated percentile of verbal comprehension index. (91)

Table 4

Descriptive statistics for fMRI and clinical variables across baseline and 18-month follow-up.

	Entire sample (*N*=129)					At-risk for ADHD (*n*=50)					Not at-risk for ADHD (*n*=79)				
	Min	Max	*M*	*SD*	range	Min	Max	*M*	*SD*	range	Min	Max	*M*	*SD*	range
	Baseline														
PA	13	48	34.473	6.076	10-50	13.00	47.00	33.620	6.633	10-50	20	48	35.013	5.674	10-50
NA	10	35	18.806	6.145	10-50	10.00	33.00	19.620	6.246	10-50	10	35	18.291	6.064	10-50
AP	0	11	3.80	3.225	0-18	0	11	3.96	3.482	0-18	0	11	3.69	3.072	0-18
DP	0	21	4.11	4.118	0-26	0	21	4.43	4.646	0-26	0	16	3.91	3.767	0-26
ODD	8	30	14.062	5.284	0-24	8	30	17.180	5.263	0-24	8	27	12.090	4.270	0-24
AUD	0	8	1.492	1.948	0-12	0	8	1.660	2.134	0-12	0	8	1.385	1.825	0-12
NAcc	-.44	.65	.134	.205	-	-.44	.61	.140	.234	-	-.24	.65	.130	.185	-
Caud/Put	-.83	.64	.135	.215	-	-.83	.64	.130	.271	-	-.30	.53	.137	.173	-
Put	-.76	.65	.081	.193	-	-.76	.49	.058	.208	-	-.43	.65	.096	.183	-
SFG	-.82	.96	.122	.265	-	-.56	.70	.100	.265	-	-.82	.96	.136	.266	-
	18-month follow-up														
PA T1	18	50	34.216	6.579	10-50	18	50	32.818	7.362	10-50	24	49	35.069	5.944	10-50
NA T1	10	36	20.009	6.138	10-50	10	32	18.864	5.948	10-50	10	36	20.708	6.188	10-50
AP T1	0	17	4.966	4.049	0-18	0	14	4.489	3.952	0-18	0	17	5.264	4.108	0-18
DP T1	0	21	6.017	4.911	0-26	0	20	5.733	5.132	0-26	0	21	6.194	4.796	0-26
ODD T1	8	29	13.066	4.851	0-24	8	29	16.152	5.734	0-24	8	20	11.310	3.169	0-24
AUD T1	0	9	2.551	2.159	0-12	0	9	2.422	2.210	0-12	0	7	2.630	2.138	0-12

Notes. PA=positive affectivity; NA=negative affectivity; AP=YSR anxiety problems total score; DP=YSR depressive problems total score; ODD=Disruptive Behavior Disorders Rating Scale (DBD-RS) ODD symptoms; AUD= hazardous alcohol use score of Alcohol Use Disorders Identification Test measuring alcohol problems; T1=measured at 18-month follow-up; NAcc=nucleus accumbens; Caud/Put=region spanning the caudate nucleus and putamen; Put=putamen; SFG=superior frontal gyrus; range=possible minimum-maximum scores of measures. (91)

Table 5

Associations of neural reward response with baseline affectivity and externalizing, internalizing, and substance use problems in adolescents at-risk for ADHD.

			PA*	NA	Anxiety problems	Depressive problems	ODD	AUD
NAcc	*r (p)*		.224 (.122)	-.119 (.416)	-.096 (.513)	-.146 (.316)	.225 (.121)	-.188 (.196)
	Bootstrap	Bias (SE)	.000 (.158)	.005 (.148)	.007 (.143)	.005 (.128)	.002 (.139)	-.002 (.140)
		95% CI	-.107; .498	-.385; .187	-.358; .201	-.386; .105	-.059; .491	-.455; .090
Caud/Put	*r (p)*		.142 (.331)	-.089 (.544)	-.191 (.189)	-.085 (.560)	.134 (.359)	-.160 (.271)
	Bootstrap	Bias (SE)	.005 (.147)	.001 (.134)	.002 (.147)	.000 (.130)	.001 (.143)	-.001 (.138)
		95% CI	-.143; .419	-.332; .199	-.457; .114	-.345; .160	-.148; .411	-.422; .111
Put	*r (p)*		.269 (.062)	-.194 (.182)	-.235 (.104)	-.116 (.429)	-.050 (.735)	.027 (.856)
	Bootstrap	Bias (SE)	-.001 (.122)	.008 (150)	.008 (.146)	.006 (.144)	.004 (.150)	-.005 (.152)
		95% CI	.029; .504	-.463; .136	-.511; .079	-.390; .192	-.338; .245	-.286; .333
SFG	*r (p)*		**.283** (.049)	**-.324** (.023)	**-.333** (.019)	**-.393** (.005)	.062 (.673)	.064 (.664)
	Bootstrap	Bias (SE)	-.011 (.124)	.007 (.144)	.007 (.145)	.005 (.128)	.005 (.145)	-.008 (.138)
		95% CI	.035; .502	-.578; -.010	-.594; -.026	-.614; -.130	-.224; .338	-.216; .318

Notes. NAcc=nucleus accumbens; Caud/Put=region spanning the caudate nucleus and putamen; Put=putamen; SFG=superior frontal gyrus; PA=positive affectivity; NA=negative affectivity; Anxiety problems=YSR anxiety problems total score; Depressive problems=YSR depressive problems total score; ODD=Disruptive Behavior Disorders Rating Scale (DBD-RS) ODD symptoms; AUD= hazardous alcohol use score of Alcohol Use Disorders Identification Test measuring alcohol problems. Neural response to gain was elicited by the win vs. loss contrast and extracted from voxels (with an uncorrected $p<.001$) within a 6 mm sphere centered on the coordinates.
*Pearson's correlation coefficient is reported in case of correlation pairs involving variables both with normal distribution.
Correlations compared across groups are shaded in grey. (91)
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Table 6

Associations of neural reward response baseline affectivity and externalizing, internalizing, and substance use problems in adolescents not at-risk for ADHD.

			PA*	NA	Anxiety problems	Depressive problems	ODD	AUD
NAcc	*r (p)*		-.054 (.645)	.069 (.552)	-.139 (.231)	-.104 (.370)	-.108 (.355)	-.150 (.197)
	Bootstrap	Bias (SE)	-.008 (.114)	.001 (.118)	.000 (.106)	.000 (.115)	.001 (.114)	.000 (.118)
		95% CI	-.286; .175	-.164; .323	-.340; .076	-.334; .126	-.330; .104	-.388; .085
Caud/Put	*r (p)*		-.089 (.446)	.149 (.199)	.042 (.721)	.000 (.997)	-.136 (.240)	-.193 (.096)
	Bootstrap	Bias (SE)	-.001 (.114)	.003 (.117)	.002 (.113)	.001 (.117)	-.002 (.123)	.002 (.115)
		95% CI	-.305; .125	-.071; .389	-.171; .273	-.235; .234	-.384; .083	-.415; .042
Put	*r (p)*		.090 (.441)	.058 (.616)	.025 (.828)	-.012 (.919)	.019 (.872)	-.194 (.092)
	Bootstrap	Bias (SE)	-.007 (.097)	.001 (.133)	.001 (.112)	.003 (.114)	-.004 (.110)	.002 (.108)
		95% CI	-.117; .272	-.189; .319	-.195; .251	-.233; .220	-.201; .230	-.413; .024
SFG	*r (p)*		.001 (.990)	.171 (.140)	-.002 (.984)	.057 (.623)	.147 (.206)	.041 (.725)
	Bootstrap	Bias (SE)	-.008 (.111)	.004 (.119)	.000 (.116)	-.003 (.116)	-.002 (.118)	-.001 (.117)
		95% CI	-.243; .200	-.066; .404	-.239; .213	-.178; .278	-.090; .375	-.179; .276

Notes. NAcc=nucleus accumbens; Caud/Put=region spanning the caudate nucleus and putamen; Put=putamen; SFG=superior frontal gyrus; PA=positive affectivity; NA=negative affectivity; Anxiety problems=YSR anxiety problems total score; Depressive problems=YSR depressive problems total score; ODD=Disruptive Behavior Disorders Rating Scale (DBD-RS) ODD symptoms; AUD= hazardous alcohol use score of Alcohol Use Disorders Identification Test measuring alcohol problems. Neural response to gain was elicited by the win vs. loss contrast and extracted from voxels (with an uncorrected $p<.001$) within a 6 mm sphere centered on the coordinates.

*Pearson's correlation coefficient is reported in case of correlation pairs involving variables both with normal distribution.

Correlations compared across groups are shaded in grey. (91)

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Table 7

Associations of neural reward response with 18-month follow-up affectivity and externalizing, internalizing, and substance use problems in adolescents at-risk for ADHD.

		Anxiety problems _T1	Depressive problems_T1	*NA_T1	*PA_T1	ODD_T1	AUD_T1
NAcc	*r (p)*	.010 (.949)	.006 (.968)	.193 (.215)	-.144 (.358)	-.075 (.682)	.017 (.911)
Caud/Put	*r (p)*	-.063 (.685)	-.111 (.472)	.129 (.409)	-.115 (.461)	-.045 (.808)	.124 (.423)
Put	*r (p)*	-.040 (.799)	-.021 (.892)	-.013 (.934)	.024 (.879)	.145 (.427)	.292 (.054)
SFG	*r (p)*	-.243 (.112)	-.051 (.744)	-.093 (.553)	-.173 (.267)	.202 (.268)	.034 (.827)

Notes. NAcc=nucleus accumbens; Caud/Put=region spanning the caudate nucleus and putamen; Put=putamen; SFG=superior frontal gyrus; T1=measured at 18-month follow-up; PA=positive affectivity; NA=negative affectivity; Anxiety problems=YSR anxiety problems total score; Depressive problems=YSR depressive problems total score; ODD=Disruptive Behavior Disorders Rating Scale (DBD-RS) ODD symptoms; AUD= hazardous alcohol use score of Alcohol Use Disorders Identification Test measuring alcohol problems.
Neural response to gain was elicited by the win vs. loss contrast and extracted from voxels (with an uncorrected $p<.001$) within a 6 mm sphere centered on the coordinates.
*Pearson's correlation coefficient is reported in case of correlation pairs involving variables both with normal distribution.
Baseline scores are controlled across analyses. Correlations compared across groups are shaded in grey. (91)
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Table 8

Associations of neural reward response with 18-month follow-up affectivity and externalizing, internalizing, and substance use problems in adolescents not at-risk for ADHD.

		Anxiety problems_ T1	Depression problems_T1	*NA_T1	*PA_T1	ODD_T1	AUD_T1
NAcc	*r (p)*	.121 (.317)	.160 (.185)	.058 (.629)	-.060 (.620)	.082 (.542)	-.104 (.383)
Caud/Put	*r (p)*	.018 (.880)	.138 (.255)	-.013 (.911)	-.088 (.464)	.094 (.485)	-.184 (.121)
Put	*r (p)*	.032 (.793)	.020 (.872)	.114 (.344)	-.025 (.837)	.153 (.254)	-.230 (.051)
SFG	*r (p)*	-.178 (.140)	-.052 (.672)	-.054 (.652)	-.103 (.395)	.065 (.633)	-.133 (.267)

Notes. NAcc=nucleus accumbens; Caud/Put=region spanning the caudate nucleus and putamen; Put=putamen; SFG=superior frontal gyrus; T1=measured at 18-month follow-up; PA=positive affectivity; NA=negative affectivity; Anxiety problems=YSR anxiety problems total score; Depressive problems=YSR depressive problems total score; ODD=Disruptive Behavior Disorders Rating Scale (DBD-RS) ODD symptoms; AUD= hazardous alcohol use score of Alcohol Use Disorders Identification Test measuring alcohol problems.
Neural response to gain was elicited by the win vs. loss contrast and extracted from voxels (with an uncorrected $p<.001$) within a 6 mm sphere centered on the coordinates.
*Pearson's correlation coefficient is reported in case of correlation pairs involving variables both with normal distribution.
Baseline scores are controlled across analyses. Correlations compared across groups are shaded in grey. (91)
(Reproduced from Rádosi et al., 2023 DOI: 10.1007/s10964-023-01794-7 with permission from Springer Nature.)

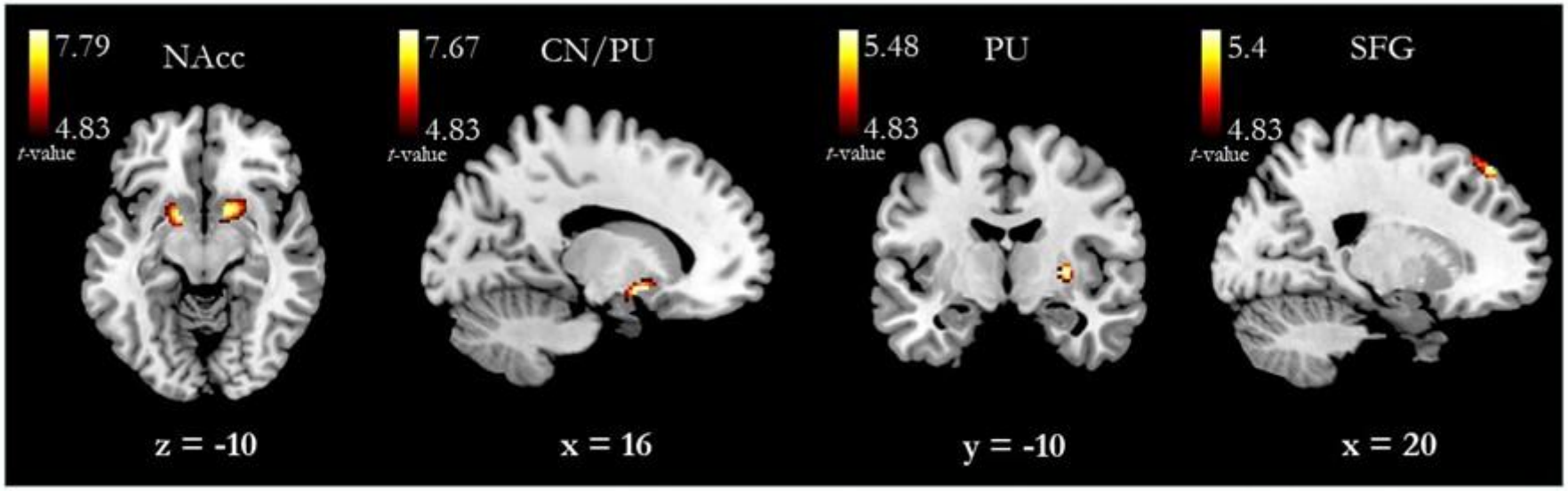

Figure 2. **Reward vs. loss related activations.** Greater activation was observed for monetary wins compared to losses in the left nucleus accumbens (NAcc; MNI coordinates: -14, 4, -10; voxels: 111; *t*-value: 7.79) in a region spanning the caudate nucleus and putamen in the right hemisphere (CN/PU; MNI coordinates: 16, 10, -10; voxels: 154; *t*-value: 7.67), in the right putamen (PU; MNI coordinates: 30, -10, 4; voxels: 45; *t*-value: 5.48) and the right superior frontal gyrus (SFG; MNI coordinates: 20, 40, 52; voxels: 41; *t*-value: 5.4). Reported activations were significant at $p<.05$ family-wise error corrected. (Rádosi et al., 2023)

5. DISCUSSION

In this dissertation, my overall aim was to examine the boundary conditions and mechanisms of the relation between reinforcement sensitivity and adolescent substance use. The focus of **Study I** was to assess mechanistic pathways of adolescent substance use considering individual differences in reinforcement sensitivity and dispositional affectivity **(AIM 1)**. The focus of **Study II** was to determine if ADHD risk modulates the relation between response to reward and adolescent affective, clinical, and substance use outcomes **(AIM 2)**. Specifically, I evaluated whether the association between initial neural response to reward and concurrent and prospective measures of affective, externalizing, internalizing, and alcohol problems (1) *differs* between adolescents at-risk for and not at-risk for ADHD and (2) is *moderated by* ADHD risk.

In case of **AIM 1**, findings add to the limited available literature (38,39) on the mechanisms by which individual variances in reinforcement sensitivity are linked to adolescent substance use. With regard to the nature of observed relations, individual differences in reinforcement sensitivity exert both shared (BAS and BIS on nicotine use) and unique (BAS on cannabis and BIS on alcohol) effects on youth substance use, and dispositional affectivity is the mechanism through which these effects are exerted. Regarding unique influences, greater BIS sensitivity may predispose adolescents to alcohol use and problems through greater NA. On the other hand, greater BAS sensitivity may reduce the probability of adolescent cannabis use. Therefore, it is also important to consider the type of substance and domains of affectivity besides domains of reinforcement sensitivity, when defining the nature of the associations across these characteristics. Regarding the context of the outcomes of reinforcement sensitivity, different affectivity domains may have contradictory effects on substance use: positive affect may decrease, whereas negative affect may increase use. Furthermore, additionally within the context of reinforcement sensitivity, there is a variation in the association between a given aspect of affectivity and substance use: PA tends to be more relevant in case of cannabis use, whereas NA tends to be more relevant in case of alcohol use and problems.

The direction of the effect between reinforcement sensitivity and affectivity variables was consistent with hypotheses and the literature, such that greater BAS

sensitivity was associated with greater PA (148) and greater BIS sensitivity was associated with greater NA (149,150). Of note, none of the alternative models were supported (with roles of dispositional affectivity and reinforcement sensitivity reversed), suggesting a unidirectional link between the mediators and predictors.

In case of **AIM 2, across primary and sensitivity analyses,** the association between neural response to monetary reward and adolescent depressive and alcohol outcomes differ depending on ADHD risk. Specifically, in adolescents at-risk for ADHD, greater SFG response to monetary reward was linked to lower NA and lower depressive problems but in adolescents not at-risk for ADHD, this association was not observable. Further, in adolescents at-risk for ADHD, greater PU response to monetary reward was associated with greater 18-month hazardous alcohol use, whereas in youth not at-risk for ADHD, greater PU response to monetary reward was linked to lower 18-month hazardous alcohol use.

5.1. Conceptual and practical implications of Study I and II Results

5.1.1. Mediation analyses with BAS and with BIS sensitivity

Accordingly, the conflict (e.g., approach-avoidance conflict) detecting, monitoring, and resolving system (37,151) exerts its effect on alcohol use/problems through a greater tendency to experience negative emotions (152) but, at least in the current sample, this effect does not appear to operate independently. Others also revealed that although the BIS did not directly correlate with substance use (i.e., a composite measure of nicotine, alcohol, and any drug use), it did indirectly influence this outcome, through subjective well-being and educational aspirations (42).

Considering explanatory hypotheses of mediational results, two conceptualizations are relevant. *First*, the association between BIS, NA, and alcohol use may be explained by alterations in serotonergic activity implicated in all three variables: the BIS operates through serotonergic activity (153), alcohol consumption results in serotonin depletion (154), and affective biases in depression are reduced by serotonergic medications (155). Contrary to earlier findings where BAS was indirectly, positively related to composite substance use (42), here, BAS was indirectly, negatively associated with cannabis use. This discrepancy between earlier and our results can be explained by additional characteristics (such as extraversion) that are associated with BAS sensitivity

that may influence its association with substance use. *Second*, the association between BAS, PA, and cannabis use may also be explained by alterations in dopaminergic activity implicated in all three variables: the BAS operates via dopaminergic reward pathways (156), and the primary psychoactive component in Cannabis sativa, Δ9-tetrahydrocannabinol, exerts its effects by elevating dopamine concentrations in the mesolimbic system (157)**.** Experiencing positive emotions is linked to dopamine release (158). For future research, both the serotonergic hypothesis of the BIS > NA > alcohol use relation and the dopaminergic hypothesis of the BAS > PA > cannabis use relation are testable.

Finally, the association between reinforcement sensitivity and nicotine use was not limited to any given domain of affectivity or reinforcement sensitivity. Specifically, PA (but not NA) mediated the association between BAS sensitivity and nicotine use, whereas both NA and PA mediated the link between BIS sensitivity and nicotine use. Notably, when examined with attitude/ environmental influences promoting nicotine use and actual use separately, the association between BIS sensitivity and actual use was mediated by NA, whereas the association between BIS sensitivity and attitude/ environmental influences was mediated by PA. The association between BAS sensitivity and both the attitude/ environmental influences and actual nicotine use was mediated by PA. Hence, pertaining to greater BIS sensitivity, NA – similarly to alcohol use – only has relevance in actual use as a potential risk factor for nicotine use. On the contrary, PA – in relation to reinforcement sensitivity – has relevance in both actual use as well as in risk factors for actual use, such as peer/parental beliefs and influences about health effects, as a potential protective factor with regard to these outcomes.

The relation of reinforcement sensitivity with smoking is likely complex. Mixed (reward vs. punishment) motivational cues (e.g., negative health outcomes vs. tension-reducing effects of smoking) may both be associated with smoking. Consequently, smoking may trigger both the approach and conflict detecting systems, as our current research would also suggest. Based on the joint subsystems hypothesis of BAS/BIS effects, the activity of one system influences how the other system will affect behavior (159). Examining how affectivity influences the subsystems is another testable hypothesis.

The associations between the BAS and PA as well as BIS and NA through the perspective of the revised RST (37) are relatively well-understood. The well-established

self-medication hypothesis postulates that the aim of substance use is to attenuate negative affect and dysphoria (160). This hypothesis has a few limitations. Firstly, it only explains the association between NA and substance use but does not explain the link between PA and substance use, even though some previous and current results suggest that PA may influence susceptibility for use. A pertinent explanatory hypothesis suggests that high PA is inconsistent with ascribing a coping role to substance use (47). Undoubtedly, substance use and affectivity have a more complex relation than these theories imply. Supporting evidence includes the observation that self-medication processes function in some circumstances but not in others (161) and also that PA may both protect against and increase the risk of substance use, since positive affect enhancement may also serve as an aim of use (162). There have also been findings of relevant differential effects of sex, whereby childhood abuse and alcohol use in men are mediated by enhancement (of PA) motives, whereas this association in women are mediated by attenuation (of NA) motives (163). Apart from the characteristics examined in Study I and as previously described, these and additional variables will provide valuable insights for further refining and therefore personalizing prevention and treatment methods targeted at problematic substance use.

Overall, findings represent novel contributions to the literature indicating that beyond disobedience to adults, tolerance for illegal activity, affiliation with peers (38), dispositional affectivity is a mechanism through which youth substance use is associated with reinforcement sensitivity. Individual differences in affectivity may therefore be promising targets for substance use prevention. Although there are well-established, evidence-based interventions that target adolescent substance use (33), relatively low reduction and abstinence rates in substance use indicate potential for improvement, for instance, via identifying alternative intervention targets. Although in Study I, effectiveness of interventions was not evaluated, identifying mechanisms of youth substance use may eventually have implications in this regard. For reducing nicotine and alcohol use, decreasing the influence of BIS on negative affect and thus reducing negative affect may be beneficial. Preventing nicotine and cannabis use may benefit from enhancing the influence of BAS sensitivity on positive affect and hence boosting its protective effect.

5.1.2. Concurrent and prospective associations between initial response to reward and outcomes given ADHD risk

Generally, that there are differences between at-risk for and not at-risk for ADHD groups regarding the relations between a hypothesized risk or susceptibility characteristic (e.g., response to monetary reward) and relevant outcomes (e.g., alcohol and depressive problems), is consistent with work suggesting that it may be more informative to assess between-group differences in the relations *across* variables rather than between-group differences in those variables.

The same risk characteristic may increase risk in one group, but not in another, and new findings lend credence to this conceptualization. In the absence of group differences, characteristics including genetic polymorphisms (48), electrophysiology (51), and emotional lability (49) predict behavioral (49), cognitive (51), and electrophysiological outcomes (ERPs of reward; (48)) in youth with but not without ADHD, or predicted related outcomes in the opposite direction (memory performance (50)). It is important to highlight that this was observed in the absence of between-group differences.

There were two questions addressed to determine whether associations between the hypothesized risk trait (response to monetary reward) and outcomes differ between adolescents not at-risk for and at-risk for ADHD: *first*, whether and to what extent the magnitude of the association between *X* and *Y* differs between the groups, and *second*, whether the association between *X* and *Y* changes as a function of *W*. Henceforward, this discussion will focus solely on results that were consistently replicated across analyses, specifically, on the differences in concurrent associations with depressive problems and prospective associations with alcohol problems.

It is now almost axiomatic that greater depressive problems are linked to an attenuated response to reward. It is less clear how externalizing problems, especially ODD are associated with response to punishment and reward, and evidence suggest that ODD may be associated with atypical punishment sensitivity rather than atypical reward sensitivity (164). Here, in the entire sample, neural response to monetary reward showed no association with ODD problems and there was no differential association between neural response to monetary reward and ODD problems across adolescents at-risk for ADHD and adolescents not at-risk.

The finding that less affective problems were linked to greater SFG response in youth at-risk for ADHD is in line with prior research (165) on the direction of this relation. Earlier evidence also suggests that PU response to reward anticipation is positively related to alcohol dependence (166). Notably, in the broader literature, the SFG has been linked to both depressive and alcohol problems and the PU has also been linked to both (165–168).

As stated, in youth at-risk for ADHD, greater SFG response was linked to lower depressive problems and greater PU response was linked to greater hazardous alcohol use whereas in youth not at-risk for ADHD, SFG response was not associated with depressive problems and greater PU response was linked to lower hazardous alcohol use.

Our findings are in line with a hypothesis of differential ADHD-related vulnerability due to differences in neural response to reward. Protective effects may be particularly pronounced in youth with ADHD exhibiting SFG-related vulnerabilities, as cross-sectional data indicate decreased cortical thickness in the fronto-striatal pathway, particularly the SFG in children with, compared to those without ADHD (169,170). Furthermore, the SFG thickness has been proved to account for ~10% of the variance in hyperactivity/impulsivity and inattention (169).

A parallel can be drawn here with the differential susceptibility hypothesis; the differential susceptibility hypothesis posits that certain individuals are not only more vulnerable to the "risk" effects of negative circumstances but they are (also) more susceptible to the "protective" effects of positive circumstances, i.e. they are developmentally plastic (171). In humans, physiological reactivity and NA are consistently observed outcomes of prenatal maternal stress. Individuals high on physiological reactivity and NA, when reared in aversive rearing environments, exert greatest deficits in a range of relevant psychological and behavioral phenotypes, whereas when reared in a supporting environment, exert greatest benefits on these measures (of note, individuals who score lower on NA fall in-between these extremes) (172). In this framework, ADHD risk status represents the vulnerability or the diathesis whereas neural response to reward represents the circumstance that, in the case of an enhanced neural response, may provide a protective effect to which individuals at-risk for ADHD are particularly sensitive.

There is a different explanation that appears more appropriate in case of PU response to monetary reward. Regarding the association of PU and alcohol problems, ADHD risk status may modulate whether greater PU sensitivity to reward functions as a risk or a protective factor in temporal increases in alcohol problems. Even though less is known about the PU-ADHD relation than the SFG-ADHD relation, data support this hypothesis insofar as those show reversal of PU asymmetry in children with ADHD compared to children without ADHD (children with ADHD more often have a smaller left, whereas those without ADHD more often have a smaller right putamen) (173).

Overall, there is a difference between the temporal characteristics across observed associations. Associations with depression were only apparent when assessed concurrently but not when assessed prospectively. It may be that the effects of reward sensitivity on depression are short-term. With alcohol problems, there were no concurrent associations but there were prospective relations, indicating the effects of reward sensitivity on alcohol problems may only manifest over time. Type I or II error is an alternative explanation of this observed temporal inconsistency in findings, highlighting the importance of evaluating how consistently this pattern of findings replicates in independent samples.

5.2. General discussion

5.2.1. Overarching conceptual and practical implications

Findings of Study I show that different domains of reinforcement sensitivity were associated with different domains of substance use (i.e., nicotine, cannabis and alcohol use/ alcohol problems), and that the mediational effect of affectivity on the association between reinforcement sensitivity and substance differed as a function of domain of **affectivity** (i.e., PA or NA). Findings of Study II also underscore the role of **psychopathology** (i.e., ADHD) in the association between neural reward sensitivity and outcomes. Greater PU response to monetary reward was associated with later alcohol problems in an opposite direction across youth at-risk for and not at-risk for ADHD such that in the former group, it was associated with greater use whereas in the latter group, it was associated with lower use. That alcohol problems were associated with both punishment (Study I) and reward (Study II) sensitivity is not surprising given findings that alcohol use can be motivated both by the intention to attenuate negative emotions

and to enhance positive emotions (163). To our knowledge, there are no prior studies employing the Doors task with middle-late adolescents to examine the association between reinforcement sensitivity and substance use while also accounting for ADHD status.

Taken together, our findings on the reinforcement sensitivity-substance use association shed light on the importance of an approach that is nuanced with regard to domains of reinforcement sensitivity, substance use, and other relevant variables (i.e. affectivity) and that accounts for the effects of relevant third variables i.e., psychopathology. In line with others, our findings also underscore the heterogeneity of underlying mechanisms of the reinforcement sensitivity-substance use relation (157,174).

5.2.2. Limitations and future directions

Regarding Study I (AIM 1), we restricted our analyses to the most widely used measures of adolescent substance use. Future research should focus on temperamental predictors of substance use for different classes of substances in the relation of reinforcement sensitivity to provide generalization of findings. Related, we assessed cannabis use using a single item, and further study along these lines might call for a more thorough evaluation of this substance. We did not find evidence for moderation by variables known to confound the analyzed associations during adolescence, such as sex, age, medication status, and comorbid mental health symptoms, possibly because there were relatively few adolescents with greater severity of substance use and/or comparatively small number of comorbid symptoms. In more comorbid and/or severe samples, there may be evidence supporting moderation. Furthermore, in our sample, the range of alcohol problems fell below the clinical cutoff, indicating results cannot be interpreted in the context of clinically significant alcohol problems. In addition, the lack of ethnic heterogeneity restricts the applicability of our findings to non-Caucasian populations.

In cross-sectional studies, only atemporal mediation can be demonstrated, statistically (175–179). As our findings show unidirectionality of the effects that we observed, those suggest that further prospective research is warranted to establish temporal mediation and, consequently, causation (128,180).

It will be important to examine the research questions examined across these two studies in larger samples that allow for greater statistical power to detect smaller effects that we may have been underpowered to detect.

Regarding Study II, the following points are relevant. When considering generalizability of AIM 2 findings, our sample was variable regarding alcohol use scores and internalizing problems. To our knowledge, this is one of the small number of fMRI studies that use the Doors task with youth (previous research examined maternal anhedonia (181), early parenting (182), and positive and negative life events (183) on adolescent reward and affective processing along with psychometrics (184)). Additionally, this is the first fMRI study to use the Doors task with middle-late adolescents. Therefore, our study needs confirmatory evidence on the appropriateness of the Doors task to probe initial response to attainment of reward in this age-group, during fMRI measurement. It is an empirical question whether findings are generalizable to other indices of reinforcement sensitivity associated with ADHD (e.g., reward learning or anticipation) and relevant comorbidities. Alcohol consumption was also investigated as one domain of substance use; however, it remains uncertain whether similar associations would be observed for other substances relevant to ADHD and reinforcement sensitivity, such as nicotine. Furthermore, regarding ADHD classification, the "at-risk" for ADHD label was used in analyses, not the "diagnosed" with ADHD, which means that how ADHD was captured as a psychopathology and involved in analyses could have an impact on results (i.e., the at-risk group had less severe or pronounced symptoms than a diagnosed group would). It is also important to note that the "money" earned in the current study (as in (97)) was virtual money that was exchanged for snacks at the end of the task. However, in prior studies using this paradigm, actual money was given after completing the task; magnitude of neural response and engagement may have been affected by this.

Although biological age or pubertal status may not always coincide, in Study I and II we used chronological age to define adolescence instead of taking these factors into consideration. Therefore, it is still unclear whether these results would repeat if adolescence were defined by biological maturity. Also, it would also be advantageous to add to self-report in future research by using additional, objective measures of substance use, for example measuring the amount of drugs from a blood sample. Lastly, taking into consideration of additional variables would be useful in deeper understanding the

mechanisms contributing to adolescent substance use, such as family background (e.g., social economic status, quality of relationship with family members) or emotion regulation skills.

6. CONCLUSIONS

Affectivity and ADHD risk play a mediating and modulating role, respectively, of the association between reinforcement sensitivity and adolescent affective, clinical, and substance use outcomes.

Affectivity (and the type of substance) determine the association between reinforcement sensitivity and substance use. ADHD risk modulates the association between reinforcement sensitivity and ADHD-relevant outcomes. Altogether, affectivity and ADHD are promising characteristics along which heterogeneity can be parsed in adolescent substance use. Reinforcement sensitivity and affectivity may be relevant targets for personalized intervention targeting adolescent substance use.

7. SUMMARY

Introduction: Adolescent substance use has both short- and long-term consequences underscoring the importance of identifying relevant targets for improving interventions. Reinforcement sensitivity is one such target. Yet, gaps in knowledge remain about specifics of the association between reinforcement sensitivity and adolescent substance use, particularly regarding mechanisms and modulators.

Objectives: The overarching aim of this dissertation is to examine the boundary conditions and mechanisms of the relation between reinforcement sensitivity and adolescent substance use.

Methods: 14–17-year-old adolescents were involved in the Budapest Longitudinal Study of ADHD and Externalizing Disorders. Neural (i.e., the Doors task via fMRI) and self-reported (i.e., RSTPQ) indices of reinforcement sensitivity, self-reported indices of affectivity, internalizing and externalizing symptoms, and substance use were used in addition to parent-report measures of externalizing symptoms. Associations between variables were evaluated by conducting bivariate and partial bivariate correlations, Fisher's *r* to *z* transformations, as well as via mediational and moderational analyses.

Results: The BAS-cannabis use and the BAS-nicotine use associations were mediated by PA, the BIS-alcohol use/alcohol problems by NA, and the BAS/BIS-nicotine use by both PA and NA, respectively, with effects in a different direction. The association of SFG response to gain with depressive problems differed across groups such that in youth at-risk for ADHD, greater SFG response to gain was linked to lower depressive problems. Controlling for baseline hazardous alcohol use, the association of PU response to gain with 18-month hazardous alcohol use differed across groups such that in youth at-risk for ADHD, greater PU response to gain was associated with greater 18-month hazardous alcohol use, whereas in youth not at-risk for ADHD, greater PU response to gain was linked to lower 18-month hazardous alcohol use.

Conclusions: Affectivity and ADHD risk play a mediating and modulating role, respectively, between predictors and outcomes. In the context of differences in reinforcement sensitivity, affectivity and ADHD show promise in explaining the heterogeneity of adolescent substance use outcomes. Reinforcement sensitivity and affectivity may be relevant targets for personalized intervention targeting adolescent substance use.

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9. BIBLIOGRAPHY OF PUBLICATIONS

List of publications related to the PhD thesis:

1. **Rádosi A**[1], Pászthy B[1], Welker TÉ, Zubovics EA, Réthelyi JM, Ulbert I, Bunford N. The Association between Reinforcement Sensitivity and Substance Use is Mediated by Individual Differences in Dispositional Affectivity in Adolescents. Addictive Behaviors. 2021 Mar 1;114:106719. IF: 4,591
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[1]first author shared

List of publications not related to the PhD thesis:

1. Hámori G, **Rádosi A**, Pászthy B, Réthelyi JM, Ulbert I, Fiáth R, Bunford, N. Reliability of reward ERPs in middle-late adolescents using a custom and a standardized preprocessing pipeline. Psychophysiology. 2022 Aug;59(8):e14043. IF: 3,7
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