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Affect-Related Brain Activity and Adolescent Substance Use: A Systematic Review

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Abstract

Purpose of review: This review aims to summarize the research on brain activity during affective processing (i.e., reward, negative emotional stimuli, loss) and adolescent substance use (SU).

Recent findings: Most research revealed links between altered neural activity in midcingulo-insular, frontoparietal and other network regions and adolescent SU. Increased recruitment of 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 decreased recruitment of these regions was most often associated with SUD and higher risk SU. In regards to negative affective stimuli, most research demonstrated increased recruitment of midcingulo-insular network regions. There is also evidence that these associations may be sex-specific.

Summary: Future research should employ longitudinal designs that assess affect-related brain activity prior to and following SU initiation and escalation. Moreover, examining sex as as moderating variable may help clarify if affective neural risk factors are sex-specific.

Keywords

substance use; adolescent; fMRI; reward; emotion; affect

Introduction

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 (1). It is therefore advantageous to understand the brain activity that characterizes adolescent SU.

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Conflicts of Interesst

The authors declare no conflict of interest.

Human and Animal Rights

All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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 (2,3). This is consistent with theories stating that individuals initiate and engage in problematic SU to regulate altered emotion and reward arousal (4,5).

Among adults, altered neural activation during affective processing has been associated with SU (6,7). 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 (8).

The present paper will systematically review fMRI studies of adolescents' neural responses to affective processing tasks and SU. Other reviews have similiarly examined associations between affective processing and SUD risk in adolescents and young adults (9); however, the present paper more specifically targets adolescence as a developmental period and focuses on actual SU behavior.

Method

We searched for studies on "PubMed" and "PsycInfo" databases. We used keywords to obtain search results on studies employing fMRI and examining SU outcomes in adolescent samples. Please see Supplementary File 1 for more details about our methodology. We screened and coded eligible studies and included them in the review (using Uddin and colleagues' (10) brain network taxonomy; see Table 1 for results).

Results/Discussion

Positive Valence Systems

Within the RDoC framework (11), 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 responesivness) and associations with adolescent SU.

Reward Valuation

Reward valuation refers to processes of encoding the probability and magnitude of reward in the future (11). 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 (12) and Dalwani and colleagues (13) 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- to 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 processsing (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 (14)—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- to 16-year-old adolescents after they initiated binge drinking compared to controls (15). 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 (16).

Claus and colleagues (17•) employed a different task, the balloon analogue risk-taking task, to examine neural responses during risky decisions. In a sample of 14- to 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 the aforementioned 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 (18).

Kim-Spoon and colleagues (19•) 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 (20•) who also found that reduced AI activation during reward valuation indirectly predicted increased alcohol use (AU) two years later through externalizing symptoms in 13- to 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- to 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 (21). Furthermore, De Bellis and colleagues (22) found that 13- to 17-year-old boys with cannabis use disorder (CUD) had increased activation in the frontoparietal attention orienting (i.e., superior parietal lobule), 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 (23•) 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 (e.g., precuneus) involved in self-referential/information processing predicted earlier onset of binge drinking in 14- to 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 (11). Most studies examined neural responses to reward anticipation/receipt and SU, with two examining reponses 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- to 27-year-olds (24) and prospectively among 8- to 12-year-olds (25••). Similarly, among 14- to 16-year- olds, increased caudate and putamen activation to receipt of money was associated with SU prospectively (not cross-sectionally) (26). 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 (27••) and one year later (28) in 12- to 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 (5). This may be more likely among boys who demonstrate higher reward sensitivity than girls in studies (29).

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 (5, 30). Indeed, two studies linked reduced putamen and NAcc activation to monetary reward receipt and anticipation to increased drinking in 14-year-olds (31) and 14- to 18-year-olds in residential treatment (for a range of concerns, including SUDs) (32•). Further- more, 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) (33, 34). Two studies demonstrated sex differences in these associations. Swartz and colleagues (27••) and Chaplin and colleagues (35••) showed that reduced NAcc activation to reward anticipation and receipt was associated with increased SU in 16-year-old girls and 12- to 14-year-old boys a few years later. The latter findings are in contrast to aforementioned studies that found that boys are more likely to take a pathway to SU characterized by increased striatal activation. This may be due to the fact that adolescents in Chaplin and colleagues (35••) 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, espe- cially 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- to 19-year-old adolescents (36, 37).

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)) was also associated with SU. Bertocci and colleagues (38•) found that increased activation in the mPFC—involved in cognitively demanding tasks (39)—to receipt of monetary reward predicted SU two years later among 13- to 14-year-olds. Swartz and colleagues (27••) 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 (40) and emotion awareness (41) 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

(27••) 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 (41) and decreased NAcc activation in adolescents overall with depression (42) and lend credence to theories that girls are more likely to take an internalizing pathway to SU (43).

Other Monetary Reward Tasks.—Four studies employed different tasks (i.e., economic lottery tasks and antisac- cade 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- to 18-year-olds recruited from an intensive outpatient program for SU problems (44). Similarly, Crowley and colleagues (12) and De Bellis and colleagues (22) demonstrated that in response to monetary reward receipt, 13- to 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- to 16-year-olds (45). Crowley and colleagues (12) 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 (46).

Drug and Food Cue Tasks.—Two studies examined neural responses to drug cues specifically. Brumback and colleagues (47) found that 16- to 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 (48) 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 (49) demonstrated that, in 11- to 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 (50) found that 13- to 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 encode less value to food reward.

Non-Monetary, Non-Drug Cue Tasks.—Three studies employed different affective tasks. Migliorini and colleagues (51) found that 15- to 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 (52)—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 (53•) and Leiker and colleagues (54•) 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- to 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 processsing, 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 to threat, negative emotional stimuli, and loss (11). 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- to 14-year-olds that had increased activation in the amygdala, a midcingulo-insular salience region involved in emotional processing (14), to negative emotion faces initiated AU earlier (55•) and used cannabis (compared to controls) (56). Chaplin and colleagues (57•) similarly found that increased activation in the AI to negative emotional images was associated with lifetime SU in 12- to 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- to 18-year-olds (53•). 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 (49) found that 11- to 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 (57•) may suggest that this link is stronger in girls compared to boys.

Another study had 15- to 17-year-olds with SUD complete a combined drug cue reactivity and aversive interoceptive task (58•) 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- to 17-year-olds with SUD compared to controls (59).

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 (54•). Similarly, Blair and colleagues (60•) found that decreased activation in the OFC, ventromedial PFC (vmPFC), and rostromedial PFC (rmPFC)—frontoparietal region 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 (32•) 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- to 16-year-olds. Similarly, Bertocci and colleagues (37) found that decreased AI activation—a midcingulo-insular network region—to monetary loss was associated with increased SU two years later in 9- to 17-year-olds. On the other hand, Crowley and colleagues (12) found that 14- to 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 3-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 (61••). 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 are 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, decision making, cognitive control and visual processsing in response to negative emotional stimuli is associated with increased SU. In regards 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.

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.

A majority of 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 (43).

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.

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 the 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. More research on low-risk adolescent SU is needed more generally, with most work done in high-risk adolescents. Future research should also explore sex as a moderating variable, as well as examine neural activation during reward learning and in response to loss and threat.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Main findings from systematic review

Publication	Age Range	Sample Size	Cross-Sectional or Longitudinal	SU Outcome	Task Name	Stimulus	Condition and/or Contrast	Main Finding	Analysis Type
Reward Valuation									
Claus et al. (2018)	14–18	198	Cross-Sectional	Heavy (alcohol + cannabis) SU > Con	Balloon Analogue Risk Task	Money	Mean color > mean white	↓ bilateral NAcc, L AI, L IFG, thalamus/brainstem	Whole Brain
Crowley et al. (2010)	14–18	40	Cross-Sectional	SUD > Con	Colorado Balloon Game	Money	Choice selection (safe and risky) > no choice selection	↓ OFC, dlPFC, bilateral ACC, basal ganglia, bilateral insula, R amygdala, L hippocampus, and cerebellum	Whole Brain
Dalwani et al. (2014)	14–18	40	Cross-Sectional	SUD > Con	Colorado Balloon Game	Money	N/A	↓ bilateral SFG, L MFG, bilateral MTG, bilateral retrosplenial cortex, bilateral LG ↑ bilateral cuneus	ICA/Whole Brain
De Bellis et al. (2013)	13–17	56	Cross-Sectional	SUD > Con (w/ psychopathology but not SUD)	Decision-Reward Uncertainty Task	Money	Risky choice selection (with uncertainty) > risky choice selection (no uncertainty) + no risk choice selection	↑ L SPL, L lateral occipital cortex, and bilateral precuneus	Whole Brain
Elder et al. (2019)	13–14	167	Longitudinal	Prospective SU	Economic Lottery Choice Task	Money	Coefficient of variation – measure of risk for each gamble	↑ AI predicted ↑alcohol use two years later through externalizing symptoms	ROI
Jones et al. (2016)	13–16	26	Longitudinal	Future binge drinking > Con	Wheel of Fortune	Money	Risky choice selection > safe choice selection	↓ caudate ↓L IPL, L IFG, bilateral MTG, bilateral STG	ROI Whole Brain
Kim-Spoon et al. (2019)	13–14	167	Longitudinal	Prospective SU	Economic Lottery Choice Task	Money	Coefficient of variation – measure of risk for each gamble	↑ AI predicted ↑ SU over time among adolescents low in cognitive control	Whole Brain
Morales et al. (2018)	14–15	47	Longitudinal	Prospective AU	Wheel of Fortune	Money	High risk choice selection > moderate risk choice selection	↑ R middle occipital gyrus, L FG, R precuneus predicted ↑ binge drinking	ROI and Whole Brain
Xiao et al. (2012)	16–18	28	Cross-Sectional	Binge drinkers > Con	Iowa Gambling Task Control Task	Money	Iowa Gambling Task > Control Task	↑ L amygdala, bilateral insula	Whole Brain
Responses to Reward									
Aloi et al. (2019)	14–18	150	Cross-Sectional	Current SU	Monetary Incentive Delay Task	Money	Reward > Punishment Accurate > Inaccurate	↓ bilateral NAcc, bilateral PCC, ↑ AU ↓ LG, ↑ AU	ROI and Whole Brain

Publication	Age Range	Sample Size	Cross-Sectional or Longitudinal	SU Outcome	Task Name	Stimulus	Condition and/or Contrast	Main Finding	Analysis Type
Aloi et al. (2018)	14–18	96	Cross-Sectional	Current SU	Affective Stroop Task	Positive Emotional Images	Positive > Negative + Neutral stimuli	↑ R amygdala, ↑ AU	ROI
Bertocci et al. (2017)	9–17	73	Longitudinal	Prospective SU	Monetary Incentive Delay Task	Money	Monetary reward receipt > no loss/ reward receipt	↑ L vmPFC, ↑ SU two years later	ROI
Braams et al. (2016)	9–24	169	Cross-Sectional	Current SU	Gambling Task	Money	Monetary reward receipt > loss receipt when playing self	↑ R NAcc predicted ↑ AU	ROI and Whole Brain
Brumback et al. (2015)	16–18	38	Longitudinal	Binge drinkers > Con	Alcohol Cue Reactivity	Drug	Alcoholic > neutral beverage images	↑ bilateral dorsal striatum/ globus pallidus, L ACC, bilateral cerebellum, and L PHG	ROI
Chaplin et al. (in preparation)	12–14	66	Longitudinal	Prospective SU	Monetary Incentive Delay Task	Money	Monetary reward receipt > no reward receipt	↑ NAcc, ↑ SU one year later in boys, not girls	ROI
Chung et al. (2015)	14–18	14	Longitudinal	Current and Prospective SU	Reward Cue Antisaccade Task	Money	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)	8–12	34	Longitudinal	Prospective SU	Monetary Incentive Delay Task	Money	Large monetary reward anticipation > no reward anticipation	↑ bilateral NAcc predicted ↑ SU one year later	Whole Brain
Crowley et al. (2010)	14–18	40	Cross-Sectional	SUD > Con	Colorado Balloon Game	Money	Correct choice selection reward receipt > No choice selection	↓ bilateral ACC, bilateral STG, R ITG, R MTG, R precuneus, R FG, bilateral cerebellum	Whole Brain
Cservenka et al. (2015)	12–16	34	Longitudinal	Heavy AU > Con	Wheel of Fortune	Money	Monetary reward receipt > no reward receipt	↓ L cerebellum at 1 year follow-up, inversely correlated with AU severity	ROI and Whole Brain
De Bellis et al. (2013)	13–17	44	Cross-Sectional	CUD > Con	Decision Reward Uncertainty Task	Money	Monetary reward receipt after risky decision > no reward receipt after risky decision	↓ OFC	Whole Brain
Jager et al. (2013)	13–19	45	Cross-Sectional	Heavy CU > Con	Monetary Incentive Delay Task	Money	Monetary reward anticipation > no reward anticipation	↑ L caudate nucleus during no reward anticipation —no findings for reward anticipation	ROI
Karoly et al. (2015)	14–18	132	Cross-Sectional	Heavy TU > Con	Monetary Incentive Delay Task	Money	Monetary reward anticipation > no reward anticipation	↓ bilateral NAcc	ROI

Publication	Age Range	Sample Size	Cross-Sectional or Longitudinal	SU Outcome	Task Name	Stimulus	Condition and/or Contrast	Main Finding	Analysis Type
Leiker et al. (2019)	14–18	104	Cross-Sectional	Current SU	Morphed Emotion Face Processing Task	Positive and negative emotional faces	Happy face > neutral face	↑ MTP, ↑ AU	ROI
Migliorini et al. (2013)	15–17	32	Cross-Sectional	SUD > Con	CPT with positively valenced soft touch	Touch	Pleasant touch receipt > pleasant touch anticipation	↑ L AI ↓ bilateral PI	Whole Brain & ROI
Nees et al. (2012)	14	324	Cross-Sectional	Current SU	Monetary Incentive Delay Task	Money	Big monetary reward anticipation > small monetary reward anticipation	BOLD activation was not associated with drinking	ROI
Nees et al. (2015)	14	530	Longitudinal	Heavy AU > Light AU	Monetary Incentive Delay Task	Money	Monetary reward anticipation > neutral monetary reward anticipation	Among Val66Met carriers: ↓ putamen	ROI
				Prospective AU			Monetary reward receipt > neutral receipt	↓ putamen, ↑ AU two years later	
Peters et al. (2011)	14	86	Cross-Sectional	Tobacco user > Con	Monetary Incentive Delay Task	Money	Monetary reward anticipation > no reward anticipation	↓ bilateral NAcc, putamen	Whole Brain
Rubinstein et al. (2011)	13–17	24	Cross-Sectional	Tobacco user > Con	Food Picture Cues	Food	Pleasurable foods > Everyday objects	↓ R insula, R putamen, R inferior frontal cortex	Whole Brain
Stice et al. (2013f)	14–16	162	Longitudinal	Future SU > Con Current SU > Con	Monetary Incentive Delay Task	Money	Monetary reward receipt > no reward receipt	↑ L caudate associated with ↑ SU cross-sectionally ↑ L caudate and R putamen predicted ↑ SU initiation one year later	Whole Brain
Swartz et al. (2020)	15–17	262	Cross-Sectional	Prospective SU	Monetary Incentive Delay Task	Money	Monetary reward anticipation > no reward anticipation	↑ NAcc, ↑ drinking among boys ↑ NAcc, ↓ drinking among girls ↑ dmPFC, ↑ drinking among girls	ROI
Tapert et al. (2003)	14–17	30	Cross-Sectional	AUD > HC	Alcohol and Neutral Picture Cues	Drug	Alcoholic > neutral beverage images	Several regions in frontoparietal and midcingulo-insular regions	Whole Brain
Yip et al. (2016)	11–17	68	Cross-Sectional	Illicit SU > Con	Imagery Script	Food	Favorite food	Adolescents with prenatal cocaine exposure compared to HC: ↓ PHG and cerebellum, ↑ illicit SU ↑ OFC and IFG, ↑ illicit SU	Whole Brain
Responses to Negative Emotional Stimuli									

Publication	Age Range	Sample Size	Cross-Sectional or Longitudinal	SU Outcome	Task Name	Stimulus	Condition and/or Contrast	Main Finding	Analysis Type
Aloi et al. (2018)	14–18	96	Cross-Sectional	Current SU	Affective Stroop Task	Negative Emotional Images	Negative Viewing	↓ IFG, ↑ AU at lower CUD symptoms ↑ IFG, ↑ AU at higher CUD symptoms ↓ L amygdala, ↑ AU at lower CUD symptoms ↑ L amygdala, ↑ AU at higher CUD symptoms	Whole Brain ROI
Berk et al. (2015)	15–17	33	Cross-Sectional	SUD > Con	Breathing Load Task	Breathing load	Breathing load > Anticipation of breathing load	↑ L AI, bilateral PI	Whole Brain ROI
Blair et al. (2019)	14–18	87	Cross-Sectional	Current SU	Looming Threat Task	Negative Emotional Faces	Looming > receding negative emotion faces	↓ rmPFC, L fusiform gyrus, cerebellum, ↑ CU	Whole Brain
Chaplin et al. (2019)	12–14	66	Cross-Sectional	Current SU	Negative Emotional Images Task	Negative emotional images	Negative > neutral emotional stimuli	↑ L AI, ↑ lifetime SU among boys	ROI
Elsayed et al. (2018)	12–14	330	Cross-Sectional	Early alcohol initiators > Late alcohol initiators	Emotion Faces Task	Negative emotional faces	Fearful faces > geometric shapes	↑ bilateral amygdala, early SU initiation	ROI
Leiker et al. (2019)	14–18	104	Cross-Sectional	Current AU	Morphed Emotion Face Processing Task	Positive and negative emotional faces	Fear face > neutral face	↑ R MTP, ↑ AU ↓ L IPL, ↑ AU	ROI
May et al. (2020)	15–17	47	Cross-Sectional	SUD > Con and experimenters	Drug Cues with Breathing Cues	Breathing load	High breathing load > no breathing load	↓ R amygdala, L IFG, L PHG	Whole Brain
Spechler et al. (2015)	14	140	Cross-Sectional	Cannabis User > Non-User	Emotion Face Video Clips	Negative emotional faces	Angry faces > Neutral faces	↑ bilateral amygdala among cannabis users; no difference between groups	ROI
Yip et al. (2016)	11–17	68	Longitudinal	Current SU	Imagery Script Task	Stressful imagery	Stressful imagery	Adolescents with prenatal cocaine exposure compared to those without: ↓ OFC, anterior prefrontal cortex, PCC, hippocampus, ACC, amygdala, brainstem, ↑ SU	Whole Brain
Responses to Non-Reward and Loss									
Aloi et al. (2019)	14–18	175	Cross-Sectional	Current SU	Monetary Incentive Delay Task	Money	Inaccurate punishment > all other outcomes	↓ R putamen, L ACC/ dmPFC, ↑ CU	ROI and Whole Brain
							Inaccurate feedback > Accurate feedback	↑ L cuneus, ↑ drinking ↓ bilateral LG, R putamen, ↑ CU	

Publication	Age Range	Sample Size	Cross-Sectional or Longitudinal	SU Outcome	Task Name	Stimulus	Condition and/or Contrast	Main Finding	Analysis Type
Bertocci et al. (2017)	9–17	73	Longitudinal	Prospective SU	Monetary Incentive Delay Task	Money	Monetary loss > no loss/reward	↓ L AI to loss, ↑ SU two years later	ROI
Crowley et al. (2010)	14–18	40	Cross-Sectional	SUD > Con	Colorado Balloon Game	Money	Choice selection monetary loss receipt > No choice selection	↑ bilateral SFG, bilateral MFG, L IFG, bilateral MTG, L precuneus, R paracentral lobule, L brainstem, R cingulate gyrus, L cerebellum	Whole Brain
Gonçalves et al. (in press)	12–14	64	Longitudinal	Prospective AU	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*, middle frontal gyrus; *MeFG*, 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; *mPFC*, middle prefrontal cortex; *OFC*, orbitofrontal gyrus; *dmPFC*, dorsomedial frontal gyrus