An Examination of Affect-Related Brain Activity and Substance Use Among Adolescents

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by

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DEDICATION

This dissertation is dedicated to my parents, Armando and Lucia. Close to thirty years ago, they moved from Portugal to the United States to provide me and my sister with a better life. And I have seen first-hand how hard it has been for them—learning a new language, tolerating long hours of manual labor, and navigating bureaucratic systems that were never designed to benefit them. Still, they gave us everything they could. They provided us with unconditional love and support, instilled in us the value of education, and encouraged us to work hard and pursue our dreams. I am here today because of them, and all my successes are their own.

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Substance Use Disorder (SUD)
Substance Use (SU)
Functional Magnetic Resonance Imaging: fMRI
Research Domain Criteria: RDoC
Anterior Cingulate Cortex: ACC
Middle Frontal Gyrus: MFG
Middle Temporal Gyrus: MTG
Superior Temporal Gyrus: STG
Nucleus Accumbens: NAcc
Anterior Insula: AI
Inferior Frontal Gyrus: IFG
Alcohol Use: AU
Cannabis Use Disorder: CUD
Middle Prefrontal Cortex: mPFC
Dorsomedial Prefrontal Cortex: dmPFC
Ventrolateral Prefrontal Cortex: vlPFC
Cannabis Use: CU
Orbitofrontal Cortex: OFC
Parahippocampal Gyrus : PHG
Parent-Adolescent Interaction Task : PAIT
International Affective Picture Set: IAPS
Inter-trial Interval: ITI
Blood Oxygen Level Dependent: BOLD
Youth Risk Behavior Survey: YRBS
Timeline Follow-Back: TLFB
Mini-International Neuropsychiatric Interview for Children and Adolescents: MINI-Kid
Alcohol Use Disorder: AUD
T1-weighted: T1w
Intensity Non-uniformity: INU
Cerebrospinal Fluid: CSF
White-matter: WM
Gray-matter: GM
Echo-planar imaging: EPI
Independent Component Analysis: ICA-AROMA
Full-width Half-maximum: FWHM
Framewise Displacement: FD
fMRI Expert Analysis Tool: FEAT
Coefficient of Parameter Estimate: COPE
Support Vector Machine: SVM
Mean Squared Error: MSE

Inferior Temporal Gyrus: ITG

ABSTRACT

AN EXAMINATION OF AFFECT-RELATED BRAIN ACTIVITY AND SUBSTANCE USE AMONG ADOLESCENTS

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Death and disability related to substance use disorder have increased substantially over the past couple of decades. Most adults with substance use disorder initiated substance use as adolescents, making adolescence a critical period for the prevention of substance use and substance use disorder. It is therefore important to identify risk factors for adolescent substance use. Recent research has demonstrated the role of altered affective processing in adolescent substance use. Unfortunately, most of this research has employed self-report and behavioral methods, which, while valuable, are limited in comparison to other methods, namely functional neuroimaging, in detecting subtle neural-level differences in affective processing and how it relates to adolescent substance use. Thus, the focus of this dissertation is on neural affective processing and adolescent substance use employing functional neuroimaging. In Study 1 of this dissertation, a systematic review of neuroimaging studies examining affective processing and adolescent substance use was conducted. Results revealed that higher activation in

midcingulo-insular regions—particularly the striatum—to positive affective stimuli (e.g., monetary reward) was most often associated with initiation and low-level use of substances, whereas lower activation in these regions was most often associated with substance use disorder and higher-risk substance use. In regard to negative affective stimuli, most research demonstrated associations between higher activation of midcingulo-insular network regions and adolescent substance use. Associations between activation in additional network regions (e.g., frontoparietal, pericentral) and adolescent substance use were mixed. To extend findings from Study 1, Study 2 of this dissertation was an empirical study examining how patterns of neural activation in two standardized and one naturalistic affective processing tasks classify substance use as well as predict substance use intentions and expectancies in 11–15-year-old adolescents (n = 168). Machine learning analyses were performed. Results did not provide evidence that neural activation to negative or positive affective stimuli—neither standardized nor naturalistic—could reliably classify adolescent substance use and predict adolescent substance use intentions and expectancies. Implications of all findings, as well as limitations and directions for future research are discussed.

An Examination of Affect-Related Brain Activity and Substance Use Among Adolescents

Most adults with substance use disorder (SUD) initiated substance use (SU) as adolescents, making adolescence a vulnerable period for the development of SUD (Substance Abuse and Mental Health Services Administration, 2014). This is problematic given the devastating consequences of SUD, including disability and death (Bahorik et al., 2017; Merikangas et al., 1998). Unfortunately, despite public health efforts, death related to SU and SUD has increased over the past several years (Hedegaard et al., 2017). It is therefore more important than ever to identify risk factors of SUD, particularly in adolescence, that can inform public health efforts to prevent or minimize effects of SUD.

One risk factor of SUD is altered affective processing. This refers to heightened or blunted responses to positively- and negatively-valanced stimuli, such as monetary reward and peer rejection. With mounting research linking altered affective processing to SU in adolescence (e.g., Colder et al., 2013; Chaplin et al., 2012), it is important that neural markers of altered affective processing underlying adolescent SU are better understood.

The body of literature on affect-related brain activity and adolescent SU is growing; however, there are several gaps that the present dissertation addressed. First, even though this literature has been synthesized in narrative and meta-analytic reviews (e.g., Tervo-Clemmens et al., 2020; Silveri et al., 2016), no review to our knowledge has focused exclusively on the adolescent developmental period (prior to 18 years of age) and included studies examining various SU behaviors (e.g., SUD, initiation, escalation).

Consequently, for Dissertation Study 1, I conducted a systematic review of all neuroimaging studies of neural affective processing and adolescent SU.

Secondly, the existing literature on affect-related brain function and adolescent SU is almost exclusively made up of neuroimaging studies that employed traditional statistical approaches instead of machine learning approaches. Machine learning approaches are better at yielding more generalizable findings (Norman et al., 2006; Scheinost et al., 2019). The existing research examining affective processing and adolescent SU have also generally used standardized paradigms. Although these paradigms have increased our understanding of affect-SU associations, it would be important to supplement these with more naturalistic affective paradigms, preferably within a social context. This would increase the ecological validity of our findings. Consequently, for Dissertation Study 2, I used machine learning approaches to analyze affect-related neural activation and SU using both standardized and naturalistic affective paradigms.

STUDY ONE: SYSTEMATIC REVIEW OF AFFECT-RELATED BRAIN ACTIVITY AND ADOLESCENT SUBSTANCE USE

Adolescence is a critical period in the development of substance use disorder (SUD). Research suggests that most adults with SUD initiated substance use (SU) prior to age 18 (Substance Abuse and Mental Health Services Administration, 2014). It is therefore advantageous to understand the brain activity that characterizes adolescent SU.

It is particularly important to examine how *affect-related* brain activity is associated with adolescent SU. In this review, affect-related brain activity refers to neural networks recruited during processing of emotionally and/or motivationally (i.e., reward) salient stimuli. In behavioral studies, altered affective processing has been identified as a risk factor for SU (Cheetham et al., 2010; Colder et al., 2013). This is consistent with theories stating that individuals initiate and engage in problematic SU to regulate altered emotion and reward arousal (Khantzian, 1997; Luijten et al., 2017).

Among adults, altered neural activation during affective processing has been associated with SU (Balodis & Potenza, 2015; Gruber et al., 2009). Comparatively less research has been conducted on affective neural correlates of SU in adolescence, however. This is particularly important because of research demonstrating that neural networks supporting affective processing mature more rapidly than cognitive control-related networks in adolescents (Casey et al., 2011).

The current study systematically reviewed fMRI studies of adolescents' neural responses to affective processing tasks and SU. Other reviews have similarly examined associations between affective processing and SUD risk in adolescents and young adults

(Tervo-Clemmens et al., 2020); however, the present study more specifically targeted adolescence as a developmental period and focused on actual SU behavior.

Method

We searched for studies on "PubMed" and "PsycInfo" databases. We used keywords to obtain search results on studies employing functional magnetic resonance imaging (fMRI) and examining SU outcomes in adolescent samples. We searched for studies on "PubMed" and "PsycInfo" databases. We used keywords to obtain search results on English language peer-reviewed studies employing fMRI (fMRI, functional magnetic resonance imaging) and examining SU outcomes (substance use, drug use, alcohol use, cannabis use, tobacco use) in adolescent samples (youth, adolescen*, pediatric, teen*, child*). After manually removing duplicate papers, we had 244 total studies. These studies were coded based on inclusion and exclusion criteria by three independent coders. In order for a study to be included in this review it had to: (1) examine neural activation with fMRI; (2) employ an affect-related task; (3) include SU as an outcome (e.g., initiation, SUD diagnosis); and (4) employ a sample with a mean age below 18 years. Studies were excluded if they only examined family history of SUD or prenatal SU exposure as correlates of fMRI activation. Studies were also excluded if they only employed working memory (i.e., no affective component) fMRI tasks, as well as if they were treatment studies. Studies were deemed eligible if they met all inclusion criteria and no exclusion criteria.

Next, the three independent coders coded each eligible study for: age range, sample size, task type, task stimulus, analysis type (whole brain or ROI; longitudinal or

cross-sectional), contrast of interest, SU outcome, main finding, and brain network corresponding to main findings (based on Uddin et al., 2019). Regarding task type, the three coders coded based on Research Domain Criteria (RDoC; Cuthbert & Insel; 2013). Studies were coded as positive valence systems if they included tasks that reflected the following sub-domains: reward responsiveness (e.g., monetary incentive delay task), reward valuation (i.e., probability choice task), and/or reward learning (e.g., probabilistic reward task). Studies were coded as negative valence systems if they reflected the following sub-domains: acute fear (e.g., trier social stress task), potential threat (e.g., no threat-predictable threat-unpredictable threat task (NU-threat task)), sustained threat (i.e., no task established), loss (e.g., sadness eliciting film clips), and frustrative nonreward (e.g., point subtraction aggression paradigm (PSAP)). Given that the focus of this review was on affective processing, no eligible studies were related to other RDoC domains, including cognitive systems, social processes, arousal and regulatory systems, and sensorimotor systems. Most studies were coded based on the domain and sub-domain (e.g., a study was coded as a reward responsiveness positive valence system study); however, some studies examining the domain negative valence only indirectly examined sub-domains (e.g., potential threat) and were therefore coded as "responses to negative emotional stimuli." There were no disagreements among coders on coding.

Results/Discussion

Positive Valence Systems

Within the RDoC framework (Cuthbert & Insel, 2013), positive valence systems refer to systems underlying approach motivation, which may be altered in youth at risk

for SUD. In total, 31 studies examined positive valence systems (mostly reward valuation and responsiveness) and associations with adolescent SU.

Reward Valuation

Reward valuation refers to processes of encoding the probability and magnitude of reward in the future (Cuthbert & Insel, 2013). Most often this is assessed during choice selection phases of tasks that can lead to a reward.

Monetary Reward Tasks. Most studies employed variants of an economic lottery task wherein adolescents select between risky and safe choices in order to earn money. These studies found that altered activation during choice selection (which reflects reward valuation) was associated with adolescent SU.

Crowley and colleagues (2010) and Dalwani and colleagues (2014) found that *reduced* activation in brain regions belonging to the midcingulo-insular, frontoparietal, and occipital networks during choice selection was associated with SUDs in 14–18-year-old boys. Compared to controls, boys with SUD had decreased activation in midcingulo-insular regions involved in salience (e.g., anterior cingulate cortex [ACC], insula, amygdala, putamen, caudate), frontoparietal regions involved in cognitive control (e.g., middle frontal gyrus [MFG]) and self-referential/information processing (e.g., middle temporal gyrus [MTG], hippocampus, restrosplenial cortex, precuneus), as well as occipital regions involved in visual processing (i.e., lingual gyrus). A third study also found reduced activation in a midcingulo-insular salience region—the caudate, involved in learning stimulus-outcome associations (Balleine et al., 2007)—as well as in frontoparietal self-referential/information processing (e.g., MTG) and pericentral

language processing regions (e.g., superior temporal gyrus [STG]) during risky choice selection in 13–16-year-old adolescents after they initiated binge drinking compared to controls (Jones et al., 2016). Taken together, these results suggest that adolescents with heavy use or SUD may undervalue potential future monetary rewards. Given that these adolescents have been heavily using substances, they may have developed over time a tendency to undervalue monetary reward and instead overvalue drug reward (van Hell et al., 2010).

Claus and colleagues (2018) employed a different task, the balloon analogue risk-taking task, to examine neural responses during risky decisions. In a sample of 14–18-year-olds in an "alternative to incarceration" program, Claus and colleagues found that relative to controls, adolescent substance users had decreased activation in midcingulo-insular and medial frontoparietal networks implicated in salience and self-referential/information processing, including in the nucleus accumbens [NAcc], anterior insula [AI], inferior frontal gyrus [IFG], as well as in the thalamus/brainstem. These results align with aformentioned studies and indicate blunted neural activation during reward valuation in youth who are high-risk. This may suggest lower arousal to potential monetary reward and shifting of reward arousal to drug cues. Alternatively, as these youth have conduct problems, they may show lower activation in general to affective stimuli, which may lead them to be under-aroused and to seek out substances to up-regulate arousal (Blair et al., 2018).

Kim-Spoon and colleagues (2019) similarly found that reduced activation in the AI—a midcingulo-insular salience region—during risky choice selection in an economic

lottery task longitudinally predicted increases in SU from early to middle adolescence in adolescents with high cognitive control. Notably, among adolescents low in cognitive control, increased AI activation predicted increases in SU, suggesting that adolescents with low cognitive control may take a different pathway towards SU compared to most adolescents. This study was extended by Elder and colleagues (2019) who also found that reduced AI activation during reward valuation indirectly predicted increased alcohol use (AU) two years later through externalizing symptoms in 13–14-year-old boys, not girls. This finding underscores that reduced midcingulo-insular activation during reward valuation may be a more likely pathway to SU for adolescent boys.

Three studies linked *increased* activation during reward valuation to adolescent SU. One study examining 16–18-year-old binge drinkers found increased activation of midcingulo-insular network regions; however, this study compared two tasks making these results challenging to interpret (Xiao et al., 2013). Further, De Bellis and colleagues (2013) found that 13–17-year-old boys with cannabis use disorder (CUD) had increased activation in the frontoparietal attention orienting (i.e., superior parietal lobule), frontoparietal self-referential/information processing (i.e., precuneus), and occipital visual processing networks (e.g., cuneus) during selection of risky choices that had uncertainty versus controls. Morales and colleagues (2018) similarly found that during reward valuation increased recruitment of midcingulo-insular salience (e.g., bilateral NAcc), occipital visual (e.g., middle occipital gyrus) and medial frontoparietal network regions (i.e., fusiform gyrus, precuneus) involved in self-referential/information processing predicted earlier onset of binge drinking in 14–15-year-olds.

Taken together, these results indicate that adolescents with heavy SU and SUDs mostly show blunted activation in midcingulo-insular networks, as well as both increased and decreased activation in networks implicated in attention, self-referential/information processing and visual processing during reward valuation. These mixed findings could be due to task type, as De Bellis and colleagues and Morales and colleagues examined reward valuation under more cognitively demanding circumstances, possibly suggesting that heightened activation in these networks is related to inefficient resource deployment during reward valuation in youth with SUDs or heavy SU.

Reward Responsiveness

Reward responsiveness refers to responses to the anticipation or receipt of reward (Cuthbert & Insel, 2013). Most studies examined neural responses to monetary reward anticipation/receipt and SU, with two examining responses to drug cues.

Monetary Reward Tasks. ***Monetary Incentive Delay Task***. Most studies employed adapted versions of the monetary incentive delay task. This task has two phases assessing reward anticipation and reward receipt. During reward anticipation, subjects are presented with an anticipation cue indicating the magnitude or probability of a monetary outcome (e.g., "possible win $5"). They are then presented with the actual monetary outcome (e.g., "win $5") during the reward receipt phase. Depending on the specific version of the task, the monetary outcome (e.g., "win $5") may be determined by how the subject responds to the anticipation cue (e.g., guessing card correctly to win money).

Most of these studies found an association between altered activation of striatal regions (part of the greater midcingulo-insular salience network) to monetary reward and adolescent SU. Five linked *increased* striatal activation to SU. Two studies found that increased NAcc activation to monetary reward receipt and anticipation was associated with increased SU cross-sectionally in 8–27-year-olds (Braams et al., 2016) and prospectively among 8–12-year-olds (Cope et al., 2019). Similarly, among 14–16-year-olds, increased caudate and putamen activation to receipt of money was associated with SU prospectively (not cross-sectionally) (Stice et al., 2013). There is also evidence that the association between NAcc activation and SU is sex-specific. Increased NAcc activation to monetary reward anticipation and receipt, respectively, predicted increased SU prospectively two years (Swartz et al., 2020) and one year later (Chaplin et al., 2021) in 12–16-year-old boys, but not girls. Taken together, these studies suggest that increased striatal activation to monetary reward among lower-risk youth (i.e., less SU history) is associated with current and prospective SU across the adolescent period, which is consistent with theories that SUDs begin as a result of a high reward sensitivity that drives individuals to use substances (Luijten et al., 2017). This may be more likely among boys who demonstrate higher reward sensitivity than girls in studies (Harden et al., 2018).

In contrast to these findings, six studies found associations between *decreased* striatal activation to monetary reward and SU. These studies are more consistent with theoretical models that posit that SU may be a function of blunted reward arousal that drives adolescents to up-regulate arousal (Luijten et al., 2017; Blum et al., 2996). Indeed,

two studies linked reduced putamen and NAcc activation to monetary reward receipt and anticipation to increased drinking in 14-year-olds (Nees et al., 2015) and 14–18-year-olds in residential treatment (for a range of concerns, including SUDs) (Aloi et al., 2019). Further, 14- to 18-year-old adolescent tobacco smokers had reduced NAcc and putamen activation to monetary reward anticipation versus controls (and non-tobacco substance users) (Karoly et al., 2015; Peters et al., 2011). Two studies demonstrated sex differences in these associations. Swartz and colleagues (2020) and Chaplin and colleagues (in preparation) showed that reduced NAcc activation to reward anticipation and receipt was associated with increased SU in 16-year-olds girls and 12–14-year-old boys a few years later. The latter findings contrast with aforementioned studies that found that boys are more likely to take a pathway to SU characterized by increased striatal activation. This may be because adolescents in Chaplin and colleagues (in preparation) are a higher-risk sample (i.e., substance-using boys) and may show blunted arousal to monetary reward compared to a lower-risk sample of boys. Girls, even lower-risk girls, may take a pathway to SU characterized by blunted striatal activation.

Thus, there is evidence to suggest that both heightened and blunted recruitment of striatal regions to monetary reward anticipation and receipt are associated with SU in adolescents, with heightened activation observed more often in lower-risk youth with minimal SU history, especially boys, and blunted activation observed more often in higher-risk youth, with more SU history, especially girls. This may suggest that decreased activation is a consequence of SU, leading these youth to develop reduced sensitivity to non-drug reward compared to drug reward. Also, notably, two studies did

not find that neural activation to monetary reward anticipation was associated with SU in 13–19-year-old adolescents (Nees et al., 2012; Jager et al., 2013).

Additional studies found that, in addition to the striatum, increased activation in frontoparietal regions involved in decision making and emotion (middle PFC [mPFC], dorsomedial PFC [dmPFC]) were also associated with SU. Bertocci and colleagues (2017) found that increased activation in the mPFC—involved in cognitively demanding tasks (Pochon et al., 2002)—to receipt of monetary reward predicted SU two years later among 13–14-year-olds. Swartz and colleagues (2020) additionally found that increased activation of the dmPFC to monetary reward anticipation was associated with more drinking in 16-year-old girls two years later. The dmPFC is implicated in both response monitoring (de Ruiter et al., 2012) and emotion awareness (Vilgis et al., 2018) and heightened recruitment of this region to monetary reward anticipation may indicate that adolescent girls who are more attentive to potential reward and its emotional impacts may be at risk for SU. As mentioned previously, Swartz and colleagues (2020) also found decreased NAcc activation to monetary reward anticipation in this sample for girls, suggesting that girls may show a pathway to SU characterized by high emotionality but blunted reward system activation. This is consistent with research linking increased dmPFC activation in girls (Vilgis et al., 2018) and decreased NAcc activation in adolescents overall with depression (Hanson et al., 2015) and lend credence to theories that girls are more likely to take an internalizing pathway to SU (Chaplin et al., 2018).

Other Monetary Reward Tasks. Four studies employed different tasks (i.e., economic lottery tasks and antisaccade reward task) and found *decreased* activation in

midcingulo-insular and frontoparietal network regions. One study using an antisaccade reward task found that decreased activation in the NAcc, putamen, amygdala—midcingulo-insular regions implicated in salience—and a lateral frontoparietal region, the ventrolateral prefrontal cortex (vlPFC), implicated in cognitive control, to reward anticipation was associated with increased cannabis use (CU) among 14–18-year-olds recruited from an intensive outpatient program for SU problems (Chung et al., 2015). Similarly, Crowley and colleagues (2010) and De Bellis and colleagues (2013) demonstrated that in response to monetary reward receipt, 13–18-year-old boys with SUD, relative to controls, had reduced activation in midcingulo-insular regions (e.g., ACC) involved in salience, as well as in frontoparietal (e.g., orbitofrontal cortex [OFC], precuneus) and pericentral regions (e.g., STG) involved in cognitive control, self-referential, visual, and language processing. These results suggest that adolescents, especially boys, with SUD are hyporesponsive to monetary reward, possibly an effect of using high amounts of substances over time.

Another study found that binge drinking predicted decreased activation in the cerebellum to monetary reward receipt among 12–16-year-olds (Cservenka et al., 2015). Crowley and colleagues (2010) similarly found an association with reduced activation in the cerebellum, suggesting that adolescents with SUD or problematic SU may have disrupted cognitive/affective processing more broadly (Strick et al., 2009).

Drug and Food Cue Tasks. Two studies examined neural responses to drug cues specifically. Brumback and colleagues (2015) found that 16–18-year-olds with histories of heavy drinking, compared with light drinking youth, had increased activation in

midcingulo-insular network regions (i.e., putamen/NAcc, ACC, parahippocampal gyrus [PHG]) as well as the cerebellum, to alcohol images (although differences diminished following one month of abstinence). Tapert and colleagues (2003) similarly found that 14- to 17-year- olds with AUD had increased activation in frontoparietal regions involved in decision-making (e.g., MFG), midcingulo-insular regions involved in salience (e.g., amygdala), and in occipital regions involved in visual processing (e.g., cuneus) to alcohol cues compared to healthy controls. These findings suggest that adolescents engaging in higher-risk SU had increased recruitment of salience, decision making, and visual processing systems in response to alcohol cues. This is in opposition with studies in higher-risk adolescents showing blunted activation in these regions to monetary reward and supports that youth with extended exposure to substances may undervalue monetary reward and shift to over-valuing drug reward.

Additionally, two studies found links between altered activation in midcingulo-insular networks and frontoparietal networks to food cues and adolescent SU. Yip and colleagues (2016) demonstrated that, in 11–17-year-olds (with and without prenatal cocaine exposure), increased activation in midcingulo-insular regions (e.g., caudate, insula) and frontoparietal regions (e.g., dorsolateral prefrontal cortex) involved in reward encoding and cognitive control to food imagery was associated with illicit SU. Moreover, Rubinstein and colleagues (2011) found that 13–17-year-old smokers had decreased activation in frontoparietal and midcingulo-insular regions involved in salience and decision making (i.e., putamen, insula, inferior frontal cortex) to pleasurable food images compared to nonsmokers. Taken together, these studies suggest that youth who engage in

illicit SU may attach more value to food reward and that youth who smoke may assign less value to food reward.

Non-Monetary, Non-Drug Cue Tasks. Three studies employed different affective tasks. Migliorini and colleagues (2013) found that 15–17-year-olds with SUD had increased and decreased activation in the AI and posterior insula (PI), respectively—midcingulo-insular regions implicated in salience, including somatosensation/pain processing (2017)—to pleasant tactile stimulation compared to controls. Adolescents with SUD also had increased medial frontal gyrus and MFG activation, indicating increased recruitment of regions involved in self-referential/information processing and cognitive control. In addition, Aloi and colleagues (2018) and Leiker and colleagues (2019) found that increased amygdala—a midcingulo-insular region—and medial temporal lobe activation to positive emotion stimuli during an affective stroop task and an emotion faces task was associated with higher AU among 14–18-year-olds (some with SUDs). These findings are inconsistent (except for PI finding) with other research cited above linking decreased recruitment of midcingulo-insular regions to reward and adolescent heavy SU/SUD. It is possible that adolescents with SUDs may not lose sensitivity to certain non-drug rewards, such as tactile stimulation or positive emotional images.

Summary

Overall, these findings suggest that altered activation during monetary reward valuation and in response to monetary reward are associated with altered activation in regions across midcingulo-insular, frontoparietal, pericentral, and occipital networks.

Most studies linked decreased recruitment of the striatum, ACC, and AI—midcingulo-insular regions involved in salience—with adolescent SUD and heavy SU. In contrast to this research, some research found that increased midcingulo-insular activation was associated with lower-risk SU among adolescents. Thus, it is possible that decreased midcingulo-insular activation during monetary reward valuation and in response to reward is a consequence of heavy SU over time; these adolescents may develop a tendency to undervalue monetary reward, and likely, overvalue drug reward. This is underscored by research demonstrating that adolescents with SUD have increased recruitment of midcingulo-insular regions, including the striatum, to drug cues. These associations may also be sex-specific. Among youth at lower risk for SU (e.g., less SU history), boys may be more likely to recruit these midcingulo-insular regions, whereas girls may be less likely to activate these regions.

There was also evidence of both decreased and increased activation in frontoparietal, pericentral and occipital regions, including in regions important for cognitive control, decision-making, self-referential/information processing, and visual processing. It is less clear what may explain these discrepant findings, although it may be that different contextual factors (e.g., choices involving uncertainty versus not) are driving these differences.

Negative Valence Systems

Negative valence systems refer to processes involving responses negative emotional stimuli and loss (Cuthbert & Insel, 2013). In total, thirteen studies examined neural correlates of negative valence systems as related to adolescent SU. Most studies

examined responding to negative emotional stimuli, which more indirectly assesses processing of threat and harm.

Responses to Negative Emotional Stimuli

Several studies found an association between increased activation in midcingulo-insular and frontoparietal network regions and increased adolescent SU. Two studies found that 12–14-year-olds that had increased activation in the amydgala, a midcingulo-insular salience region involved in emotional processing (Balleine et al., 2007), to negative emotion faces initiated AU earlier (Elsayed et al., 2018) and used cannabis (compared to controls) (Spechler et al., 2015). Chaplin and colleagues (2019) similarly found that increased activation in the AI to negative emotional images was associated with lifetime SU in 12–14-year-old girls, but not boys. Moreover, one study found that increased AU along with increased CU was associated with increased activation in the amygdala and IFG—a frontoparietal network region involved in self-referential/information processing—to negative emotional stimuli in 14–18-year-olds (Aloi et al., 2018). Interestingly, increased AU was associated with decreased activation in the amygdala and IFG at low levels of CU. Polysubstance use, such as heavy AU and CU, is higher risk and may be associated with increased reactivity compared to lower-risk substance use (i.e., one substance only). Consistent with these findings, Yip and colleagues (2016) found that 11–17-year-old, illicit substance using adolescents (without prenatal cocaine exposure) had increased response to a negative personalized stress imagery script in midcingulo-insular and frontoparietal networks involved in salience (e.g., caudate) and self-referential/information processing (hippocampus) compared to

controls. Taken together, these findings demonstrate a link between increased activation of midcingulo-insular regions and adolescent SU and suggest that adolescents with heightened arousal to negative emotional stimuli may use substances to down-regulate this arousal. Moreover, the finding by Chaplin and colleagues (2019) may suggest that this link is stronger in girls compared to boys.

Another study had 15–17-year-olds with SUD complete a combined drug cue reactivity and aversive interoceptive task (May et al., 2020) and found *decreased* activation in midcingulo-insular and frontoparietal network regions as well. Specifically, adolescents had to view images of drug and neutral cues that were either paired with an aversive interoceptive stimulus (i.e., higher breathing load) or not. Results revealed that adolescents with SUD had decreased activation to higher breathing load in the amygdala, IFG, and PHG (midcingulo-insular and frontoparietal regions) than controls and adolescents with SU experimentation. Across adolescents, decreased activation in the IFG and PHG was correlated to increased lifetime AU and CU. Notably, these findings are in contrast to most research, including earlier work showing increased activation in the PI (as well as PHG and STG) to breathing load in 15–17-year-olds with SUD compared to controls (Berk et al., 2015).

Research has also demonstrated decreased activation in frontoparietal networks involved in cognitive control and self-referential/information processing to increased SU. One study found that decreased activation in frontoparietal regions involved in cognitive control (e.g., IPL) was associated with increased AU in 14- to 18-year-olds (Leiker et al., 2019). Similarly, Blair and colleagues (2019) found that decreased activation in the OFC,

ventromedial PFC, and rostromedial PFC—frontoparietal regions implicated in self-referential/information processing and decision-making—as well as occipital network regions to looming negative emotional faces was associated with increased CU. These studies may indicate that decreased recruitment of regions involved in cognitive control and information processing to negative stimuli is associated with increased SU.

Non-Reward and Loss Responsiveness

Finally, four studies examined associations between neural responses to non-reward and loss and adolescent SU. Aloi and colleagues (2019) found that decreased activation of midcingulo-insular regions involved in salience (e.g., putamen, ACC/dmPFC) to punishment was related to increased CU in 14–16-year-olds. Similarly, Bertocci and colleagues (2013) found that decreased AI activation—a midcingulo-insular network region—to monetary loss was associated with increased SU two years later in 9–17-year-olds. On the other hand, Crowley and colleagues (2010) found that 14–18-year-old boys with SUD had increased activation in midcingulo-insular network regions (e.g., cingulate gyrus), as well as frontoparietal regions involved in cognitive control (e.g., MFG) and self-referential/information processing (e.g., MTG, precuneus, IFG, superior frontal gyrus), pericentral network regions (e.g., paracentral lobule) involved in sensorimotor functioning, and the cerebellum and brainstem. Finally, another study found that prior to first drink, adolescents that went on to initiate SU within a three-year period had increased activation in the midcingulo-insular networks involved in salience (i.e., left putamen) and frontoparietal networks involved in error detection and self-referential processing (i.e., right precuneus), as well as the brainstem/pons, to monetary loss

compared to adolescents that remained abstinent (Gonçalves et al., 2021). Given that these adolescents were alcohol naive while undergoing fMRI, these results may indicate that increased recruitment of salience and error detection/self-referential processing networks is an initial vulnerability factor for SU. Thus, there is evidence that both increased and decreased midcingulo-insular activation to loss/non-reward is associated with low-risk SU and SUDs.

Summary

Overall, altered activation in midcingulo-insular, occipital, pericentral and frontoparietal regions to negative emotional stimuli is implicated in adolescent SU. Most studies, including studies examining low-risk adolescents with minimal SU history and high-risk adolescents with SUDs, linked increased amygdala activation (as well as other regions involved in emotional arousal, such as the ACC and insula) to negative emotional stimuli to increased SU. This suggests that increased midcingulo-insular activation to negative emotional stimuli may be a vulnerability factor for SU/SUD that remains unchanged after extensive exposure to SU. Most research also indicates that reduced frontoparietal activation involved in self-referential/information processing, cognitive control, decision-making, and visual processing in response to negative emotional stimuli is associated with increased SU. In regard to non-reward and loss, there is much less research. Of the four studies that are published, there is evidence of both increased and decreased activation in midcingulo-insular regions to loss.

Table 1

Main findings from systematic review

Study	Sample Size	Age Range	Sex	Cross-Sectional or Longitudinal	Task	Stimulus	Condition or Contrast	Main Findings	Analysis
Reward Valuation									
Claus et al. (2018)	198	14-18	M/F	Cross-Sectional	Balloon Analogue Risk Task	Money	Mean response for risky decisions > riskless decisions (mean color > mean white)	Substance user (alcohol and cannabis) > Con: ↓ bilateral NAcc, L AI/IFG, thalamus/brainstem	Whole Brain
Crowley et al. (2010)	40	14-18	M	Cross-Sectional	Colorado Balloon Game	Money	Choice selection (safe and risky) > no choice selection	SUD (any non-nicotine substance) > Con: ↓ bilateral ACC, bilateral MFG, bilateral middle frontal gyrus, bilateral SFG, R MTG, R putamen/caudate, L STG, bilateral insula, R amygdala, L precuneus, L postcentral gyrus, R supramarginal gyrus, R LG, L hippocampus, and bilateral cerebellum	Whole Brain

Dalwani et al. (2014)	40	14-18	M	Cross-Sectional	Colorado Balloon Game	Money	N/A	SUD (any non-nicotine substance) > Con: ↓ bilateral SFG, L middle frontal gyrus, L MFG, bilateral MTG, bilateral retrosplenial cortex, bilateral LG ↑ bilateral cuneus	ICA/Whole Brain
De Bellis et al. (2013)	56	13-17	M	Cross-Sectional	Decision-Reward Uncertainty Task	Money	Risky choice selection (with uncertainty) > risky choice selection (no uncertainty) + no risky choice selection	CUD > Con (w/psychopathology but not SUD): ↑ L SPL, L lateral occipital cortex, and bilateral precuneus	Whole Brain
Elder et al. (2019)	167	13-14	M/F	Longitudinal	Economic Lottery Choice Task	Money	N/A	↓ AI predicted ↑ AU two years later through externalizing symptoms for boys, not girls	ROI
Jones et al. (2016)	26	13-16	M/F	Longitudinal	Wheel of Fortune	Money	Risky choice selection > safe choice selection	Binge drinker: ↓ L caudate at revisit compared to baseline (prior to drinking) Binge drinker > Con at revisit: ↓ L caudate, L IPL, L IFG, bilateral MTG, bilateral STG	ROI and Whole Brain

								↓ L caudate associated with ↑ drinking	
Kim-Spoon et al. (2019)	167	13-14	M/F	Longitudinal	Economic Lottery Choice Task	Money	N/A	↑ AI predicted ↑ SU (nicotine, alcohol, and cannabis) over time among adolescents ↓ in cognitive control (i.e., ↑ mPFC activation) ↓ AI predicted ↑ SU (nicotine, alcohol, and cannabis) over time among adolescents ↑ in cognitive control (i.e., ↓ mPFC activation)	ROI
Morales et al. (2018)	47	14-15	M/F	Longitudinal	Wheel of Fortune	Money	High risk choice selection > moderate risk choice selection	↑ bilateral NAcc, R middle occipital gyrus, L FG, R precuneus predicted ↓ duration to binge drinking	ROI and Whole Brain
Xiao et al. (2012)	28	16-18		Cross-Sectional	Iowa Gambling Task Control Task	Money	Iowa Gambling Task > Control Task	Heavy alcohol user > Con: ↑ L amygdala, bilateral insula	Whole Brain
Responses to Reward									
Aloi et al. (2019)	150	14-18	M/F	Cross-Sectional	Monetary Incentive Delay Task	Money	Monetary reward receipt (to accurate	↓ bilateral NAcc, bilateral PCC, ↑ AU	ROI and Whole Brain

							and inaccurate response) > monetary loss receipt (to accurate and inaccurate response)		
Aloi et al. (2018)	96	14-18	M/F	Cross-Sectional	Affective Stroop Task	Positive Emotional Images	Positive stimuli > negative and neutral stimuli	↑ R amygdala, ↑ AU	ROI
Bertocci et al. (2017)	73	9-17	M/F	Longitudinal	Monetary Incentive Delay Task	Money	Monetary reward receipt > no loss/reward receipt	↑ L mPFC, ↑ SU (any substance) two years later	ROI
Braams et al. (2016)	169	9-24	M/F	Longitudinal	Gambling Task	Money	Monetary reward receipt > loss receipt when playing self	↑ R NAcc predicted ↑ AU cross-sectionally	ROI and Whole Brain
Brumback et al. (2015)	38	16-18	M/F	Longitudinal	Alcohol Cue Reactivity	Drug	Alcoholic > neutral beverage images	Heavy AU > Con: ↑ bilateral dorsal striatum/globus pallidus, L ACC, bilateral cerebellum, and L PHG at baseline (not one month later after abstinence)	ROI and Whole Brain
Chaplin et al. (2021)	66	12-14	M/F	Longitudinal	Monetary Incentive	Money	Monetary reward receipt	↑ NAcc, ↑ SU (any substance) one year later in boys, not girls	ROI

					Delay Task		> no reward receipt		
Chaplin et al. (in preparation)	66	12-14	M/F	Longitudinal	Monetary Incentive Delay Task	Money	Monetary reward receipt > no reward receipt	↓ NAcc, ↑ SU (any substance) frequency one year later in boys, not girls	ROI
Chung et al. (2015)	14	14-18	M/F	Longitudinal	Reward Cue Antisaccade Task	Money	Large monetary reward anticipation > no reward anticipation	↓ L NAcc, L amygdala, R vlPFC, and bilateral putamen predicted ↑ CU six months later	ROI
Cope et al. (2019)	34	8-12	M/F	Longitudinal	Monetary Incentive Delay Task	Money	Large monetary reward anticipation > no reward anticipation	↑ bilateral NAcc predicted ↑ SU (any substance) initiation	ROI
Crowley et al. (2010)	40	14-18	M	Cross-Sectional	Colorado Balloon Game	Money	Correct choice selection reward receipt > correct choice selection no reward	SUD (any non-nicotine substance) > Con: ↓ bilateral ACC, bilateral STG, R ITG, R MTG, R precuneus, R FG, bilateral cerebellum	Whole Brain
Cservenka et al. (2015)	34	12-16	M/F	Longitudinal	Wheel of Fortune	Money	Monetary reward receipt > no reward receipt	Binge drinkers > Con: ↓ L cerebellum at revisit (not baseline) ↓ L cerebellum at revisit, ↑ AU	ROI and Whole Brain
De Bellis	44	13-17	M	Cross-Sectional	Decision Reward	Money	Monetary reward receipt after risky	CUD > (w/psychopathology but not SUD):	Whole Brain

et al. (2013)					Uncertainty Task		decision > no reward receipt after risky decision	↓ L OFC ↓ L OFC, ↑ SU experimentation	
Jager et al. (2013)	45	13-19	M	Cross-Sectional	Monetary Incentive Delay Task	Money	Monetary reward anticipation > no reward anticipation	Heavy cannabis user > Con: No significant findings	ROI
Karoly et al. (2015)	132	14-18	M/F	Cross-Sectional	Monetary Incentive Delay Task	Money	Monetary reward anticipation > no reward anticipation	Heavy tobacco user > Con: ↓ bilateral NAcc	ROI
Leiker et al. (2019)	104	14-18	M/F	Cross-Sectional	Morphed Emotion Face Processing Task	Positive and negative emotional faces	Happy face > neutral face	↑ MTP, ↑ AU	Whole Brain
Miglioriini et al. (2013)	32	15-17	M/F	Cross-Sectional	CPT with positively valenced soft touch	Touch	Pleasant touch receipt > pleasant touch anticipation	SUD (any substance) > Con: ↑ L AI ↓ bilateral PI , R MFG, R MeFG	ROI and Whole Brain
Nees et al. (2012)	324	14	M/F	Cross-Sectional	Monetary Incentive Delay Task	Money	Big monetary reward anticipation > small monetary reward anticipation	No significant findings for brain activation and AU	ROI

Nees et al. (2015)	530	14	M/F	Longitudinal	Monetary Incentive Delay Task	Money	Monetary reward anticipation > neutral monetary reward anticipation Monetary reward receipt > neutral receipt	Heavy alcohol user > Light alcohol user: Among Val66Met carriers: ↓ putamen Among Val66Met carriers: ↓ putamen, ↑ AU two years later	ROI
Peters et al. (2011)	86	14	M/F	Cross-Sectional	Monetary Incentive Delay Task	Money	Monetary reward anticipation > no reward anticipation	Tobacco user > Con: ↓ bilateral NAcc, putamen ↓ bilateral NAcc, putamen, ↑ smoking frequency	ROI and Whole Brain
Rubinstein et al. (2011)	24	13-17	M/F	Cross-Sectional	Food Picture Cues	Food	Pleasurable foods > Everyday objects	Tobacco user > Con: ↓ R insula, R putamen, R inferior frontal cortex	Whole Brain
Stice et al. (2013)	162	14-16	M/F	Longitudinal	Monetary Incentive Delay Task	Money	Monetary reward receipt > no reward receipt	↓ L caudate associated with ↑ SU (any substance) cross-sectionally ↑ L caudate and R putamen predicted ↑ SU (any substance) initiation one year later	Whole Brain

Swartz et al. (2020)	262	15-17	M/F	Longitudinal	Monetary Incentive Delay Task	Money	Monetary reward anticipation > no reward anticipation	↑ NAcc, ↑ drinking among boys two year later ↑ NAcc, ↓ drinking among girls two years later ↑ dmPFC, ↑ drinking among girls two years later	ROI
Tapert et al. (2003)	30	14-17	M/F	Cross-Sectional	Alcohol and Neutral Picture Cues	Drug	Alcoholic > neutral beverage images	AUD > Con: ↑ several regions in frontoparietal and midcingulo-insular regions (e.g., bilateral amygdala, L MFG, bilateral cuneus) ↓ R MFG, R IFG ↑ L IFG, L paracentral lobule, R precuneus/cuneus, R posterior cingulate, ↑ drinks consumed among AUD group	Whole Brain
Yip et al. (2016)	68	11-17	M/F	Cross-Sectional	Imagery Script	Food	Favorite food	Illicit substance user > Con: Adolescents without prenatal cocaine exposure: ↑ several regions in frontoparietal and midcingulo-insular	Whole Brain

								regions (e.g., insula, dlPFC, IFG and primary gustatory cortex) Illicit substance user > Con: Adolescents with prenatal cocaine exposure: ↑ several regions in frontoparietal and midcingulo-insular regions (e.g., thalamus, putamen, caudate, MFG) Illicit SU > Con: Adolescents with prenatal cocaine exposure compared to those without prenatal cocaine exposure: ↓ PHG and cerebellum ↑ OFC and IFG	
Responses to Negative Emotional Stimuli									
Aloi et al. (2018)	96	14-18	M/F	Cross-Sectional	Affective Stroop Task	Negative Emotional Images	Negative stimuli	↓ IFG, ↑ AU at lower CU ↑ IFG, ↑ AU at higher CU ↓ L amygdala, ↑ AU at lower CU	ROI and Whole Brain

								↑ L amygdala, ↑ AU at higher CU	
Berk et al. (2015)	33	15-17	M/F	Cross-Sectional	Breathing Load Task	Breathing load	Breathing load	SUD (alcohol and/or cannabis) > Con: ↑ R PI, L PHG, L STG Among SUD: ↑ bilateral PI, L AI, L MFG, R IFG	ROI and Whole Brain
							Breathing load > anticipation (no breathing load)		
Blair et al. (2019)	87	14-18	M/F	Cross-Sectional	Looming Threat Task	Negative Emotional Faces	Looming > receding negative emotion faces	↓ L rmPFC, L FG, R cerebellum, ↑ CU CUD > Con: ↓ L rmPFC, L OFC, R STG AUD > Con: ↓ R vmPFC, R STG	Whole Brain
Chaplin et al. (2019)	66	12-14	M/F	Cross-Sectional	Negative Emotional Images Task	Negative emotional images	Negative > neutral emotional stimuli	↑ L AI, ↑ SU (any substance) among girls	ROI
Elsayed et al. (2018)	330	12-14	M/F	Cross-Sectional	Emotion Faces Task	Negative emotional faces	Fearful faces > geometric shapes	Early alcohol initiators > Late alcohol initiators: ↑ bilateral amygdala	ROI
Leiker et al. (2019)	104	14-18	M/F	Cross-Sectional	Morphed Emotion Face Processing Task	Positive and negative emotional faces	Fear face > neutral face	↑ R MTP, ↑ AU ↓ L IPL, ↑ AU	Whole Brain

May et al. (2020)	47	15-17	M/F	Cross-Sectional	Drug Cues with Breathing Cues	Breathing load	High breathing load (across substance and neutral images)	SUD (alcohol and/or cannabis) > Con and experimenters: ↓ R amygdala, L IFG, L PHG Among SUD and experimenters: ↓ L IFG, ↑ lifetime AU ↓ L PHG, ↑ lifetime CU and AU	Whole Brain
Spechler et al. (2015)	140	14	M/F	Cross-Sectional	Emotion Face Video Clips	Negative emotional faces	Angry faces > neutral faces	Cannabis users: ↑ bilateral amygdala among cannabis users; no difference between groups	ROI and Whole Brain
Yip et al. (2016)	68	11-17	M/F	Longitudinal	Imagery Script Task	Stressful imagery	Stressful imagery	Illicit substance user > Con: Adolescents without prenatal cocaine exposure: ↑ several regions in frontoparietal and midcingulo-insular regions: hippocampus, thalamus, caudate and cingulate Illicit substance user > Con:	Whole Brain

								Adolescents with prenatal cocaine exposure: ↓ cuneus and other occipital regions Illicit substance user > Con: Adolescents with prenatal cocaine exposure compared to those without: ↓ OFC, ACC, PCC, R hippocampus, ACC, amygdala, brainstem	
Responses to Non-Reward and Loss									
Aloi et al. (2019)	175	14-18	M/L	Cross-Sectional	Monetary Incentive Delay Task	Money	Inaccurate punishment > all other outcomes	↓ R putamen, L ACC/dmPFC, ↑ CU	ROI and Whole Brain
Bertocci et al. (2017)	73	9-17	M/F	Longitudinal	Monetary Incentive Delay Task	Money	Monetary loss > no loss/reward	↓ L AI to loss, ↑ SU (any substance) two years later	ROI
Crowley et al. (2010)	40	14-18	M	Cross-Sectional	Colorado Balloon Game	Money	Choice selection monetary loss receipt > No choice selection	SUD (any non-nicotine substance) > Con: ↑ bilateral SFG, bilateral MFG, bilateral, R MeFG, L MTG/ITG, L precuneus, R paracentral lobule, L	Whole Brain

							brainstem, R cingulate gyrus, L cerebellum	
Gonçalves et al. (in press)	64	12-14	Longitudinal	Monetary Incentive Delay Task	Money	Monetary Loss Outcome > Neutral Outcome	↑ L putamen/NAcc, R precuneus, brainstem/pons, ↑ AU initiation	Whole Brain

Note. Con; control; L, left; R, right; SU, substance use; AU, alcohol use; CU; cannabis use; SUD, substance use disorder; AUD, alcohol use disorder; CUD, cannabis use disorder; NAcc, nucleus accumbens; AI, anterior insula; PI, posterior insula; IFG, inferior frontal gyrus; ITG, inferior temporal gyrus; IPL, inferior parietal lobule; SFG, superior frontal gyrus; SPL, superior parietal lobule; STG, superior temporal gyrus; MFG, medial frontal gyrus; MTG, medial temporal gyrus; MTP, medial temporal pole; LG, lingual gyrus; FG, fusiform gyrus; PHG, parahippocampal gyrus; PCC, posterior cingulate cortex; ACC, anterior cingulate cortex; dlPFC, dorsolateral prefrontal cortex; rmPFC, rostromedial prefrontal cortex; vmPFC, ventromedial prefrontal cortex; vlPFC, ventrolateral prefrontal cortex.

Conclusions

A growing body of research is examining affect-related brain activity and SU among adolescents. Although extant research in this area is mixed, several clear patterns are emerging.

Most of the research has been on positive valence systems, including the processes of reward valuation and especially reward responsiveness. Most studies found that increased activation during monetary reward valuation and reward responsiveness in midcingulo-insular regions (i.e., ACC, AI), including striatal regions, involved in salience signaling, was associated with SU in youth without heavy SU histories. In contrast, decreased activation in those regions was found for youth with SUDs and heavy SU. Thus, it may be the case that increased striatal and midcingulo-insular activation may represent an initial vulnerability factor to SU and SUD, and that decreased striatal and midcingulo-insular activation to monetary reward valuation and reward responsiveness may occur over time with heavy SU exposure as youth devalue monetary reward and overvalue drug cue reward. This theory is reinforced by studies examining responses to drug cues wherein higher SU was linked to increased activation of midcingulo-insular regions. Also, altered activation (both increased and decreased activation) in frontoparietal, pericentral and occipital regions to reward was also associated with SU in adolescence, although it is unclear what may be driving these discrepant findings.

There is also some evidence that altered activation to reward valuation and responsiveness may also be sex-specific. In some studies, examining low-risk substance-using samples, boys were more likely to demonstrate increased midcingulo-insular

network (involved in salience signaling) recruitment, whereas girls were more likely to demonstrate decreased recruitment of these regions (increased recruitment of some frontoparietal network regions). This supports theories that girls may be more likely to take an internalizing pathway to SU (Chaplin et al., 2018).

A smaller, but sizeable amount of research has also examined negative valence systems and adolescent SU. Most studies on adolescents with minimal SU history and SUDs found that increased recruitment of midcingulo-insular regions (e.g., ACC, AI) and the amygdala, involved in negative emotion processing, to negative emotional stimuli was associated with SU. Thus, heightened emotion reactivity to negative emotional stimuli likely serves as a vulnerability factor for SU and is unchanged after extensive exposure to SU.

Overall, the current review benefitted from several strengths, particularly the inclusion of studies examining all SU behavior types in samples with an average age below 18, as well as limitations that should be addressed moving forward. First, future research should use longitudinal designs to directly examine affect-related brain activity before and after SU initiation and escalation. This will allow us to better identify initial vulnerability factors of SU/SUDs that are not confounded with the effects of SU over time. This is particularly important because it is possible that aforementioned differences between low-risk adolescents and high-risk adolescents are unrelated to the effects of SU over time, but rather innate, pre-existing differences between these two groups. This was unable to be parsed in the current review and should be a focus of future work.

In addition, more research on low-risk adolescent SU is needed more generally, with most work done in high-risk adolescents that are particularly vulnerable and do not represent most adolescents that go on to develop SUD in adulthood (Merikangas & McClair, 2012). The challenge in performing this work, however, is that it is frequently done in community samples with low endorsement of SU overall (Johnston et al., 2014; Masten et al., 2008). This is problematic for conducting high-powered analyses without the need for specialized statistics (e.g., zero-inflated modeling). One potential solution for this is to recruit community samples that are oversampled with a risk factor for adolescent SU, such as family history of SUD (Handley et al., 2013).

Finally, future research should also be expanded to examine sex as a moderating variable, as well as examine neural activation during reward learning and in response to loss and threat. The current review was limited in exploring these constructs given the lack of studies in these areas. The studies that do exist, however, demonstrate meaningful findings that should be replicated and expanded in the future.

STUDY TWO: USING MACHINE LEARNING APPROACHES TO EXAMINE AFFECT-RELATED BRAIN ACTIVITY AND ADOLESCENT SUBSTANCE USE

Despite public health efforts to reduce SU, death related to SU and SUD have significantly increased over the past several decades (Hedegaard et al., 2017). SU is also associated with increased risk of medical conditions (Bahorik et al., 2017), comorbid psychiatric disorders (i.e., depression; Merikangas et al., 1998), and health risk behaviors (e.g., unsafe sex; Staton et al., 1999; DuRant et al., 1999). Overall, it is estimated that the economic burden of death and disability due to SU and SUD exceeds 400 billion dollars (Sacks et al., 2015). Importantly, most adults with SUD began using these substances as adolescents (Substance Abuse and Mental Health Services Administration, 2014), making adolescence a critical period for the development of SU and SUD.

One major contributing factor to adolescent SU is altered affective processing, or the processing of negatively- (e.g., negative emotion, loss) and positively- (e.g., reward) valanced stimuli (NIMH RDoC; Cuthbert & Insel, 2013). As adolescents undergo significant biological and psychosocial changes (Rice & Dolgin, 2005), they may experience altered responsivity (i.e., heightened and blunted responses) to negatively-valanced (e.g., Dahl & Gunnar, 2009; van Leeuwen et al., 2011) and positively-valanced (e.g., Urošević et al., 2012) stimuli that can lead to SU if not appropriately regulated (Tschann et al., 1994). Unfortunately, our understanding of affective processing and SU among adolescents is limited. For example, although all adolescents experience negative emotion to social rejection on occasion, not all of these adolescents engage in SU; moreover, not all adolescents highly responsive to monetary reward will engage in SU

either. This suggests that there is something specific about these positive and negative valence systems in these adolescents that do engage in SU. It is therefore important to employ methods, such as functional neuroimaging, that are sensitive enough to identify subtle neural level differences in affective processing across adolescents that do and do not engage in SU (differences that can go undetected using behavioral or laboratory methods).

Previous research has begun to explore the neural correlates of affective processing that relate to SU and SUD risk among adolescents. These have found both increased and decreased activation within midcingulo-insular and frontoparietal network regions (e.g., Spechler et al., 2015; Chaplin et al., 2019; Claus et al., 2018). However, these neuroimaging studies have employed traditional statistical methods instead of machine learning methods, which yield more generalizable findings (Norman et al., 2006; Scheinost et al., 2019). Prior neuroimaging studies of affective processing and adolescent SU have also generally used standardized paradigms. Although these paradigms have increased our understanding of affect-SU associations, it would be important to supplement these with more naturalistic affective paradigms, preferably within a social context. This would increase the ecological validity of our findings. The current study employed machine learning to classify patterns of neural activation in two standardized affective processing tasks (one on negative emotion responsiveness and another on reward responsiveness) *and* in a novel naturalistic affective responsiveness task using data collected as part of a larger study on SU, parenting, and fMRI. These patterns of neural activation can be used to improve our understanding of SUD risk, which can be

used to improve SUD prevention and intervention efforts. In the longer-term, these patterns of neural activation can serve as neurobiological markers to identify adolescents at risk for SUD.

Model of Adolescent Neurodevelopment

Throughout the adolescent developmental period, there is significant development in brain networks that support affective processing. Most models converge on the principle that adolescence is specifically characterized by exaggerated activation of midcingulo-insular networks involved in salience, particularly the striatum, and blunted activation of frontoparietal networks involved in cognitive control, including regions of the prefrontal and parietal cortex (Shulman et al., 2016; Casey & Jones, 2010). These differences are related to the amount of time it takes for these networks to fully mature. Compared to networks involved in salience that mature in adolescence, networks involved in cognitive control are not fully matured until adulthood (Shulman et al., 2016; Casey & Jones, 2010). The result is that adolescents, more so than children and adults, are biased towards engaging in affect-driven behavior (e.g., reward seeking behavior) and are less able to modulate this behavior to promote health and well-being (Shulman et al., 2016; Casey & Jones, 2010; Geier, 2013; Duell et al., 2018; Faden, 2006). This may help explain the escalation of SU (and other risk-taking) during adolescence (Chaplin et al., 2018).

Negative Valence Systems and SU

Behavioral Studies on Negative Valence Systems and SU

A large body of literature has demonstrated an association between altered negative valence systems and SU in adolescence. Most behavioral studies point to the role of heightened negative emotion in SU and SUD among adolescents. It is theorized in self-medication models of SU (Hussong et al., 2011) that adolescents with heightened negative emotion experience this emotion as overwhelming and down-regulate this emotion with substances. Indeed, several studies have found that higher levels of negative emotion, based on self-report and laboratory measures, are correlated with higher SU (i.e., frequency and escalation) among adolescents, cross-sectionally and longitudinally (Cooper et al., 1995; Myers et al., 2003; Mason et al., 2009; Chaplin et al., 2012; Hops et al., 1990). In addition, higher levels of internalizing symptoms, which are characterized by high negative emotion, are correlated with SU in adolescents (Swendsen & Merikangas, 2000; Poulin et al., 2005). Importantly, there are studies that have shown that blunted negative emotion is also associated with a heightened risk for SU among adolescents. Theories suggest that adolescents with blunted negative emotion try to up-regulate this negative emotional arousal through SU (Steinberg, 2004). For example, research has found that adolescents with low levels of negative emotion, measured primarily with laboratory measures, consume higher quantities of substances (van Leeuwen et al., 2011; Gunnarsson et al., 2008; Evans et al., 2013; Chaplin et al., 2015). Relatedly, adolescents with higher levels of callous-unemotional symptoms endorse

higher levels of SU (Wymbs et al., 2012). Overall, evidence suggests that both heightened and blunted negative emotion responsiveness is associated with adolescent SU.

Neuroimaging Studies on Negative Valence Systems and SU

Over the past few years, burgeoning research has examined negative valence systems and SU utilizing neuroimaging methods. These studies have used traditional statistical analysis, which do not test models on previously unseen subjects. These studies have found associations between altered activation in midcingulo-insular and frontoparietal network regions (involved in salience and self-referential/information processing) and SU. Two studies found that increased midcingulo-insular network activation in the amygdala to negative emotion faces was associated with problematic drinking among late adolescents (Nikolova et al., 2016; Ray et al., 2010) and history of cannabis use among middle adolescents (Spechler et al., 2015). In addition, Chaplin and colleagues (2019) found that increased activation in the left anterior insula (AI) and bilateral anterior cingulate cortex (ACC)—midcingulo-insular network regions—to negative emotion images was associated with SU in early adolescent girls. In contrast, two additional studies found that blunted activation in midcingulo-insular and frontoparietal regions that support salience—including the amygdala, ACC, AI, striatum, orbitofrontal cortex (OFC)—and self-referential/information processing—the hippocampus—to negative emotional stimuli were associated with SU in youth who were at risk for SU due to family history of alcohol use disorder (Heitzeg et al., 2008) or to prenatal cocaine exposure (Yip et al., 2016).

In sum, initial fMRI studies using traditional statistical approaches find that altered brain activation (particularly in midcingulo-insular and frontoparietal regions) to negative emotional stimuli are related to SU and SUD risk among adolescents—with most research, except for two studies, showing increased activation in brain regions implicated in salience and self-referential processing. The current study took the next step by using machine learning approaches that have higher sensitivity and yield more generalizable, replicable findings to examine neural patterns of activation to negatively-valanced stimuli related to SU and SUD risk.

Positive Valence Systems and SU

Behavioral Studies on Positive Valence Systems and SU

Several studies have demonstrated that altered positive valence systems are associated with adolescent SU. Most of this evidence specifically links increased reward responsiveness assessed via self-report and laboratory measures with increased adolescent SU cross-sectionally and longitudinally (Genovese & Wallace, 2007; van Hemel-Ruiter et al., 2013; Colder et al., 2013; Peeters et al., 2017). This is consistent with reward surfeit models of addiction wherein individuals engage in SU due to high reward responsiveness that drives them to seek substances (Hariri et al., 2006; McClure et al., 2004). Another theory of addiction posits that addiction results from blunted reward responsiveness that individuals attempt to up-regulate with substances (Blum et al., 2015). Interestingly, there is less behavioral research to support this. However, a few studies show that anhedonia, characterized by an inability to experience pleasure, predicts increased SU among adolescents (e.g., Christodoulou et al., 2020). Thus, most behavioral

research supports that increased reward responsiveness is associated with adolescent SU, with less research linking decreased reward responsiveness (i.e., anhedonia) with adolescent SU.

Neuroimaging Studies on Positive Valence Systems and SU

Most of the research examining positive valence systems has employed fMRI, with several studies (using traditional statistical methods) finding links between altered activation in midcingulo-insular and frontoparietal network regions (involved in salience, self-referential/information processing, and cognitive control) and adolescent SU. Some studies demonstrated that adolescents with heavy SU/SUD had decreased activation during reward valuation and to receipt/anticipation of reward in midcingulo-insular regions (ACC, AI), including the striatum (particularly the nucleus accumbens) involved in salience signaling, as well as frontoparietal regions involved in cognitive control (e.g., dorsolateral prefrontal cortex [dlPFC]) and value encoding (e.g., orbitofrontal cortex [OFC]) compared to controls cross-sectionally and longitudinally (Claus et al., 2018; Crowley et al., 2010; Dalwani et al., 2014; Peters et al., 2011). In contrast, a few studies found that increased activation in midcingulo-insular salience regions (e.g., AI, amygdala; Elder et al., 2019; Xiao et al., 2012; Aloi et al., 2019; Aloi et al., 2018; Cope et al., 2019; Swartz et al., 2020) and frontoparietal regions (e.g., precuneus) involved in self-referential processing (de Bellis et al., 2013; Morales et al., 2018) were associated with increased adolescent SU. These aforementioned studies mostly examined monetary reward. Most of the studies examining drug cues, however, consistently found increased recruitment of midcingulo-insular regions involved in salience (Brumback et al., 2015;

Tapert et al., 2003). For example, Brumback and colleagues (2015) found that middle adolescents with histories of heavy drinking, compared with light drinking youth, had increased activation in midcingulo-insular network regions (i.e., striatum, ACC) to alcohol images. The current study examined neural patterns of activation to positively-valanced stimuli related to SU and SUD risk using machine learning approaches that yield more generalizable, replicable findings.

Affective Processing in Social Contexts

Across the adolescent developmental period, there is an increased emphasis on social functioning (Collins et al., 1997). Compared to children, adolescents begin to dedicate more resources to developing their social relationships (Larson & Richards, 1991; Westenberg et al., 2004) and show heightened brain activation in networks involved in social processing (Burnett et al., 2011). The implication of this is that many of the stressors for adolescents are related to their social functioning (e.g., parental acceptance) (Violato & Holden, 1988; de Anda, 1997). This includes processing of peer and parent stimuli (e.g., Masten et al., 2011; Stoker & Swadi, 1990). These stressors require substantial emotion regulation and have implications for SU involvement.

Despite the importance of considering positive and negative valence systems within social contexts in this developmental period, there is relatively little research using social emotional tasks. Recently, some studies have examined neural activation during negative emotion processing to peer negative stimuli. These studies find that increased activation of midcingulo-insular regions involved in salience (i.e., ACC, amygdala) in the

social context of peer rejection is associated with increased psychopathology among adolescents (Masten et al., 2011; Silk et al., 2013; Groschwitz et al., 2016).

Although early adolescents begin to prioritize peer relationships, they remain heavily dependent on their parents (Levitt et al., 1993). Research suggests that a negative parent-adolescent relationship (i.e., low connectedness, high negative parenting) is associated with increased adolescent SU, while a positive parent-adolescent relationship (i.e., high connectedness, high negative parenting) is associated with decreased adolescent SU (Stoker & Swadi, 1990). Importantly, among adolescents with peer pressure to use substances, those with negative parent-adolescent relationships are much more likely to initiate SU than those with positive relationships (Farrell & White, 1998). Thus, it is important to examine adolescent affective processing and SU within a parental social context. One way to do this is by looking at how adolescents process video clips of their own parents expressing negative and positive emotion towards them. Neural activation to parental negative and positive emotional stimuli may be more predictive of SU than standardized negative and positive emotional stimuli because it is more salient to adolescents and related to the circumstances leading to SU in the real world. For instance, we might expect that adolescents with high activation in midcingulo-insular salience regions to negative parent stimuli might experience heightened negative emotion while with parents that in the real world would lead them to distance themselves from their parent and use substances. On the other hand, adolescents with high activation in midcingulo-insular salience regions to positive parent stimuli might experience

heightened positive emotion while with parents that in the real world would lead them to get closer with their parent, thereby reducing likelihood of engagement in SU.

Empirical research has begun to examine emotion processing within more naturalistic social contexts, including within the parent-child interaction context. One paradigm used in the current study involves adolescents viewing video clips of their parents expressing negative and positive emotion that were filmed during a parent-adolescent conflict interaction task. One study found that activation in midcingulo-insular salience regions—such as in the insula, caudate, and amygdala—to negative parent video clips was associated with increased aggression among adolescents (Whittle et al., 2012). Using a similar paradigm, another study found that adolescents showed decreased activation in the cingulate cortex—a midcingulo-insular network region—to parent positive emotional clips and that this decreased activation was correlated with adolescents' increased depressive symptoms (Saxbe et al., 2016). Other research using similar parent emotion paradigms have found similar findings. For example, one study showed increased (i.e., amygdala, insula) and decreased (i.e., amygdala, dlPFC, ACC, precuneus) BOLD responses in midcingulo-insular salience regions and frontoparietal regions involved in cognitive control and self-referential processing (Aupperle et al., 2016), as well as evidence that these BOLD responses are associated with increased psychopathology in tasks in which adolescents listen to audio clips of their mothers making critical statements about them. Taken together, these studies suggest that naturalistic, parent-based fMRI paradigms reveal patterns of activation among

adolescents that predict psychopathology. Extant research, however, has not examined these paradigms using machine learning approaches to classify/predict SU.

Using Machine Learning Approaches to Examine Affect-Related Neural Signatures of Adolescent SU

It is important to note that all of the aforementioned fMRI studies employed traditional statistical approaches. Although these methods have advanced our understanding of affective processing and SU, they do not frequently generalize to novel individuals. Machine learning overcomes these limitations by developing models based on fMRI data from previously unseen individuals and testing them in new individuals (Norman et al., 2006; Scheinost et al., 2019. In other words, machine learning models are more likely than traditional statistical analyses to produce neurobiological markers of SU and SUD risk that can detect substance using adolescents from non-using adolescents.

To date, no studies have employed machine learning approaches to examine affective processing (i.e., negative and positive valence systems) and adolescent SU. There have been a few studies using machine learning to examine affective processing and other forms of adolescent psychopathology (Just et al., 2017; Mourão-Miranda et al., 2012). For example, one study had adolescents with or without suicidal ideation undergo fMRI while viewing emotion words (Just et al., 2017). Machine learning accurately discriminated between the two groups of adolescents based on activation in specific frontoparietal regions involved in self-referential processing (Just et al., 2017). There have also been a few studies that used machine learning to examine neural responses to drug cues in adults (Elton et al., 2019; Havermans et al., 2017). These studies employing

machine learning have yielded neurobiomarkers of SU and psychopathology overall that are more spatially sensitive and more likely to generalize to new individuals than those neurobiomarkers identified using traditional statistical approaches.

SU Intentions and Expectancies

Adolescents frequently have SU intentions, or the intention to use substances in the future (Wolford & Swisher, 1986). Youth can also have expectancies about what will happen if they use substances, including positive (e.g., feeling relaxed) and negative (e.g., lead to poor school performance) expectancies (Montes et al., 2019). Several studies have established intentions to use substances, as well as high positive and low negative SU expectancies held during early adolescence as strong predictors of future adolescent SU (Maddahian et al., 1988; Andrews et al., 2003). This is important because relatively low rates of SU among adolescent samples (particularly in early adolescence, or from ages 11-14) makes it difficult for studies with early adolescents to have sufficient variance in SU and power to detect significant associations with SU. Thus, in the current study, affect-related brain activity was examined as being associated with actual SU behavior and also with SU intentions and expectancies.

The Current Study

In the current study, machine learning approaches were used to classify and predict SU and SU intentions and expectancies based on patterns of neural activation in affective processing tasks. The two aims and associated hypotheses were as follows:

Aim 1. Examine neural activation to standardized negative and positive affective stimuli in relation to adolescent SU using machine learning.

Hypothesis 1.1. A machine learning classifier will accurately differentiate adolescent substance users from non-users based on patterns of neural activity in midcingulo-insular (salience; AI, ACC, amygdala, striatum) and frontoparietal (cognitive control and self-referential processing; dlPFC; precuneus; OFC) network regions.

Hypothesis 1.2. A machine learning classifier will accurately predict higher SU intentions and expectancies among adolescents based on patterns of neural activity in midcingulo-insular (salience; AI, ACC, amygdala, striatum) and frontoparietal (cognitive control and self-referential processing; dlPFC; precuneus; OFC) network regions.

Aim 2. Examine neural activation to naturalistic negative and positive affective stimuli in relation to adolescent SU using machine learning.

Hypothesis 2.1. A machine learning classifier will accurately differentiate adolescent substance users from non-users based on patterns of neural activity in midcingulo-insular (salience; AI, ACC, amygdala, striatum) and frontoparietal (cognitive control and self-referential processing; dlPFC; precuneus; OFC) network regions.

Hypothesis 2.2. A machine learning classifier will accurately predict higher SU intentions and expectancies among adolescents based on patterns of neural activity in midcingulo-insular (salience; AI, ACC, amygdala, striatum) and frontoparietal (cognitive control and self-referential processing; dlPFC; precuneus; OFC) network regions.

Hypothesis 2.3. Predictive accuracy for machine learning models on naturalistic affective stimuli will be significantly higher than machine learning models on naturalistic affective stimuli.

Method

Participants

One hundred sixty-eight 11–15-year-old adolescents (M_{age} = 12.60, SD_{age} = .85) were drawn from a larger R01 study that investigates parenting and adolescent SU using MRI. This sample of adolescents was oversampled (40%) for maladaptive parenting (based on parenting screener) and were recruited from Northern Virginia through mailings, social media, and community advertisements. Eighty-five adolescents were cisgender boys, 75 were cisgender girls and 8 were non-binary assigned female at birth. Adolescents were predominately White (*n* = 108, 64.3%; 8.9% Black, 6.5% Asian, 1.2% American Indian/Alaskan, 17.9% biracial, 2.3% unknown or not reported), non-Hispanic (*n* = 130; 77.4%) and upper-middle class (> $100,000, *n* = 123, 73.2%; 12.5% $75-100,000, 4.2% $60-75,000; 3.6% $45-60,000, 1.8% $35-45,000, 2.4% < $35,000, 2.4% not reported).

The inclusion criteria for participation in this study included: 1) adolescent between 11-15 years of age; 2) adolescent with no prenatal substance exposure; 3) adequate English proficiency to complete questionnaires for adolescent and at least one parent; and 5) adolescent safety-eligible for MRI (e.g., no metal in body, no pregnancy). The exclusion criteria were: 1) diagnosis of intellectual disability, pervasive developmental disorder, or psychosis for adolescent, and 2) adolescent with history of

congenital brain defect or severe traumatic brain injury (due to impacts on brain structure and function; e.g., Newsome et al., 2008). We included adolescents that are on psychotropic medications, given that we did not want to exclude adolescents with psychopathology who are at greater risk for SU (e.g., Deas et al., 2006).

Procedure

Adolescents participated in: 1) a 4-hour behavioral session with their parents and 2) a 1.5-hour MRI session. The MRI session took place approximately two weeks following the behavioral session (except for a few adolescents who completed their behavioral session just prior to March 2020 and had their MRI session scheduled for a couple of months after). Adolescents returned for yearly follow-up behavior sessions. The current study used baseline MRI and baseline behavior session data.

Due to the COVID-19 pandemic, procedures were modified mid-way through the study. Specifically, families that enrolled in the study after March 2020 completed certain self-report and parent-report measures, such as demographics and all SU questionnaires, remotely in their homes as opposed to the laboratory. Other modifications were related to the fMRI procedures and are detailed below.

Baseline Behavioral Session

Adolescents completed self-report, parent-report, interviews, and physical measures (urine screens, breathalyzers) of adolescent SU and SU intentions and expectancies, as well as the parent-adolescent interaction task (PAIT).

PAIT Task. Adolescents and their parent(s) completed a video-recorded parent-adolescent interaction task, during which they discussed a highly mutually rated conflict

topic (i.e., spending money, swearing etc.) for 10 minutes. Adolescents and their parent(s) also completed a shorter PAIT in which they discussed a fun, pleasant event from the past couple of months. Parent negative and positive emotion was micro-coded from this interaction, using the PAIT Coding System (Chaplin, 2010). Trained coders rated parents' expressions of negative and positive emotion every 5 seconds from videotapes of the PAIT task based on facial, vocal, gestural, and postural cues indicative of negative and positive emotion (e.g., downturned mouth, narrowed eyes). 20% of the tapes were double-coded and checked for inter-rater reliability. This task and coding system has been used in previous studies (Chaplin et al., 2012; Chaplin et al., 2014) and the coding system shows high reliability (ICCs = .67 - .81; Ave K = .91).

Baseline fMRI Session

MRI scans were conducted using a Siemens 3T Prisma MRI scanner with a 32-channel coil. First, upon arrival to the MRI facility, adolescents were safety screened by an MRI technologist. Next, adolescents completed practice trials of the card guessing task outside of the scanner. Following the start of the COVID-19 pandemic, adolescents reviewed the card guessing task on Zoom prior to the MRI session. Adolescents then underwent MRI, including a T1-weighted structural scan and several functional scans. All visual stimuli were projected to the bore of the scanner and viewed on a mirror mounted on the head coil. In order to reduce motion, reduce noise, and increase comfort, adolescents were padded with foam inserts and given earbuds.

Standardized (Positive Affect) Card Guessing Task. This task is a card guessing task (like a monetary incentive delay task) developed by Forbes and colleagues

(2009). This task is a single run, event-related design that takes approximately 10 minutes. There are 24 trials, including 12 potential win trials (i.e., win $1) and 12 potential loss trials (i.e., lose $.50); half of the trials have neutral outcomes (i.e., no winning money, no losing money). Participants are told that the trial outcomes are random, although in actuality the trial outcomes are predetermined. In addition, participants are told that their performance on the task determines how much monetary compensation they will receive. Trial order is pseudorandomized. Each trial is 20 seconds. A trial begins with a question mark where participants have 4 seconds to guess whether the next card is greater than or less than five. Participants use the response button pad to guess. Next, a six second image of shuffling cards appears that indicates the trial type (i.e., win $1, lose $.50, or neither win or lose). This is followed by a 500ms image of the actual card number and then a 500ms image of the outcome (i.e., win $1, lose $.50, or neither win or lose). The trial ends with a 9 second crosshair.

Standardized (Negative Affect) IAPS Task. This task involves viewing negative, neutral, and positive emotional images from the International Affective Picture Set (IAPS) (Lang et al., 2008). IAPS images are empirically validated and shown to elicit emotion-related neural activation in adolescents (McRae et al., 2012). The images utilized are matched to one another on subject type, color, and luminance. The task includes 81 trials with 27 negative, 27 positive, and 27 negative images that are presented using an event-related design in a pseudo-randomized order across two 7-minute runs. Trial order and timing are determined using Optseq2. Three different presentation schedules are used (one for each run) with the order of these counterbalanced across

participants. Each trial consists of viewing a picture (4s) and an inter-trial interval (ITI) jittered between 2s and 12s (jitter determined with optseq2). Participants are asked to press a button for each picture to ensure attention, but no further response will be done in-scanner.

Naturalistic Parent Emotion (Negative and Positive Affect) Task. This task involves passive viewing of 16-sec video clips of adolescent's own mother and father showing negative, positive, and neutral emotion during the PAIT task (completed in the behavioral session). Previous research has shown that emotional video clips can be obtained from parent-adolescent interactions with early adolescents and that these clips yield brain activation in regions involved in emotional arousal and that this brain activation is correlated with psychopathology symptoms (Whittle et al., 2012; Saxbe et al., 2016). Adolescents additionally view clips of an unfamiliar mother and father actor (matched in ethnicity to the family) showing negative, positive, and neutral emotion towards an adolescent actor. The video clips are presented in block design interspersed with 8-sec rest (fixation cross) across two 6 minutes runs. In each run, negative, positive, and neutral video clips are alternated within alternating own-mother, other-mother, own-father, and other-father clips, for a total of 12 clips. Order of presentation is counterbalanced across runs and participants.

fMRI Data Acquisition. Functional images of the blood oxygen level dependent (BOLD) response during tasks and resting state are acquired using T2*-weighted gradient echo echoplanar imaging (GE EPI) (TR/TE = 1200/33ms; FOV = 230mm; matrix = 96x96; voxel size=2.5 x 2.5 x 2.5mm; MB=4; P/E=AP)). Opposing P/E direction

acquisition field maps is acquired for the reduction of geometric distortion. A high resolution T1-weighted volumetric MPRAGE sequence (TR/TE = 2400/2.14ms; Flip: 8 degrees; 256 sagittal slices; 0.8mm isotropic voxels; GRAPPA = 2) and a T2-weighted SPACE sequence (TR/TE = 3200/560ms; 256 sagittal slices; 0.8mm isotropic voxels; GRAPPA = 2) scan is acquired for anatomical co-registration.

Measures

SU

Adolescent SU was measured through self-report and parent-report questionnaires, interviews and physical toxicology screens. Given low-level endorsement of SU across the sample, SU was scored as a binary variable. Adolescents were considered positive for lifetime SU (scored 1) if they or their parent endorsed any SU across all SU measures and negative for lifetime SU (scored 0) if they or their parent denied all SU across all SU measures. In the total sample (n = 168), 40 adolescents (23.81%) were substance-using.

Questionnaires. Adolescents completed the Youth Risk Behavior Survey (YRBS; Brener et al., 2002). On the YRBS, adolescents were asked to indicate how many days (on a 6 or 7-point scale from "0 days" to "40 days or more") they used 10 different substances (i.e., alcohol, cannabis, cocaine, inhalants, heroin, methamphetamine, ecstasy, hallucinogens, prescription pills, steroids). An example item was: "during your life, on how many days have you had at least one drink of alcohol (for example, a full can of beer, a full glass of wine, a full shot of liquor)?" Adolescents were also asked if they have ever tried "cigarette smoking, even one or two puffs" or used an "electronic vapor

(vaping) product." Parents completed a parent-report version of the YRBS to indicate their adolescent's lifetime SU. Example items included: "during your child's life, on how many days has he/she had at least on drink of alcohol (for example, a full can of beer, a full glass of wine, a full shot of liquor)?" and "has your child ever used an electronic vapor (vaping) product?"

Interviews. Adolescents participated in three SU interviews: the 60-day timeline follow-back (TLFB; Rueger et al., 2012), the SUD module and AUD module of the Mini-International Neuropsychiatric Interview for Children and Adolescents (MINI-Kid; Sheehan et al., 2010) and a lifetime SU interview. For the TLFB, adolescents were asked by a research assistant if they had used any substances in the past 60 days. If adolescents endorsed "yes" to this question, they worked with the research assistant to review the past 60 days in reverse chronological order and indicate which days they used a specific substance (e.g., alcohol). They also indicated the quantity (e.g., full drinks of alcohol) of the specific substance consumed on those days. Adolescents completed the TLFB for each substance used in the past 60 days.

For the substance use disorder (SUD) module of the MINI-Kid, adolescents were asked if they used nine substances (e.g., stimulants, cocaine, opiates, hallucinogens, dissociative drugs, inhalants, cannabis, tranquilizers, and miscellaneous/other drugs) in the past year. For the alcohol use disorder (AUD) module of the MINI-Kid, adolescents were asked the screener question of "in the past year, have you had three or more drinks of alcohol in a day?" An answer of "yes" to these screeners (or positive endorsement of SU) prompted the research assistant to administer the entire SUD/AUD module.

For the lifetime substance use interview, adolescents were asked by a research assistant how many times (on a 7-point scale from "never" to "40 times or more") they have used 12 separate substances (e.g., alcohol, cannabis, tobacco, amphetamines, heroin, opiates, methadone, barbiturates, sedatives, cocaine, inhalants, hallucinogens) in their life.

Physical Toxicology Screens. Adolescents provided urine samples for the Reditest Redcup Urine 10 Panel Drug Screen for opiates, PCP, cocaine, cannabis (i.e., THC), alcohol (i.e., ETG), amphetamines (if on prescribed medication, not counted) and benzodiazepines. The urine was also used to measure the presence of cotinine, indicating nicotine use. Additionally, adolescents completed a breath screen for tobacco (i.e., carbon monoxide) and alcohol.

SU Expectancies and Intentions

Adolescents reported on SU expectancies and intentions using a measure based on prior work (Brown et al., 1987). Specifically, adolescents answered "no," "maybe," or "yes" to the following questions: (1) Do you think you would drink alcohol, smoke cigarettes, or use drugs as a teenager (or, if you are a teenager, when you are an older teenager)?; (2) Do you think that [specific substance] would relax you or let you have more fun?; and (3) Do you think that [specific substance] would make you do poorly in school or make others not want to hang around you? The two questions on expectancies are asked separately for alcohol, cigarettes, vaping, and other illicit drugs (i.e., four times for each expectancy question for a total of eight questions). For these nine items (one item for intentions, four items for positive expectancies, four items for negative

expectancies) “no” was scored as 0, “maybe” was scored as 1, and “yes” was scored as 2. The four items on negative expectancies were reverse-scored. Then, all items were summed to create an overall intentions/expectancies number, with higher values reflecting higher SU intentions and expectancies.

Data Analytic Plan

fMRI Image Pre-Processing

Neuroimaging data was preprocessed using *fMRIPrep 20.0.5* (Esteban et al., 2019; Esteban et al., 2019; RRID:SCR_016216), which is based on Nipype 1.4.2 (Gorgolewski et al., 2011; Gorgolewksi et al., 2018; RRID:SCR_002502).

Anatomical Data Preprocessing. The T1-weighted (T1w) image was corrected for intensity non-uniformity (INU) with N4BiasFieldCorrection (Tustison et al. 2010), distributed with ANTs 2.2.0 (Avants et al. 2008, RRID:SCR_004757), and used as T1w-reference throughout the workflow. The T1w-reference was then skull-stripped with a *Nipype* implementation of the antsBrainExtraction.sh workflow (from ANTs), using OASIS30ANTs as target template. Brain tissue segmentation of cerebrospinal fluid (CSF), white-matter (WM) and gray-matter (GM) was performed on the brain-extracted T1w using fast (FSL 5.0.9, RRID:SCR_002823; Zhang, Brady, & Smith, 2001). Brain surfaces were reconstructed using recon-all (FreeSurfer 6.0.1, RRID:SCR_001847; Dale, Fischl, & Sereno, 1999), and the brain mask estimated previously was refined with a custom variation of the method to reconcile ANTs-derived and FreeSurfer-derived segmentations of the cortical gray-matter of Mindboggle (RRID:SCR_002438; Klein et al., 2017). Volume-based spatial normalization to two standard spaces

(MNI152NLin2009cAsym, MNI152NLin6Asym) was performed through nonlinear registration with antsRegistration (ANTs 2.2.0), using brain-extracted versions of both T1w reference and the T1w template. The following templates were selected for spatial normalization: *ICBM 152 Nonlinear Asymmetrical template version 2009c* [Fonov et al. (2009), RRID:SCR_008796; TemplateFlow ID: MNI152NLin2009cAsym], *FSL's MNI ICBM 152 non-linear 6th Generation Asymmetric Average Brain Stereotaxic Registration Model* [Evans et al. (2012), RRID:SCR_002823; TemplateFlow ID: MNI152NLin6Asym],

Functional Data Preprocessing. For each of the BOLD runs found per subject (across all tasks and sessions), the following preprocessing was performed. First, a reference volume and its skull-stripped version were generated using a custom methodology of *fMRIPrep*. A B0-nonuniformity map (or *fieldmap*) was estimated based on two (or more) echo-planar imaging (EPI) references with opposing phase-encoding directions, with 3dQwarp Cox and Hyde (1997) (AFNI 20160207). Based on the estimated susceptibility distortion, a corrected EPI (echo-planar imaging) reference was calculated for a more accurate co-registration with the anatomical reference. The BOLD reference was then co-registered to the T1w reference using bbregister (FreeSurfer) which implements boundary-based registration (Greve & Fischl, 2009). Co-registration was configured with six degrees of freedom. Head-motion parameters with respect to the BOLD reference (transformation matrices, and six corresponding rotation and translation parameters) are estimated before any spatiotemporal filtering using mcflirt (FSL 5.0.9; Jenkinson et al., 2002). BOLD runs were slice-time corrected using 3dTshift from AFNI

20160207 (Cox & Hyde, 1997; RRID:SCR_005927). The BOLD time-series were resampled onto the following surfaces (FreeSurfer reconstruction nomenclature): *fsaverage*. The BOLD time-series (including slice-timing correction when applied) were resampled onto their original, native space by applying a single, composite transform to correct for head-motion and susceptibility distortions. These resampled BOLD time-series will be referred to as *preprocessed BOLD in original space*, or just *preprocessed BOLD*. The BOLD time-series were resampled into standard space, generating a *preprocessed BOLD run in MNI152NLin2009cAsym space*. First, a reference volume and its skull-stripped version were generated using a custom methodology of *fMRIPrep*. Automatic removal of motion artifacts using independent component analysis (ICA-AROMA, Pruim et al., 2015) was performed on the *preprocessed BOLD on MNI space* time-series after removal of non-steady state volumes and spatial smoothing with an isotropic, Gaussian kernel of 6mm FWHM (full-width half-maximum). Corresponding "non-aggressively" denoised runs were produced after such smoothing. Additionally, the "aggressive" noise-regressors were collected and placed in the corresponding confounds file. Several confounding time-series were calculated based on the *preprocessed BOLD*: framewise displacement (FD), DVARS and three region-wise global signals. FD and DVARS are calculated for each functional run, both using their implementations in *Nipype* (following the definitions by Power et al., 2014). The three global signals are extracted within the CSF, the WM, and the whole-brain masks. Additionally, a set of physiological regressors were extracted to allow for component-based noise correction (*CompCor*, Behzadi et al., 2007). Principal components are

estimated after high-pass filtering the *preprocessed BOLD* time-series (using a discrete cosine filter with 128s cut-off) for the two *CompCor* variants: temporal (tCompCor) and anatomical (aCompCor). tCompCor components are then calculated from the top 5% variable voxels within a mask covering the subcortical regions. This subcortical mask is obtained by heavily eroding the brain mask, which ensures it does not include cortical GM regions. For aCompCor, components are calculated within the intersection of the aforementioned mask and the union of CSF and WM masks calculated in T1w space, after their projection to the native space of each functional run (using the inverse BOLD-to-T1w transformation). Components are also calculated separately within the WM and CSF masks. For each CompCor decomposition, the *k* components with the largest singular values are retained, such that the retained components' time series are sufficient to explain 50 percent of variance across the nuisance mask (CSF, WM, combined, or temporal). The remaining components are dropped from consideration. The head-motion estimates calculated in the correction step were also placed within the corresponding confounds file. The confound time series derived from head motion estimates and global signals were expanded with the inclusion of temporal derivatives and quadratic terms for each (Satterthwaite et al. 2013). Frames that exceeded a threshold of 0.5 mm FD or 1.5 standardised DVARS were annotated as motion outliers. All resamplings can be performed with *a single interpolation step* by composing all the pertinent transformations (i.e. head-motion transform matrices, susceptibility distortion correction when available, and co-registrations to anatomical and output spaces). Gridded (volumetric) resamplings were performed using antsApplyTransforms (ANTs), configured with Lanczos

interpolation to minimize the smoothing effects of other kernels (Lanczos, 1964). Non-gridded (surface) resamplings were performed using mri_vol2surf (FreeSurfer).

Many internal operations of *fMRIPrep* use *Nilearn* 0.6.2 (Abraham et al. 2014, RRID:SCR_001362), mostly within the functional processing workflow. For more details of the pipeline, see the section corresponding to workflows in *fMRIPrep*'s documentation (https://fmriprep.org/en/latest/workflows.html).

First-Level Analyses. First-level analyses were run using FSL's fMRI Expert Analysis Tool (FEAT). For each adolescent, blood-oxygen-level-dependent (BOLD) signal at each voxel was modeled using generalized least squares with a voxel-wise, temporally and spatially regularized autocorrelation model. These models included regressors for onset and duration of events of interest, which were convolved with double gamma functions to create explanatory variables (e.g., monetary reward cue followed by monetary reward outcome). These models created coefficient of parameter estimate (COPE) values for each explanatory value that were used to create our contrasts of interest. In the current study, we examined the following contrasts: monetary reward outcome versus neutral outcome in the standardized positive affect (card guessing) task, negative emotional stimuli versus neutral stimuli in the negative affect (IAPS) task, and parent negative emotion versus parent neutral emotion and parent positive emotion versus parent neutral emotion in the naturalistic affect task. For the standardized negative affect (IAPS) task and the naturalistic affect task, contrasts of interest were averaged across two runs (if available for that adolescent) in a higher-level analysis.

fMRI Analysis

To test the study aims, machine learning models were conducted in Python using nilearn (e.g., Pedregosa et al., 2011; Abraham et al., 2014) and sklearn (Pedregosa et al., 2011). Due to extenuating circumstances (e.g., time limitations, request to leave scanner), not all adolescents completed every fMRI task. Thus, sample sizes will vary depending on the task being examined. Moreover, fMRI runs (and therefore sometimes subjects) were excluded for significant motion (i.e., more than 20% of TRs in run with greater than .5 mm FD).

Aim 1. Examine neural activation to standardized negative and positive affective stimuli in relation to adolescent SU using machine learning.

Hypothesis 1.1. A machine learning classifier will accurately differentiate adolescent substance users from non-users based on patterns of neural activity in midcingulo-insular (salience; AI, ACC, amygdala, striatum) and frontoparietal (cognitive control and self-referential processing; dlPFC; precuneus; OFC) network regions.

Hypothesis 1.2. A machine learning classifier will accurately predict higher SU intentions and expectancies among adolescents in midcingulo-insular (salience; AI, ACC, amygdala, striatum) and frontoparietal (cognitive control and self-referential processing; dlPFC; precuneus; OFC) network regions.

For these hypotheses, machine learning was used to classify SU as a dichotomous variable (yes/no lifetime use) and predicting SU intentions and expectancies as a continuous variable. A total of four machine learning models (one for each task

(standardized IAPS, standardized card guessing) and each outcome variable (dichotomous SU, continuous SU intentions and expectancies)) were conducted. The input for the machine learning models were the z-stat images for the affective stimuli > neutral affective stimuli contrasts. For the standardized IAPS task, this was responses to the negative emotional images > neutral emotional image contrast and for the standardized card guessing task this was the responses to the monetary win > neutral outcomes contrast. Each machine learning model had sex, age, race, psychotropic medication use, and family income as covariates.

For each machine learning model, we: (1) selected MRI features to analyze, (2) trained a model in classifying/predicting SU based on patterns of neural activation to affective stimuli using training data, and (3) tested the model using testing data (previously unseen data) and evaluated its performance.

1. Feature selection. The machine learning models examined neural patterns of activation across an atlas (Seitzman et al., 2020) of 300 functionally-defined cortical and subcortical regions of interests. This was done by masking a parcellation of the atlas across each subject's z-stat image using NiftiLabelsMasker (Pedregosa et al., 2011; Abraham et al., 2014) from nilearn. The number of regions of interests in our machine learning models were reduced in analyses by using lasso regularization (C = .1), which penalizes less important features by assigning them a value of 0 (Muthukrishnan & Rohini, 2016).

2. Model training and internal validation. Since the model must be trained and tested in independent data, internal 5-fold leave-one-out cross-validation was employed

to split the original dataset into 5 separate folds (or subsets) (Scheinost et al., 2019). Four of those folds were used as training data and one of those folds were used as testing data. This process was repeated five times, so that each fold was used as training and testing data in an iterative manner. Stratification was employed to ensure that adolescents that use and do not use SU were adequately represented in both the training and testing datasets. In addition, to account for the imbalanced data, random undersampling was applied (Lemaître et al., 2017). This transforms the testing data to create a more balanced dataset by randomly deleting cases in the majority class (i.e., non-substance users). For models that are classifying substance users versus non-users, we used logistic regression and support vector machine (SVM) with a linear kernel as the machine learning algorithms. For models that are predicting the continuous SU intentions and expectancies variable, we used linear regression (Formisano et al., 2008). All models included lasso regularization as parameters.

3. Model performance. We assessed how accurately the model classifies/predicts outcomes using several metrics. For models that were classifying substance users from non-users, we assessed model performance using measures of accuracy, recall, precision, F1 score and area under the ROC (receiver operating characteristic curve) curve (AUC-ROC) (Scheinost et al., 2019). For models that were predicting SU intentions and expectancies, we assessed model performance using mean squared error (MSE) and prediction R^2 (Scheinost et al., 2019). As analyses in the leave-one-out folds are not wholly independent, significance testing was conducted using permutation testing (Stelzer et al., 2013). For these analyses, data was randomly shuffled to create a null distribution

of model performance from which a *p*-value was calculated (Stelzer et al., 2013). Feature importance was determined by examining beta coefficients for each feature.

Aim 2. Examine neural activation to naturalistic negative and positive affective stimuli in relation to adolescent SU using machine learning.

Hypothesis 2.1. A machine learning classifier will accurately differentiate adolescent substance users from non-users based on patterns of neural activity in midcingulo-insular (salience; AI, ACC, amygdala, striatum) and frontoparietal (cognitive control and self-referential processing; dlPFC; precuneus; OFC) network regions.

Hypothesis 2.2. A machine learning classifier will accurately predict higher SU intentions and expectancies among adolescents based on patterns of neural activity in midcingulo-insular (salience; AI, ACC, amygdala, striatum) and frontoparietal (cognitive control and self-referential processing; dlPFC; precuneus; OFC) network regions.

Hypothesis 2.3. Predictive accuracy for machine learning models on naturalistic affective stimuli will be significantly higher than machine learning models on naturalistic affective stimuli.

Analyses for hypotheses 2.1-2.3 were done similarly to analyses for Aim 1. For hypothesis 2.3, paired-sample t-tests were used to compare metrics for the various models. Two t-tests were conducted: one to compare accuracy in classifying SU in the naturalistic parent positive emotion task and the standardized positive affect task and another to compare accuracy in classifying SU in the naturalistic parent negative affect

task and the standardized negative affect task. This was similarly done for machine learning models predicting SU intentions and expectancies.

Results

Descriptive statistics and correlations for study variables are in Table 2. SU intentions and expectancies was positively correlated with lifetime SU. Age was positively correlated with SU intentions and expectancies, but not lifetime SU. Race was negatively correlated with lifetime SU, indicating that non-White adolescents had greater lifetime SU. Additional demographic variables (i.e., sex, psychotropic medication use, income) were not correlated with either SU intentions and expectancies or lifetime SU.

Table 2

Correlations and Descriptive Statistics

Variable	1	2	3	4	5	6	7
1. Sex	1						
2. Age	-0.10	1					
3. Race	-0.00	0.02	1				
4. Med. Use	.16*	-.02	0.06	1			
5. Income	-.03	-0.04	0.16*	-.04	1		
6. SU Int. Exp.	0.4	.18*	-0.10	0.04	.17	1	
7. Lifetime SU	.05	0.12	-0.16*	0.06	-.14	.26**	1
Mean	.51	12.60	0.66	0.11	.37	0.93	0.24
SD	.50	0.85	0.48	0.32	.49	1.52	0.43

Note. Sex, Race, Med. Use and Income were dummy coded (0 = female, 1 = male; 0 = non-White, 1 = White; 0 = no medication, 1 = medication; 0 = <$100,000, 1 = >$100,000).
Med. Use = psychotropic medication use; SU Int. Exp = substance use intentions and expectancies; Lifetime SU. As described in the Method, Lifetime SU was dummy coded (0 = no lifetime SU; 1 = lifetime SU).

Aim 1

Standardized Positive Affect (Card Guessing) Task

Included Subjects. Of the 168 in the total sample, 160 completed the card guessing task and had analyzable data. Sixteen had significant motion and/or responded to fewer than 50% of presented trials and were therefore excluded, resulting in a final sample of 144. These 144 adolescents were not significantly different in age, race, income, SU, or SU intentions and expectancies from the original 168 adolescents. However, there were more female adolescents than in the original sample of 168 ($p < .05$).

SU Classification. Logistic regression and linear SVM classifiers were trained and then tested (using stratified 5-fold internal cross-validation and lasso regularization) on the classification of SU using 300 ROIs, age, race, sex, and income. Results are in Table 3. Accuracy, recall, precision, F1 score, and ROC were used as metrics of the classifiers' performances. Accuracy metrics indicate that both classifiers were able to train training data above 60%. When applied to the testing data, however, the classifiers had reduced classification ability. Logistic regression accurately classified SU at chance level (i.e., 50.02%), and linear SVM accurately classified slightly above chance level (i.e., 52.83%). Other metrics that are less biased by imbalanced data demonstrated poorer performance, with an F1 score of .31 and .13 for the logistic regression and linear SVM classifiers, respectively. The discrepancy between training and testing metrics indicates

that both classifiers overfit the data. The most important features for SU classification based on beta coefficients were age, psychotropic medication use, race, and ROIs in the right occipital pole, left intracalcarine cortex, right lateral occipital cortex, right superior temporal gyrus (STG), left temporal fusiform cortex, left amygdala, and cerebellum (see Table 4).

Prediction of SU intentions and expectancies. Results are in Table 5. A linear regression classifier was trained and then tested (using 5-fold internal cross-validation and lasso regularization) on the prediction of SU intentions and expectancies using 300 ROIs, age, race, sex, and income. R^2 and MSE were used as metrics of the classifiers' performances. The classifier was not able to train training data as evidenced by an R^2 of 0, indicating 0 variance in SU intentions and expectancies explained by the features using the classifier. When applied to the testing data, the classifier did not perform well, with an R^2 of -.13; R^2 suggests that the model is an inappropriate fit for the data (Pedregosa et al., 2011). The MSE for the training and testing was likely biased given the low R^2 values. The most important features in this model were not extracted given that the model was an inappropriate fit for the data.

Standardized Negative Affect (IAPS) Task

Included Subjects. Of the 168 in the total sample, 162 completed the IAPS task and had analyzable data. Nine had significant motion and were excluded, resulting in a final sample of 153. These 153 adolescents were not significantly different in age, race, income, SU or SU intentions and expectancies from the original 168 adolescents.

However, there were more female adolescents than in the original sample of 168 ($p < .05$).

SU Classification. Logistic regression and linear SVM classifiers were trained and then tested (using stratified 5-fold internal cross-validation and lasso regularization) on the classification of SU using 300 ROIs, age, race, sex, and income. Results are in Table 3. Accuracy, recall, precision, F1 score, and ROC were used as metrics of the classifiers' performances. Accuracy metrics indicate that both classifiers were able to train training data above 60%. When applied to the testing data, the classifiers had reduced classification ability. Logistic regression accurately classified SU above chance level (i.e., 62.77%), and linear SVM accurately classified above chance level (i.e., 62.88%). However, other metrics that are less biased by imbalanced data demonstrated poorer performance, with an F1 score of .28 and .38 for the logistic regression and linear SVM classifiers, respectively. The discrepancy between training and testing metrics indicates that both classifiers overfit the data. The most important features based on beta coefficients were race and ROIs in the left juxtapositional lobule cortex, right middle frontal gyrus (MFG), left frontal pole, right lateral occipital cortex, right supramarginal gyrus and cerebellum (see Table 4).

Prediction of SU intentions and expectancies. Results are in Table 5. A linear regression classifier was trained and then tested (using 5-fold internal cross-validation and lasso regularization) on the prediction of SU intentions and expectancies using 300 ROIs, age, race, sex, and income. R^2 and MSE were used as metrics of the classifiers' performances. The classifier was not able to train training data as evidenced by an R^2 of

0, indicating 0 variance in SU intentions and expectancies explained by the features using the classifier. When applied to the testing data, the classifier did not perform well, with an R^2 of -.12; R^2 suggests that the model is an inappropriate fit for the data (Pedregosa et al., 2011). The MSE for the training and testing were excellent and are likely biased given the low R^2 values. The most important features in this model were not extracted given that the model was an inappropriate fit for the data.

Aim 2

Naturalistic Negative and Positive Affect (Parent Emotion) Tasks

Included Subjects. Of the 168 in the total sample, 158 completed the parent emotion task and had analyzable data. Thirteen had significant motion and were excluded, resulting in a final sample of 145. These 145 adolescents were not significantly different in age, race, income, SU or SU intentions and expectancies from the original 168 adolescents. However, there were more female adolescents than in the original sample of 168 ($p < .05$).

Positive Affective Stimuli. ***SU Classification***. Logistic regression and linear SVM classifiers were trained and then tested (using stratified 5-fold internal cross-validation and lasso regularization) on the classification of SU using 300 ROIs, age, race, sex, and income. Results are in Table 3. Accuracy, recall, precision, F1 score, and ROC were used as metrics of the classifiers' performances. Accuracy metrics indicate that both classifiers were able to train training data above 60%. When applied to the testing data, the classifiers had reduced classification ability. Logistic regression and linear SVM accurately classified SU above chance level (i.e., 57-59%). However, other metrics that

are less biased by imbalanced data demonstrated poorer performance, with an F1 score of .29 and .36 for the logistic regression and linear SVM classifiers, respectively. The discrepancy between training and testing metrics indicates that both classifiers overfit the data. The most important features based on beta coefficients were race, income, sex, and ROIs in the bilateral inferior temporal gyrus (ITG), left MTG, left frontal pole, and right amygdala (see Table 4). ***Prediction of SU intentions and expectancies***. Results are in Table 5. A linear regression classifier was trained and then tested (using 5-fold internal cross-validation and lasso regularization) on the prediction of SU intentions and expectancies using 300 ROIs, age, race, sex, and income. R^2 and MSE were used as metrics of the classifiers' performances. The classifier was not able to train training data as evidenced by an R^2 of 0, indicating 0 variance in SU intentions and expectancies explained by the features using the classifier. When applied to the testing data, the classifier did not perform well, with an R^2 of -.34; R^2 suggests that the model is an inappropriate fit for the data (Pedregosa et al., 2011). The MSE for the training and testing were excellent and are likely biased given the low R^2 values. The most important features in this model were not extracted given that the model is an inappropriate fit for the data.

Negative Affective Stimuli. ***SU Classification***. Logistic regression and linear SVM classifiers were trained and then tested (using stratified 5-fold internal cross-validation and lasso regularization) on the classification of SU using 300 ROIs, age, race, sex, and income. Results are in Table 3. Accuracy, recall, precision, F1 score, and ROC were used as metrics of the classifiers' performances. Accuracy metrics indicate that both

classifiers were able to train training data above 60%. When applied to the testing data, the classifiers had reduced classification ability. Logistic regression and linear SVM accurately classified SU above chance level (i.e., 55%). However, other metrics that are less biased by imbalanced data demonstrated poorer performance, with an F1 score of .38 and .32 for the logistic regression and linear SVM classifiers, respectively. The discrepancy between training and testing metrics indicates that both classifiers overfit the data. The most important features based on beta coefficients were sex, race, income, and ROIs in the left MTG, left supramarginal gyrus, right temporal occipital fusiform gyrus, right lateral occipital cortex, bilateral hippocampus, and right amygdala (see Table 4).

Prediction of SU intentions and expectancies. Results are in Table 5. A linear regression classifier was trained and then tested (using 5-fold internal cross-validation and lasso regularization) on the prediction of SU intentions and expectancies using 300 ROIs, age, race, sex, and income. R^2 and MSE were used as metrics of the classifiers' performances. The classifier was not able to train training data as evidenced by an R^2 of 0, indicating 0 variance in SU intentions and expectancies explained by the features using the classifier. When applied to the testing data, the classifier did not perform well, with an R^2 of -.14; this R^2 suggests that the model is an inappropriate fit for the data (Pedregosa et al., 2011). The mean square error for the training and testing were excellent and are likely biased given the low R^2 values. The most important features in this model were not extracted given that the model is an inappropriate fit for the data.

Table 3

Performance of models of substance use classification

Classifier	Accuracy	Recall	Precision	F1 Score	ROC AUC	*p*-value
Std. Positive Affect Task						
Logistic Regression						
Training	61.94%	.68	.63	.64	.55	-
Testing	50.02%	.50	.24	.31	.47	.26
Linear SVC						
Training	75.70%	.76	.76	.76	.88	-
Testing	52.83%	.16	.12	.13	.44	.001
Std. Negative Affect Task						
Logistic Regression						
Training	62.62%	.47	.53	.51	.65	-
Testing	62.77%	.36	.23	.28	.54	.08
Linear SVC						
Training	77.59%	.79	.77	.78	.84	-
Testing	62.88%	.45	.33	.37	.53	.002
Nat. Negative Parent Affect Task						
Logistic Regression						
Training	62.95%	.38	.57	.64	.66	-
Testing	55.17%	.68	.66	.38	.54	.26
Linear SVC						
Training	76.36%	.77	.76	.76	.84	-
Testing	55.86%	.43	.26	.32	.22	.001
Nat. Positive Parent Affect Task						

Logistic Regression						
Training	61.70%	.49	.53	.50	.64	-
Testing	59.31%	.40	.24	.29	.52	.43
Linear SVC						
Training	71.82%	.75	.71	.73	.83	-
Testing	57.93%	.49	.30	.36	.58	.02

Note. Nat. = naturalistic; Std. = standardized; ROC AUC = area under the ROC (receiver operating characteristic curve) curve. All machine learning models included 300 ROIS, sex, age, race, income and psychotropic medication use as features. All machine learning models employed stratified 5-fold cross-validation, random undersampling, and lasso regularization.

Table 4

Most important feature in substance use classification models

Task	Network	*b*	x	y	*z*
Std. Positive Affect Task					
Med. Use	-	-.28	-	-	-
R Lateral Occipital Cortex	Occipital	.28	37.45	-64.7	40.38
L Amygdala	Midcingulo-insular	-.24	-20.3	-2.27	-22.21
Cerebellum	Not defined	-.22	-32	-78	-38
L Temporal Fusiform Cortex	Pericentral	-.22	-31.13	-9.99	-36.32
R Occipital Pole	Occipital	.18	26.68	-97.3	-13.49
R Superior Temporal Gyrus	Pericentral	-.18	51.52	-32.52	7.55
L Intracalcarine Cortex	Occipital	.17	-8.43	-80.5	7.44
Age	-	.17	-	-	-
Race	-	-.16	-	-	-
Std. Negative Affect Task					
Race	-	-.40	-	-	-

R Supramarginal Gyrus	Frontoparietal	-.26	49.18	-42.41	45.16
L Frontal Pole	Frontoparietal	.24	-17.65	63.19	-9.17
Cerebellum	Not defined	-.19	-34	-72.01	-48
L Juxtapositional Lobule Cortex	Pericentral	.15	-2.88	2.38	53.21
R Middle Frontal Gyrus	Frontoparietal	-.13	31.24	32.79	26.39
Cerebellum	Not defined	-.12	14	-48	-52
R Lateral Occipital Cortex	Occipital	.11	28.68	-76.62	25.42
<u>Nat. Negative Parent Affect Task</u>					
L Supramarginal Gyrus	Frontoparietal	-.66	-52.6	-48.83	42.5
Race	-	-.27	-	-	-
Income	-	-.20	-	-	-
R Amygdala	Midcingulo-insular	.17	19.51	-1.85	-23.11
L Hippocampus	Frontoparietal	.16	-25.57	-11.78	-21.54
R Hippocampus	Frontoparietal	.15	24.73	-11.25	-22.68
Sex	-	.15	-	-	-
R Temporal Occipital Fusiform Gyrus	Occipital	.14	45.68	-46.67	-16.85
R Lateral Occipital Cortex	Occipital	.14	25.34	-58.18	60.34
Cerebellum	Not defined	-.13	-32	-78	-38
L Middle Temporal Gyrus	Frontoparietal	.12	-49.3	-42.15	.83
<u>Nat. Positive Parent Affect Task</u>					
Race	-	-.36	-	-	-
Income	-	-.29	-	-	-
Sex	-	.15	-	-	-
L Middle Temporal Gyrus	Frontoparietal	.14	-56.47	-50.48	9.92
R Inferior Temporal Gyrus	Frontoparietal	.13	55.18	-30.8	-16.93
L Frontal Pole/OFC	Frontoparietal	.13	-21.14	40.87	-20.48
L Inferior Temporal Gyrus	Frontoparietal	-.11	-50.06	-7.09	-39.24
R Amygdala	Midcingulo-insular	.10	19.51	-1.85	-23.11

Note. Nat. = naturalistic; Std. = standardized; Med. Use = psychotropic medication use; R = right; L = left. Sex, Race, Med. Use and Income were dummy coded (0 = female, 1 = male; 0 = non-White, 1 = White; 0 = no medication, 1 = medication; 0 = <$100,000, 1 = >$100,000).
B coefficients were extracted from machine learning models using the linear support vector machine classifier.

Comparing Standardized Versus Naturalistic Tasks

Paired-sample t-tests revealed that the naturalistic parent positive affect task was not significantly more accurate in classifying SU than the standardized positive task; $t(1)= -3.43$, $p = .180$. In contrast to this, the standardized negative affect IAPS task *was* significantly more accurate in classifying SU than the naturalistic parent negative affect task; $t(1)= 25.21$ $p = .03$. Due to inappropriate model fit in predicting SU intentions and expectancies, comparisons of accuracy metrics across standardized and naturalistic tasks were not conducted.

Table 5

Performance of models predicting substance use intentions and expectancies

Classifier	R^2	MSE	*p*-value
<u>Std. Positive Affect Task</u>			
Linear Lasso			
Training	0.00	.04	-

Testing	-.13	.04	.75
Std. Negative Affect Task			
Linear Lasso			
Training	0.00	.04	-
Testing	-.12	.04	.58
Nat. Negative Parent Affect Task			
Linear Lasso			
Training	0.00	.04	-
Testing	-.34	.04	.73
Nat. Positive Parent Affect Task			
Linear Lasso			
Training	0.00	.04	-
Testing	-.34	.04	.73

Note. Nat. = naturalistic; Std. = standardized; MSE = mean square error. All machine learning models included 300 ROIS, sex, age, race, income and psychotropic medication use as features. All machine learning models employed stratified 5-fold cross-validation and lasso regularization.

Discussion

The purpose of this study was to identify neural patterns of affect-related brain activity that classify SU and predict SU intentions and expectancies using machine learning methods. Prior research has been limited by traditional statistical methods that are not designed to produce generalizable findings that translate to novel, previously unseen subjects (Norman et al., 2006; Scheinost et al., 2019). Moreover, this study aimed to examine affect-related brain activity using standardized and naturalistic paradigms, which to our knowledge is the first study to do so. This is important, particularly among

adolescents, given that social stimuli are more salient to adolescents (see Foulkes & Blakemore, 2016) and related to the circumstances leading to SU in the real world. Overall, our results did not provide sufficient evidence that affect-related neural activity is able to accurately and reliably classify substance-using adolescents and predict SU intentions and expectancies. These results and their implications are elaborated below.

Aim 1

Classifying SU Based on Neural Activation to Standardized Affective Stimuli

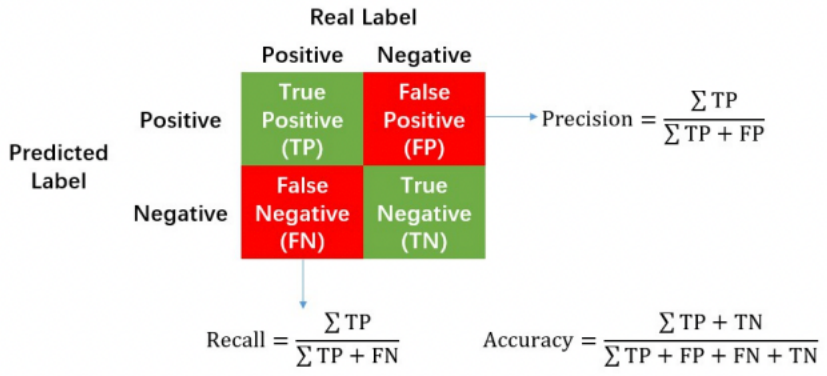
For hypothesis 1, we hypothesized that neural activity in midcingulo-insular and frontoparietal network regions during the standardized positive affect card guessing and the standardized negative affect IAPS tasks would classify substance-using adolescents from non-using adolescents. Results revealed that machine learning classifiers (i.e., logistic regression and linear SVM) classified 52.83-62.88% of previously unseen adolescents from patterns of neural activity to positive affective stimuli (i.e., monetary win) and negative affective stimuli (i.e., negative emotional pictures). These accuracy metrics were significant and indicate that machine learning classifiers did better than chance at SU classification.

However, other classification metrics reveal poorer performance of machine learning classifiers. In both tasks, the F1-score were between .13-.37, which in combination with low recall and precisions scores, suggests that less-than-half to half of adolescents were incorrectly classified as substance users or non-users. Although many studies employing machine learning do not report F1-scores, several studies report recall and precision scores (which make up the F1-score) above .50 (e.g., Grotegerd et al.,

2014). The discrepancy between the accuracy and F1-score metric is likely due to the imbalanced nature of the data, specifically the fact that there are more non-using adolescents than substance-using adolescents. That is, in an imbalanced dataset such as the one in the current study, the accuracy can be artificially higher because the classifier chooses the majority class (i.e., non-substance using adolescents) most of the time (see Figure 1 for formulas for accuracy, recall and precision). Given that the model metrics for the training datasets were higher than for the testing datasets, an additional consideration is that the machine learning classifiers overfit the data. This means that the classifiers were training on noise (versus meaningful variance) that did not generalize to previously unseen adolescents (that may not have similar types of noise).

Figure 1

Formulas for Precision, Accuracy, and Recall



Note. Reprinted from "Analyzing the Leading Causes of Traffic Fatalities Using XGBoost and Grid-Based Analysis: A City Management Perspective," by J. Ma, 2019, *IEEE Access*, *7*, p. 148064. CC BY 4.0.

Despite the poor performance of the models, several features were identified as important to the classification of SU. These features had the highest beta coefficients, signifying that they had increased predictive value compared to features with the lowest beta coefficients. Higher activation in occipital regions implicated in visual processing to both monetary reward and negative affective stimuli classified substance users. In addition, higher activation in the juxtapositional lobule cortex—a pericentral region implicated in movement—to negative affective stimuli only was important in classifying SU. Together with heightened recruitment of occipital regions, these findings suggest that substance-using adolescents are attending to standardized positive and negative affective stimuli more than non-substance-using adolescents.

In contrast, lower activation in a midcingulo-insular region (i.e., amygdala) and pericentral regions (e.g., temporal fusiform cortex) to monetary reward only was

important in SU classification. The amygdala is involved in salience and emotion arousal and thus this suggests that blunted emotion arousal to rewarding stimuli is important for SU classification. The pericentral regions are critical in recognition and are consistent with research showing that adolescents with conduct symptoms (and comorbid SU) have impaired learning of rewarding stimuli (Blair et al., 2018). It may be that for substance-using adolescents, compared to non-using adolescents, rewarding stimuli are less familiar and more novel with each occurrence and thus they are more likely to seek out rewarding stimuli (e.g., substances) later.

Moreover, in the negative affect IAPS task and positive affect card guessing task, higher and lower activation in frontoparietal regions responsible for cognitive control (e.g., frontal pole) and self-/other-referential processing (e.g., supramarginal gyrus, STG), respectively, classified substance-using adolescents. It may be that substance-using adolescents expend more prefrontal resources in processing negative affective stimuli compared to non-using adolescents. This aligns with research showing that inefficient recruitment of the prefrontal cortex during working memory tasks is associated with higher levels of negative urgency, the tendency to act impulsively in response to negative emotion (Chester et al., 2016). Interestingly, in the negative affect IAPS task, lower activation in the MFG (around dlPFC) was predictive of substance-using adolescents. This is interesting given that both the MFG and frontal pole are implicated in cognitive control. However, the MFG cluster encompasses the dmPFC—a region implicated in self-/other-referential processing; thus, this finding can reflect that lower self-/other-referential processing occurs in substance-using versus non-using adolescents.

Demographic variables were additionally found to be important by machine classifiers. Non-White adolescents were more likely to use substances based on findings from both tasks. This is consistent with literature showing higher rates of SU among Hispanic adolescents (Shih et al., 2010), but inconsistent with studies demonstrating lower SU among Black adolescents compared to their White peers (Shih et al., 2010; Wallace & Bachman, 1991). Based only on findings from the positive affect card guessing task, older adolescents and adolescents not on psychotropic medication were also more likely to be classified as substance users. Older adolescents are well-known to engage in SU compared to younger adolescents (Substance Abuse and Mental Health Services Administration, 2014). It is interesting that adolescents on psychotropic medication were less likely to be classified as substance users. While there are several studies showing that increased psychopathology (and therefore psychotropic medication use) is associated with increased SU (Friedman et al., 1987), there is also research suggesting that psychopathology may play a protective role in SU (e.g., Felton et al., 2020). Regarding other demographics, contrary to research suggesting sex differences in SU (see Chaplin et al., 2018), sex did not emerge as an important feature in SU classification in this sample, as did family income.

Overall, the machine learning classifiers were not able to accurately classify substance-using adolescents from non-using adolescents based on neural activity in the standardized positive and negative affect tasks. This is despite a higher accuracy metric, which is misleading in imbalanced data. However, the models still generated the most important features in the SU classifications. This revealed higher and lower activation in

midcingulo-insular, frontoparietal, occipital and pericentral network regions involved in emotion arousal, cognitive control, visual processing, self-/other-referential processing, and recognition. These findings are consistent with the literature on SU; however, given the poor performance of the models, should be interpreted with extreme caution.

Predicting SU Intentions & Expectancies From Neural Activation to Standardized Affective Stimuli

Regarding hypothesis 2, we hypothesized that neural activity in midcingulo-insular and frontoparietal network regions during the standardized positive affect card guessing and the standardized negative affect IAPS tasks would predict SU intentions and expectancies. We did not find support for this hypothesis, as the linear regression classifier was unable to predict any variance during training. This likely indicates that the model is a poor fit for the data—worse than a horizontal line. It is unclear what may explain these results. One possibility is that the construct of SU intentions and expectancies is too broad and therefore has limited predictive value. For instance, an adolescent scoring high in this construct may have high intentions and expectancies, or just high intentions, or just high expectancies; this is potentially problematic because they may be differentially related to SU. An adolescent high in expectancies may never intend to use substances and they are grouped with an adolescent high in intentions that likely will use substances. There is also research suggesting that SU intentions and expectancies does not predict a lot of variance in SU behavior overall among adolescents (Huba et al., 1981). In this study, SU intentions and expectancies were positively correlated with SU; however, the effect size was small with only 6% of variance explained. Thus, there is a

possibility that the construct of SU intentions and expectancies is not strong enough to be predicted by a machine learning model. Another possibility is that the link between affect-related neural processing and SU intentions and expectancies is not direct (unlike that potentially observed with SU) and therefore there is reduced power in detecting an association. For example, neural activation in the amygdala to monetary reward may not predict SU intentions because SU may be less related to reward sensitivity and perhaps more affected by substance availability irrespective of SU. Additionally, it may be that the linear regression classifier was not optimal for predicting SU intentions and expectancies given that it is zero-inflated (most adolescents reported no intentions, nor expectancies related to SU).

Aim 2

Classifying SU Based on Neural Activation to Naturalistic Parent Affective Stimuli

The results for Aim 2 paralleled those of Aim 1. For hypothesis 1, we hypothesized that neural activity in midcingulo-insular and frontoparietal network regions during the both the naturalistic positive and negative parent emotion tasks would classify substance-using adolescents from non-using adolescents. There was limited support for this hypothesis. The machine learning classifiers classified previously unseen adolescents between 55% to 59% of the time—higher than chance. However, as discussed above, given that the dataset is imbalanced, it is important to consider other metrics (e.g., F1-score). These metrics demonstrated poor performance, with all models incorrectly classifying non-users as users and vice versa.

This is similar to findings from the standardized affect tasks. This suggests that the task type (naturalistic versus standardized) is unlikely to explain the inability of these machine learning models to classify SU with high accuracy. These null findings can reflect the limited predictive value of neural activity (as measured through functional neuroimaging) overall compared to behavioral traits. Indeed, studies examining models with combined behavioral and neural measures have shown greater predictive value of behavioral traits, particularly in the prediction of SU (e.g., Nees et al., 2012). This does not mean that neural activity is unrelated to SU, rather that BOLD response during affective processing tasks is not sensitive enough to predict SU. This is particularly problematic in adolescent samples that have noisier neuroimaging data compared to adult samples. For example, in the current sample, up to 10% of adolescents were excluded from analyses due to excessive motion; this is despite a liberal threshold for motion that included adolescents in models that would ordinarily be excluded in adult samples. The tradeoff with increasing sample size by including adolescents with motion-confounded data is that more noise is introduced into the data, thereby reducing power to detect effects. Alternatively, the imbalance between the number of adolescents endorsing and denying lifetime SU may be too great for the employed machine learning classifiers. Only 23% of adolescents were substance-using and with the 5-fold cross-validation procedure, there are even fewer substance-using adolescents that the classifiers could train on. This may have resulted in poor training of SU that did not generalize well to previously unseen adolescents with and without SU. Moreover, regardless of the imbalance in SU endorsement within the data set and limited predictive ability of affect-

related brain activity, it may be the case that the sample size of 168 is insufficient. One recent study demonstrated that a sample of thousands of subjects is necessary to uncover reliable, brain-behavior associations (Marek et al., 2022).

Although the models for the naturalistic positive and negative affect parent emotion tasks were not very accurate, it is valuable to examine the most important features as determined by the machine learning classifiers. It is important, however, to interpret these findings with caution given that the models overall were not highly accurate. Both tasks had higher activation in the amygdala as classifying substance-using adolescents. Interestingly, *lower* amygdala activation was found to be important for SU classification in the standardized positive affect card guessing task. This suggests that adolescents with increased reactivity to naturalistic affective stimuli (regardless of valence) and decreased reactivity to standardized positive affective stimuli are more likely to endorse lifetime SU. It is unclear what may account for these discrepant findings. It is likely that the pathway to SU from affective reactivity differs based on whether the stimulus is naturalistic/social and standardized/monetary. One possibility is that the amygdala is being recruited more strongly during processing of *relevant* affective stimuli and less strongly during processing of *less* relevant affective stimuli (Ousdal, 2008). What is relevant will depend on the adolescent. Substance-using adolescents may find stimuli of parent affect more relevant (perhaps due to increased family conflict; Gruber & Taylor, 2006) compared to non-using adolescents. On the other hand, substance-using adolescents may find monetary reward less relevant (perhaps due to a focus on substances and other reinforcers; Büchel et al., 2017). In these cases, valence of

the relevant or less relevant stimuli is not pertinent, especially since the amygdala responds to both negatively- and positively-valanced stimuli (see Murray, 2007).

In both the naturalistic positive and negative affect parent tasks, higher and lower activation in frontoparietal network regions also classified SU. Specifically, higher activation in frontoparietal regions (and occipital regions; e.g., temporal occipital fusiform gyrus) involved in recognition (e.g., MTG, ITG) to positive and negative parent affect classified substance-using adolescents; interestingly, *lower* activation in the left ITG (not right ITG) was important in SU classification in the naturalistic positive parent affect task, suggesting distinct functions of the right and left ITG. These findings are slightly in opposition to findings showing that *lower* activation of frontoparietal and pericentral regions involved in recognition to monetary reward were important for SU classification. It is possible that enhanced recognition of parental affect as opposed to standardized affective stimuli is predictive of SU. A recent study showed that adolescents with heightened neural reactivity to peer rejection had increased depressive symptoms (Silk et al., 2022), so it is possible that the reactivity to parental affect is similarly predictive of SU.

In addition, increased activation in the hippocampus and frontal pole—frontoparietal regions implicated in memory and cognitive control, respectively—to negative parent affect only was also higher in substance-using adolescents. Given that these results are like those from the standardized negative affect IAPS task, it can be concluded that adolescents classified as substance-using were more likely to engage cognitive control resources to negative affective stimuli (not positive affective stimuli)

overall. Also, again paralleling findings on the standardized affective tasks, blunted recruitment of certain frontoparietal regions (e.g., supramarginal gyrus) to negative parental affect was important to classifying SU, indicating that substance-using adolescents are engaging in self/other-referential processing during negative (not positive) affective processing less than non-using adolescents. That this finding was not seen for the standardized and naturalistic positive affect tasks suggests that less engagement in these processes to negative affective stimuli is more predictive of SU compared to these processes to positive affective stimuli.

Demographic variables were also demonstrated as important to SU classification. Non-White adolescents and adolescents from families making less than $100,000 a year were more likely to be classified as substance-using compared to non-using. This finding on race replicates the results from the standardized affective tasks. It is notable that income emerged as an important feature in the naturalistic tasks, but not the standardized affective tasks. Because this was the case for positive and negative affective stimuli, it is unlikely to be a function of valence. It is perhaps the case that adolescents from lower-income families engage with their parents differently than adolescents from higher-income families. Although limited research has been done in this area, some studies have shown race-related variability in how parents and youth interact with one another (e.g., Gibson-Davis et al., 2010). Alternatively, the fact that this emerged only for the naturalistic task may indicate that income emerged as a highly important predictor controlling for affect-related neural activity. Also unique to the naturalistic parent affect tasks, males were more likely to be classified as substance users. This is consistent with

research demonstrating increased externalizing symptoms among boys compared to girls (Leadbeater et al., 1999). Again, the fact that sex only emerged as an important predictor for the naturalistic parent affect tasks suggests that demographic factors are more predictive of SU when controlling for affect-related neural activity compared to standardized affective tasks. This may speak to the reliability of naturalistic tasks. Although they are likely more ecologically valid, they likely generate more noisy neural data that is more difficult to identify and characterize.

Overall, the machine learning classifiers were unable to classify adolescents with and without SU with high levels of accuracy based on patterns of neural activity during the naturalistic parent affect tasks. This can be observed with classification metrics that are less biased to unbalanced data. Despite this, several brain regions were deemed important in the SU classification during training and testing. Specifically, higher midcingulo-insular activity (i.e., amygdala) involved in salience/emotion arousal and higher frontoparietal activity involved in recognition to both the negative and positive parent affect tasks classified substance-using adolescents. For the negative parent affect task only, higher frontoparietal activity involved in cognitive control and lower frontoparietal activity involved in self-/other-referential processing was important in SU classification. These findings are both consistent and in contrast with the findings for the standardized affective tasks. In contrast to the naturalistic parent affect tasks, lower midcingulo-insular and frontoparietal activity involved in salience and recognition, respectively, were important for SU classification. Consistent with the naturalistic parent affect tasks, higher activation in cognitive control and lower activation in self-/other-

referential processing classified adolescents with and without SU. Given the poor performance of the machine learning models, however, these findings need to be interpreted with caution.

Predicting SU Intentions & Expectancies From Neural Activation to Naturalistic Parent Affective Stimuli

For hypothesis 2, we hypothesized that neural activity during the naturalistic parent negative and positive affective tasks would predict SU intentions and expectancies. As was the case in Aim 1, the linear regression classifier was unable to predict any variance in SU intentions and expectancies, suggesting an extremely poor model fit.

Comparing Naturalistic and Standardized Affective Tasks

For the final hypothesis, we hypothesized that neural activity to naturalistic affective stimuli, specifically parent affective stimuli, would be a significantly better predictor of SU and SU intentions and expectancies compared to standardized affective stimuli. There was no evidence to support this hypothesis. There was no difference in how well the naturalistic parent positive affect task classified SU compared to the standardized positive affect card guessing task. However, the naturalistic parent negative affect task performed *worse* that the standardized negative affective task. This is in opposition with the hypothesis. One possibility for this finding is that the naturalistic parent negative affect task did not generate as much negative affect as expected compared to the standardized negative affective task. All families were instructed to discuss an issue they had faced over the past month during the PAIT. For some families,

this meant that they were discussing minor issues such as not making the bed or arguing with siblings. Although these were the most salient issue for some families, they were unlikely to generate high levels of conflict and negative affect. The consequence is that standardized negative affective stimuli, such as images of a starved child, may have induced more negative affect. Moreover, due to technical challenges in videorecording the parent-adolescent interaction conflict, some adolescents had difficulty hearing their parent speaking during video clips of their parent expressing negative affect towards them. This may have made it more challenging for adolescents to fully process the negative event. Given that the models predicting SU intentions and expectancies were a poor fit, comparisons between naturalistic and standardized affective tasks were not conducted.

Implications

This research has implications for the affective neuroscience field, as well as for clinical practice. There was no evidence that affect-related neural activity reliably differentiated substance-using adolescents from non-using adolescents. This was the case across four fMRI tasks—each with a different valence and stimuli type (e.g., naturalistic versus standardized). This puts into question the predictive value of affective neuroimaging data. Recent research has shown that neuroimaging data (particularly with sample sizes in the hundreds as opposed to the thousands) is limited in how much it can predict behavior, including SU (Marek et al., 2022; Nees et al., 2012). This is particularly important given that behavioral and self-report data *can* predict lifetime SU (Nees et al., 2012). Moving forward, increased focus on increasing the predictive value of affective

neuroimaging is warranted. Moreover, shifting focus to affect-related neural activity as a mechanism in the link between behavior and SU, instead of affect-related neural activity as direct predictor, may be the most advantageous path forward. Regarding clinical practice, it is not currently appropriate to rely on affect-related neural activity to predict adolescents that are or will become substance users. This means that the ability of this work to directly inform preventative and intervention efforts is limited. This line of work is still in its infancy; with advancements of affective neuroimaging in the future, the ability of using neural activity to identify at-risk youth may be much improved.

Limitations and Future Directions

The current study benefitted from several strengths, including a diverse set of affective neuroimaging tasks and a larger-than-average sample size of community adolescents. However, this study has limitations that can be addressed in subsequent studies. First, there was only 23% endorsement of lifetime SU in this study, which likely impeded machine learning classifiers from training and then accurately testing on previously unseen adolescents. Thus, in the future, analyzing more balanced datasets with a more even distribution of substance-using adolescents and non-using adolescents is critical. Given recent findings suggesting the need for large sample sizes (Marek et al., 2022), an increased emphasis on cross-laboratory studies with the ability to produce large sample sizes for investigation is warranted. Second, the sample of adolescents were not representative of the adolescent population overall, given that most were White, non-Hispanic and upper-middle class. Research has shown that White, non-Hispanic and upper-middle class adolescents differ from Black and low-income in how they respond to

certain stimuli (Romens et al., 2015). In the current dataset, it would be challenging to investigate how differences in race and income are related to associations between affect-related neural activity and SU and thus an effort to diversify future samples is justified. Third, the power to produce accurate models was further weakened by adolescents that were removed from the sample due to excessive motion and poor task performance. Although this is more commonly seen in adolescent compared to adult samples, it is problematic because it reduced the sample size and introduced more noise into the neuroimaging data. Future studies in adolescent samples would benefit from implementing protocols to reduce motion, such as practicing being still in a mock scanner. Fourth, the naturalistic parent affective tasks were limited by the relatively minimal levels of negative affect and positive affect evoked by the adolescents. This makes it a challenge to reasonably compare the value of standardized versus naturalistic fMRI tasks. One consideration for the future is to draw video stimuli from high-affect parent-adolescent encounters (e.g., Trier social stress task).

Conclusion

Given the role of altered affective processing in adolescent SU, it is critical to identify neural markers of altered affective processing that can be used to identify at-risk adolescents in need of interventive efforts. The current study used machine learning approaches to classify substance-using adolescents and predict SU intentions and expectancies based on neural activity during standardized and naturalistic affective tasks. There was insufficient evidence to demonstrate that neural activity to affective stimuli (standardized or naturalistic) could accurately classify or predict SU and SU intentions

and expectancies. This may be due to limited sample size, imbalanced SU endorsement in the sample, and excessive noise (e.g., motion) in data. Important variables for SU classification were extracted and are consistent with hypotheses but need to be interpreted with caution (given inaccurate machine learning models) and are therefore of limited applicability.

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BIOGRAPHY

Stefanie Fraga Goncalves graduated from Montgomery Blair High School, Silver Spring, Maryland, in 2011. She received her Bachelor of Science from the University of Maryland in 2014. She was employed as a rehabilitation counselor in Montgomery County, Maryland for three years and received her Master of Arts in Psychology from George Mason University in 2019. She is currently a 5th-year student in the Clinical Psychology Ph.D. program at George Mason University and will be completing her predoctoral clinical internship at Western Psychiatric Hospital/University of Pittsburgh Medical Center.