HHS Public Access

Author manuscript

Curr Behav Neurosci Rep. Author manuscript; available in PMC 2019 December 01.

Published in final edited form as:

Curr Behav Neurosci Rep. 2018 December ; 5(4): 249–262. doi:10.1007/s40473-018-0166-5.

Review of Neurobiological Influences on Externalizing and Internalizing Pathways to Alcohol Use Disorder

Jillian E. Hardee, PhD, **Lora M. Cope, PhD**, **Meghan E. Martz, PhD**, **Mary M. Heitzeg, PhD***

University of Michigan, Department of Psychiatry and Addiction Center, 4250 Plymouth Road, Ann Arbor, MI

Jillian E. Hardee: jhardee@med.umich.edu; Lora M. Cope: lcope@med.umich.edu; Meghan E. Martz: mmartz@med.umich.edu

Abstract

Purpose of review.—Two developmental courses through which alcohol use disorder (AUD) may emerge include externalizing and internalizing pathways. We review recent neuroimaging studies of potential neural risk factors for AUD and link findings to potential behavioral risk factors for AUD.

Recent findings.—There is evidence that early-emerging weakness in prefrontal functioning and later-emerging differences in reward-system functioning contribute to an externalizing risk pathway. Stress may be an important contributor in the internalizing pathway through a blunting of reward-related activation, which may act alone or in combination with heightened emotion-related reactivity.

Summary.—This review highlights areas for future work, including investigation of the relative balance between prefrontal and subcortical circuitry, attention to stages of AUD, and consideration of environmental factors such as stress and sleep. Particularly important is longitudinal work to understand the temporal ordering of associations among brain maturation, behavioral risk, and alcohol use.

Keywords

adolescence; stress; sleep; emotion; reward; inhibitory control

Introduction

Rates of alcohol use rise steadily throughout adolescence, peaking in young adulthood and declining thereafter [1, 2]. Incidence of first time alcohol use disorder (AUD) follows a similar pattern, peaking between the ages of 18 to 20 years [3]. Adolescence is a period when substantial changes occur in personality, behavior, and neural development. Models of

*Corresponding Author: Mary M. Heitzeg, University of Michigan, Department of Psychiatry and Addiction Center, 4250 Plymouth Rd, Ann Arbor, MI 48109, USA, mheitzeg@med.umich.edu.

Conflict of Interest

The authors declare no conflicts of interest

Human and Animal rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors

adolescent brain development have proposed maturational changes occurring in brain systems underlying behavioral and emotional regulation that may contribute to the normative increases in alcohol and other substance use during the teen years. Specifically, differences in the maturation rate between subcortical reward and emotion circuitry (maturing earlier) and prefrontal control circuitry (maturing later) are believed to result in increased reactivity to novel, rewarding, or emotional stimuli during adolescence [4–6]. This suggests a developmental vulnerability that may underlie normative trends in alcohol use through effects on risk-taking behavior and emotional lability. However, these models are not sufficient to understand individual differences in risk for AUD. Certainly, not every adolescent experiments with alcohol, and not all of those who use alcohol progress to have alcohol-related problems.

A large literature considers AUD from a developmental perspective and posits two pathways through which risk for AUD may emerge, with antecedents observable in childhood: an externalizing pathway and an internalizing pathway (see review in [7]). We use these pathways as an organizing heuristic in this review in an effort to bridge the gap between the established literature on behavioral risk factors for AUD and emerging findings from work grounded in developmental neuroimaging. We review studies published in the past 5 years that attempt to draw conclusions about *risk* for alcohol-related problems and AUD, with a particular focus on prospective studies and risk conferred by family history. Although the literature on *consequences* of alcohol use is outside the scope of this review, we do acknowledge there are important reciprocal relations between risk factors and alcohol use across development.

Externalizing

An externalizing risk pathway is characterized by problems with self-regulation such as aggression, impulsivity, sensation-seeking, and rule-breaking, with the primary deficit being one of behavioral undercontrol or disinhibition [8]. Disinhibited behavior may stem from an imbalance between top-down inhibitory control circuitry centered in the prefrontal cortex (PFC) and bottom-up reward-related circuitry, including the ventral striatum (VS) [8, 9]. The majority of research on this neural circuitry in the context of risk for AUD has investigated these systems separately. Therefore, we begin this section with a review of recent neuroimaging findings in each of these neural systems; we then turn to a review of the broader literature that addresses differential effects of these systems at different stages of AUD risk and the importance of the balance between these two neural systems. Recent studies reviewed in this section are detailed in Table 1.

Neuroimaging Studies of Inhibitory Control

Neural correlates of inhibitory control have received considerable attention in the neuroimaging literature on risk for alcohol and other drug problems. Early studies focused on cross-sectional comparisons of higher- versus lower-risk youth, based on family history or potential behavioral risk factors [10, 11]. More recent work has examined prospective associations between activation during inhibitory control and later substance-use outcomes [12–14] or trajectories of inhibitory control circuitry in at-risk youth [15]. As reviewed

elsewhere [16], findings from these studies converge on the conclusion that a weakness in response inhibition circuitry in childhood and early adolescence is a risk factor for later alcohol and other drug problems. In particular, the evidence suggests that blunted activation in the PFC early in development and prior to significant substance use is associated with heightened risk. Furthermore, prospective studies that have differentiated between successful and failed inhibition find that the magnitude of PFC activation specifically during inhibitory errors is associated with later problem drinking [17, 18], suggesting that differences in error monitoring and performance adjustment circuitry may underlie risk. Of note, Heitzeg and colleagues provide evidence that blunted activation in this circuitry is linked to an externalizing risk pathway [17].

Neuroimaging Studies of Reward Responsivity

Studies investigating reward circuitry in the context of risk for AUD have had mixed findings, which are likely due to differences in ages and level of prior use (reviewed in [16]). Muller and colleagues found no differences in reward activation in the VS between 13–15 year-olds with a family history of AUD and a matched control sample [19], consistent with prior work in 12–16 year-olds [20]. Heitzeg and colleagues investigated the impact of genetic variation in *GABRA2*, which has been associated with an externalizing risk pathway to AUD [21], on reward-related VS activation across development from childhood to early adulthood [22]. Carriers of the *GABRA2* risk allele had greater VS activation in adolescence but not in childhood or young adulthood. Furthermore, VS activation was positively correlated with later alcohol problems. These findings suggest that reward-related risk for AUD may be developmentally modulated, which may explain negative findings in younger samples [19, 20]. Waller and colleagues reported that escalation in alcohol use from ages 11 to 17 years was associated with increased VS activation during reward anticipation measured at age 20, which was in turn associated with a greater number of AUD symptoms at age 22 [23]. These findings not only lend support to a role for increased VS activation in risk for AUD, but also highlight the importance of attending to the reciprocal influence of alcohol use and brain function. Specifically, it is unclear from these findings whether the association between increased alcohol use during adolescence was a cause or a consequence of heightened VS activation.

The studies reviewed above all focused on effects specifically within the VS. Other work has investigated broader circuitry engaged during reward tasks that may be associated with risk. Stice and colleagues reported that 14–17 year-olds with parental substance use disorders had greater activation in the dorsolateral PFC and putamen and less activation in attentional regions to monetary reward anticipation compared with controls [24]. A prospective study found that heightened reward-related activation in the superior frontal gyrus and reduced activation in posterior regions at age 14 was associated with binge drinking by age 16 [18]. Together, these findings indicate a broader network may be involved in reward-related risk for AUD. Specifically, reduced activation to reward in posterior regions, including occipital and temporal cortices and posterior cingulate, may indicate that abnormal attention to and/or processing of rewarding stimuli contributes to risk.

The Externalizing Pathway and Stages of AUD Risk

The development of AUD is a multistage process that begins with the initiation of alcohol use, followed by recurrent use, escalation of use, and compulsive use for a subset of users. Vulnerabilities in inhibitory control and reward systems may impact the development of AUD differently across stages of the addiction cycle (reviewed in [25]). Some evidence in support of this view comes from longitudinal studies focusing on impulsivity and sensation-seeking. Impulsivity involves the tendency to act or make decisions without much forethought [26] and may be mediated by prefrontal, cognitive-control circuity. Sensation-seeking is the tendency to seek novel, intense, exciting, or risky experiences [27], and may be supported by subcortical, reward-responsive circuitry, including the VS. Consistent with the underlying neural circuitry, impulsivity decreases from late childhood to adolescence, whereas sensation-seeking follows an inverted U-shaped trajectory that peaks in middle adolescence [28]. In a longitudinal study beginning with alcohol-naïve youth (average age 12 years), Lopez-Vergara and colleagues found that sensation-seeking was associated with initiation of alcohol use, but not with escalation in use, over the next 3 years [29]. In an older sample, Quinn and colleagues reported that trajectories of sensation-seeking were not associated with changes in substance use over time whereas a slower decline in impulsivity from ages 15 to 26 years was associated with a more rapid increase in alcohol and other drug use [30]. Taken together, these studies are consistent with animal work suggesting that experimentation with substances may be related to a tendency to seek novel, rewarding, or exciting experiences, whereas the escalation of use preceding compulsive use and addiction may be more closely linked to impulsivity [31]. However, Charles and colleagues report evidence that both impulsivity and sensation-seeking may distinguish youth who used substances by age 15 years from those who did not [32], demonstrating that these associations are not clear-cut.

Recent work has shed further light on these relationships by focusing on the balance between reward and inhibitory control systems. In a cross-sectional study of 13–14 year-olds, high reward sensitivity was associated with earlier age of substance use onset when coupled with low, but not high, inhibitory control [33]. This work, however, could not address escalation of use due to the young sample and cross-sectional design. In a 4-year longitudinal neurocognitive study beginning when participants were 11–13 years old, Khurana and colleagues found that heightened reward-seeking balanced by strong executive control was associated with experimentation with substances but not progression of use, whereas an imbalance resulting from heightened reward-seeking and weak executive control was associated with progression of substance use [34]. To our knowledge, no neuroimaging studies of AUD risk to-date have investigated how the interaction between inhibitory control and reward circuitry may uniquely predict specific stages of AUD risk. This will be an important direction for future research.

Internalizing

An internalizing risk pathway is characterized by problems with negative emotionality, such as depression and anxiety, with emotion regulation being the primary deficit [35, 7]. The ability to self-regulate emotions depends on strengths of connections between the PFC and

limbic system structures, notably the amygdala [36, 37]. Similar to behavioral disinhibition, emotional dysregulation is believed to stem from an imbalance between top-down prefrontal control and bottom-up subcortical systems. The main distinction is the involvement of emotion-related limbic structures, such as the amygdala, as well as reward-related circuitry in emotional dysregulation [38, 39]. We begin this section with a review of recent neuroimaging studies that target emotion regulation or emotion processing to explore how differences in these systems may be related to risk for AUD. We highlight the importance of considering gender-related differences and then turn to a discussion of broader considerations in internalizing research. Recent studies reviewed in this section are detailed in Table 2.

Neuroimaging Studies of Emotion Circuitry

Early work has shown that non-abusing adolescents and young adults with parental AUD have reduced amygdala volumes and decreased amygdala activation in response to emotional stimuli [40, 41]. However, in the two recent studies examining possible influences of familial risk on emotion circuitry functioning in adolescents, neither supported activation differences localized to the amygdala. Peraza and colleagues assessed emotion circuitry using subliminal fearful and neutral facial expressions in youth with and without parental AUD prior to heavy alcohol use [42]. Youth with parental AUD showed altered activation in the superior parietal lobe but not the amygdala, suggesting a difference in the attention network responsible for processing the salience of emotional stimuli.

Cservenka and colleagues investigated the association between emotion processing and executive functioning in risk for AUD using an emotional go/no-go task and resting-state connectivity with a seed in the amygdala [43]. Compared with control participants, youth with parental AUD had reduced activation in the superior temporal cortex during positive emotional contexts, reduced activation in frontal and striatal regions during emotionally-valenced inhibitory control trials, and greater negative connectivity between the left amygdala and superior frontal gyrus, which was related to poorer inhibitory control. These findings suggest that emotional information influences frontal lobe functioning in at-risk youth, potentially due to altered functional connectivity between affective and cognitive networks.

Gender-Related Differences in Internalizing Risk

The positive association between internalizing symptoms and substance use may stem from motivations to offset negative affect and regulate emotions [35]. Adolescent girls are more likely than boys to use substances to cope [44] and to suffer from internalizing disorders such as depression [45], suggesting possible gender-related differences in risk pathways to AUD. Furthermore, gender-related differences in amygdala maturation and PFC-amygdala connectivity may affect vulnerability to internalizing problems (reviewed in [46]). However, the investigation of how gender-related differences in this circuitry may contribute to risk pathways for AUD has not been well studied to date. One recent exception investigated whether high-risk (based on parental AUD) males and females have different trajectories in emotion-circuitry development using longitudinal fMRI [47]. Participants performed an affective word task during an initial fMRI scan at age 8–13 years, and subsequent fMRI

scans followed at 1- to 2-year intervals until age ~17.5 years. At-risk males demonstrated significantly decreasing activation to negative versus neutral stimuli across age in the right amygdala and precentral gyrus, whereas activation in at-risk females remained steady across development in these regions. Internalizing symptomology for at-risk females significantly increased with age, whereas it decreased in at-risk males. These results suggest gender-specific neural and behavioral patterns related to internalizing vulnerabilities, which may be relevant for understanding gender differences in risk pathways to alcohol-use problems.

Considerations in Internalizing Research

The study of neural correlates of an internalizing risk pathway to AUD is in its infancy. As the field moves forward, it will be important to understand the complex nature of this pathway. While the association between depression, anxiety, and alcohol use is fairly consistent in adults, results in youth are less consistent. For example, two studies tracked childhood internalizing symptoms to determine associations with later adolescent alcohol use. One found a negative association between children who experienced elevated levels of internalizing symptoms and alcohol use in early adolescence [48], while the other found a positive relation between cumulative precursive depression symptoms and age of alcohol-use onset [49]. Hussong and colleagues posit that mixed results such as these arise from several factors including methodological differences in the measurements of internalizing symptoms and substance-use outcomes [7]. Thus, the inconsistency between the two studies above may stem from differences in specific internalizing features assessed in each study (composite internalizing versus depression), as well as the developmental periods when onset of alcohol use was measured (early adolescence only versus onset across adolescence).

Another major factor likely contributing to mixed findings in the internalizing literature is a comorbidity between externalizing and internalizing in youth that has largely been ignored until recently [7]. A systematic review by Hussong and colleagues investigated 61 prospective studies, accounting for the contribution of externalizing symptoms and considering studies by types of negative affect (anxiety, depression, or composite internalizing) and types of substance-use outcome [50]. They report that the most consistent finding was for a prospective association between depressive features and substance use—particularly for alcohol use two years later—when controlling for externalizing symptoms. This work highlights the relevance of considering both externalizing and internalizing features, as well as specific types of internalizing features (e.g., depression versus anxiety), to fully understand how AUD risk may develop.

To our knowledge, no neuroimaging studies of AUD risk to-date have investigated the unique and interacting associations between externalizing and internalizing circuitry and behavior. Of note, however, is work by Nikolova and colleagues [51], reviewed below, and that by Hulvershorn and colleagues [52], who acknowledged that mood dysregulation is often found in high-risk samples with high rates of externalizing disorders and that both are likely contributors to risk for substance-use problems. Emotion-circuitry functioning in high-risk youth, defined as having both parental substance use disorder and elevated rates of externalizing psychopathology, was compared with that of healthy control subjects. High-risk youth had greater activation in the medial PFC, precuneus, and occipital cortex during a

facial emotion (angry, fearful) matching task. Occipital activation in the high-risk group was positively correlated with emotional lability/negativity and emotional flatness. This research illustrates that deficits in affective processing and regulation may be a contributing risk factor for the development of AUD even in youth with high levels of externalizing problems. Investigating the unique and interacting contributions between externalizing and internalizing circuitry and risk behavior represents an important direction for future research.

Environmental Influences on Risk Pathways for AUD

Multiple factors may influence the risk for AUD. It has been estimated that genetic influences account for approximately 40–60% of variance in risk, with the remaining variance attributed to environmental factors [53]. In youth with parental AUD, it is difficult to disentangle genetic from environmental influences. In this section we discuss two influences that may impact the development of risk for AUD, both of which are not only likely to be increased in at-risk youth with parental AUD, but are also uniquely relevant to the sensitive developmental period of adolescence: stress and sleep disturbances.

Stress and Risk Pathways for AUD

Stressors such as adverse life events, problems at school, and arguments with parents or peers are not only normative during adolescence but also associated with increased risk for alcohol use [54]. Furthermore, familial risk for AUD increases the likelihood that the child will be exposed to early life stress [55]. Stress may impact brain maturation, influencing structure, function, and connectivity in emotion and reward systems [56, 57], heightening the risk for problem alcohol involvement through both externalizing and internalizing pathways. Here we review an emerging literature on the impact of stress on brain mechanisms associated with AUD risk.

Fava and colleagues examined prospective associations among adverse childhood experiences (ACEs), externalizing behavior, anterior cingulate activity during inhibitory errors, and problematic alcohol use [58]. They found that ACEs prior to age 11 were positively associated with externalizing behaviors at ages 12–14 years, which in turn was associated with problematic alcohol use at ages 15–17. Furthermore, greater ACEs were associated with reduced anterior cingulate activity, which in turn was associated with higher externalizing behavior, suggesting a neural pathway through which ACEs may impact alcohol-use problems. Casement and colleagues focused on the prospective impact of cumulative stressful life events on neural function related to reward responsivity and alcohol use [59]. Stressful life events were measured annually from ages 15 to 18 years, and alcohol-related problems and brain activation to reward were measured at age 20 in a community sample of males. Higher cumulative stress was associated with decreased activation in the medial PFC during reward anticipation and reward outcomes, which was in turn related to symptoms of alcohol dependence. Blunted activation to reward has been consistently associated with depression [60], suggesting that these findings may be tapping a mechanism through which stress impacts an internalizing pathway to risk for AUD.

Nikolova and colleagues explored the association between stress and AUD risk via two pathways that map onto externalizing and internalizing: behavioral disinhibition/positive

emotional enhancement probed with VS response to reward, and negative emotion relief/coping probed with amygdala response to threat [51]. A greater mismatch between VS and amygdala activity (i.e., low VS coupled with high amygdala activity, high VS coupled with low amygdala activity) was associated with stress-related problem drinking, but a balance between this activity (e.g., low VS with low amygdala activity) was protective. Furthermore, the high VS-low amygdala risk phenotype was associated with drinking to enhance positive emotions, whereas the low VS-high amygdala risk phenotype was associated with drinking to cope with negative emotionality and stress. Of note, males showed heightened activation for threat-related amygdala reactivity and reward-related VS reactivity as well as a greater extent of alcohol problems measured at the time of the scan relative to females.

The work reviewed here suggests that stress may impact both internalizing and externalizing pathways to AUD. Findings presented by Nikolova and colleagues [51] is of particular interest as it demonstrates unique neural signatures of internalizing and externalizing risk influenced by stress and begins to address gender-related differences in these associations.

Sleep and Risk Pathways for AUD

Developmental changes in sleep behavior and physiology coincide with maturational changes in the brain during adolescence, with implications for a variety of outcomes, including risk-taking, motivation, and emotional regulation [61, 62]. As such, adolescents who experience sleep deprivation or disrupted sleep may be predisposed to increased externalizing and internalizing problems, thereby impacting risk for AUD. Furthermore, recent research indicates that children sleep less and have poorer quality sleep in homes in which parents display problem drinking [63] or have an AUD diagnosis [64, 65], which may further exacerbate this risk. Here, we review recent work that has demonstrated a role of sleep on the neural circuitry involved in risk for AUD, and, in some cases, alcohol outcomes.

Telzer and colleagues tested the cross-sectional association between sleep quality and outcomes of cognitive control and risk-taking in adolescents [66]. Poor sleep quality was associated with reductions in dorsolateral prefrontal cortical activation during successful go/no-go inhibition, increased insula activation to reward processing during a balloon analogue risk-taking task, and reductions in functional coupling between the dorsolateral prefrontal cortex and insula, VS, and anterior cingulate. Although this study did not test alcohol outcomes, it suggests a connection between sleep problems and disrupted brain function related to externalizing problems. More recently, Hasler and colleagues investigated longitudinal associations between sleep-wake timing, reward responding, and alcohol use in males [67]. A preference for later sleep-wake timing was associated with increased medial PFC responses to winning money two years later, which was in turn associated with increased alcohol dependence symptoms, again supporting an effect of circadian factors on risk for AUD via an externalizing pathway.

To our knowledge, there is no existing work linking circadian factors, neural correlates of internalizing behaviors, and AUD risk in adolescents, although some associations have been established. For example, there is strong evidence from a longitudinal study for prospective relations between sleep deprivation in adolescents and depression one year later [68]. In young adults, Prather and colleagues found that sleep quality moderated an association

between amygdala reactivity and depressive symptoms, with heightened activity associated with greater depressive symptoms only is those with poor sleep quality; this association was significant in males but not females [69]. In healthy adults, poor self-reported sleep quality was found to be associated with reduced prefrontal-amygdala functional connectivity, which was further correlated with subjective psychological distress, including anxiety and depression [70]. This work suggests links between sleep, brain function, and emotion regulation. Establishing how these associations might interact across adolescence to influence internalizing risk for AUD will be an important future research direction.

Conclusions

Although high-risk behavior, including alcohol use, increases during adolescence, only a minority of adolescents develops serious alcohol-related problems. Therefore, normative neurobiological changes are not sufficient to account for the development of AUD. Two developmental pathways through which risk for AUD may emerge include externalizing and internalizing pathways. Extensive evidence supports a role for the externalizing pathway, which is underpinned by disinhibited behavior, and recent research has converged on a role for a weakness in prefrontal inhibitory control systems observable in childhood and early adolescence prior to significant substance use in this pathway. Furthermore, evidence is accumulating for an impact of both stress and sleep problems on this pathway through effects on prefrontal functioning.

Evidence for a role for reward-related circuitry in externalizing risk for AUD is less clear, which is likely due to several interacting factors. First, reward-related risk for AUD may be developmentally modulated, with the sensitive period occurring only during adolescence, which is further complicated by individual differences in rates of maturation. Second, reward-related risk factors for the initiation of, or experimentation with, alcohol use may differ from those for escalation to problem use, and these stages have not been sufficiently disentangled in the neuroimaging literature. A related consideration is that the balance between inhibitory control and reward circuitry may be more relevant to specific stages of AUD risk than the individual contribution of each considered in isolation. Finally, there is theoretical and empirical support to link both heightened and reduced reward-related activation to risk for AUD via the externalizing and internalizing pathways, respectively, suggesting a more nuanced approach is required to detect risk signatures in the reward pathway.

Extensive evidence also exists to support the internalizing risk pathway for AUD, although the manner in which it operates is complex. Thus far, there is no convergence of findings in the developmental neuroimaging literature investigating this pathway with respect to risk for AUD. Few studies have focused on emotion regulation in at-risk youth, and the methodologies are not consistent across those that have. Thus far, there is promising work to suggest that stress may an important contributor in this pathway through a blunting of reward-related brain activation, which may act alone or in combination with heightened reactivity in emotion circuitry. Furthermore, there is emerging evidence for gender-related differences in risk-related neural underpinnings of the internalizing pathway. Further exploration of these differences, effects of stress and sleep disturbances, and co-occurring

externalizing symptomology will be important future directions for research to understand the internalizing risk pathway.

A critical issue from a broader perspective is the difficulty in disentangling the temporal ordering of the associations among brain maturation, behavioral risk factors, and alcohol use. For example, while neurobiological processes may increase the likelihood of substance use, exposure to substances may also influence neural maturation in such a way as to further exacerbate substance-use problems as well as related behavior problems and psychopathology. Long-term longitudinal studies in large, diverse samples such as the Adolescent Brain Cognitive Development study will allow the comprehensive modeling of interacting and cascading associations among externalizing and internalizing behaviors and symptomatology, environmental influences, alcohol use, and brain maturation over time. This will be necessary for a thorough understanding of the interplay among the many influences that may contribute to the emergence and persistence of AUD across development.

References

Recent papers of particular interest have been highlighted as:

* Of importance

** Of major importance

1. Miech RA, Johnston LD, O'Malley PM, Bachman JG, Schulenberg JE, Patrick ME. Monitoring the Future national survey results on drug use, 1975–2017: Volume I, secondary school students. Ann Arbor: Institute for Social Research, The University of Michigan2018.
2. Schulenberg JE, Johnston LD, O'Malley PM, Bachman JG, Miech RA, Patrick ME. Monitoring the Future national survey results on drug use, 1975–2017: Volume II, college students and adults ages 19–55. Ann Arbor: Institute for Social Research, The University of Michigan, 2018.
3. 2016 National Survey on Drug Use and Health: Detailed Tables. Rockville MD: Substance Abuse and Mental Health Services Administration: Center for Behavioral Health Statistics and Quality2017.
4. Casey BJ. Beyond simple models of self-control to circuit-based accounts of adolescent behavior. Annual review of psychology. 2015;66:295–319. doi:10.1146/annurev-psych-010814-015156.
5. Shulman EP, Smith AR, Silva K, Icenogle G, Duell N, Chein J et al. The dual systems model: Review, reappraisal, and reaffirmation. Dev Cogn Neurosci. 2016;17:103–17. doi:10.1016/j.dcn.2015.12.010. [PubMed: 26774291]
6. Ernst M The triadic model perspective for the study of adolescent motivated behavior. Brain and cognition. 2014;89:104–11. doi:10.1016/j.bandc.2014.01.006. [PubMed: 24556507]
7. Hussong AM, Rothenberg WA, Smith RK, Haroon M. Implications of Heterogeneity in Alcohol Use Disorders for Understanding Developmental Pathways and Prevention Programming In: Fitzgerald HE, Puttler LI, editors. Alcohol Use Disorders: A Developmental Science Approach to Etiology. New York, NY: Oxford University Press; 2018 p. 30–8.
8. Zucker RA, Heitzeg MM, Nigg JT. Parsing the Undercontrol/Disinhibition Pathway to Substance Use Disorders: A Multilevel Developmental Problem. Child development perspectives. 2011;5(4):248–55. doi:10.1111/j.1750-8606.2011.00172.x. [PubMed: 22116786]
9. Nigg JT. On inhibition/disinhibition in developmental psychopathology: views from cognitive and personality psychology and a working inhibition taxonomy. Psychol Bull. 2000;126(2):220–46. [PubMed: 10748641]

10. McNamee RL, Dunfee KL, Luna B, Clark DB, Eddy WF, Tarter RE. Brain activation, response inhibition, and increased risk for substance use disorder. Alcohol Clin Exp Res. 2008;32(3):405–13. doi:10.1111/j.1530-0277.2007.00604.x. [PubMed: 18302723]

11. Schweinsburg AD, Paulus MP, Barlett VC, Killeen LA, Caldwell LC, Pulido C et al. An FMRI study of response inhibition in youths with a family history of alcoholism. Ann N Y Acad Sci. 2004;1021:391–4. [PubMed: 15251915]

12. Norman AL, Pulido C, Squeglia LM, Spadoni AD, Paulus MP, Tapert SF. Neural activation during inhibition predicts initiation of substance use in adolescence. Drug Alcohol Depend. 2011;119(3): 216–23. doi:10.1016/j.drugalcdep.2011.06.019S0376-8716(11)00297-3 [pii]. [PubMed: 21782354]

13. Wetherill RR, Squeglia LM, Yang TT, Tapert SF. A longitudinal examination of adolescent response inhibition: neural differences before and after the initiation of heavy drinking. Psychopharmacology (Berl). 2013;230(4):663–71. doi:10.1007/s00213-013-3198-2. [PubMed: 23832422]

14. Mahmood OM, Goldenberg D, Thayer R, Migliorini R, Simmons AN, Tapert SF. Adolescents' fMRI activation to a response inhibition task predicts future substance use. Addict Behav. 2013;38(1):1435–41. doi:10.1016/j.addbeh.2012.07.012. [PubMed: 23006248]

15. Hardee JE, Weiland BJ, Nichols TE, Welsh RC, Soules ME, Steinberg DB et al. Development of impulse control circuitry in children of alcoholics. Biological psychiatry. 2014;76(9):708–16. doi: 10.1016/j.biopsych.2014.03.005. [PubMed: 24742620]

16*. Heitzeg MM, Cope LM, Martz ME, Hardee JE. Neuroimaging Risk Markers for Substance Abuse: Recent Findings on Inhibitory Control and Reward System Functioning. Current addiction reports. 2015;2(2):91–103. doi:10.1007/s40429-015-0048-9. [PubMed: 26236575] Review paper that summarizes and discusses the functional neuroimaging literature on inhibitory control and reward in the context of risk for substance use disorder.

17. Heitzeg MM, Nigg JT, Hardee JE, Soules M, Steinberg D, Zubieta JK et al. Left middle frontal gyrus response to inhibitory errors in children prospectively predicts early problem substance use. Drug Alcohol Depend. 2014;141:51–7. doi:10.1016/j.drugalcdep.2014.05.002. [PubMed: 24882366]

18. Whelan R, Watts R, Orr CA, Althoff RR, Artiges E, Banaschewski T et al. Neuropsychosocial profiles of current and future adolescent alcohol misusers. Nature. 2015;512:185–9. doi:10.1038/ nature13402.Neuropsychosocial.

19. Muller KU, Gan G, Banaschewski T, Barker GJ, Bokde AL, Buchel C et al. No differences in ventral striatum responsivity between adolescents with a positive family history of alcoholism and controls. Addiction biology. 2015;20(3):534–45. doi:10.1111/adb.12136. [PubMed: 24903627]

20. Bjork JM, Knutson B, Hommer DW. Incentive-elicited striatal activation in adolescent children of alcoholics. Addiction. 2008;103(8):1308–19. doi:ADD2250 [pii]10.1111/j. 1360-0443.2008.02250.x. [PubMed: 18851716]

21. Dick DM, Latendresse SJ, Lansford JE, Budde JP, Goate A, Dodge KA et al. Role of GABRA2 in trajectories of externalizing behavior across development and evidence of moderation by parental monitoring. Arch Gen Psychiatry. 2009;66(6):649–57. doi:66/6/649 [pii] 10.1001/ archgenpsychiatry.2009.48. [PubMed: 19487630]

22*. Heitzeg MM, Villafuerte S, Weiland BJ, Enoch MA, Burmeister M, Zubieta JKet al. Effect of GABRA2 genotype on development of incentive-motivation circuitry in a sample enriched for alcoholism risk. Neuropsychopharmacology. 2014;39(13):3077–86. doi:10.1038/npp.2014.161. [PubMed: 24975023] This is the first study to demonstrate that risk-related reward activation may be developmentally modulated.

23*. Waller R, Murray L, Shaw DS, Forbes EE, Hyde LW. Accelerated alcohol use across adolescence predicts early adult symptoms of alcohol use disorder via reward-related neural function. Psychol Med. 2018:1–10. doi:10.1017/S003329171800137X.Using a novel analytic approach, this study identified linkages between alcohol use trajectories during adolescence, reward reactivity in the ventral striatum during young adulthood, and later alcohol use disorder symptoms in a large community sample.

24. Stice E, Yokum S. Brain reward region responsivity of adolescents with and without parental substance use disorders. Psychology of addictive behaviors : journal of the Society of

Psychologists in Addictive Behaviors. 2014;28(3):805–15. doi:10.1037/a0034460. [PubMed: 24128289]

25. Heitzeg MM, Casey BJ. Brain Development and the Risk for Substance Abuse In: Charney DS, Nestler EJ, Sklar P, Buxbaum Jd, editors. Charney & Nestler's Neurobiology of Mental Illness. 5th ed. New York, NY: Oxford University Press; 2018 p. 629–39.
26. Moeller FG, Barratt ES, Dougherty DM, Schmitz JM, Swann AC. Psychiatric aspects of impulsivity. Am J Psychiatry. 2001;158(11):1783–93. doi:10.1176/appi.ajp.158.11.1783. [PubMed: 11691682]
27. Zuckerman M Behavioral expressions and biosocial bases of sensation seeking. New York, NY: Cambridge University Press; 1994.
28. Harden KP, Tucker-Drob EM. Individual differences in the development of sensation seeking and impulsivity during adolescence: further evidence for a dual systems model. Developmental psychology. 2011;47(3):739–46. doi:10.1037/a0023279. [PubMed: 21534657]
29*. Lopez-Vergara HI, Merrill JE, Janssen T, Jackson KM. Social and individual-level predictors of alcohol use initiation and escalation: replicating and extending tests of differential effects. Journal of studies on alcohol and drugs. 2017;78(3):452–7. doi:10.15288/jsad.2017.78.452. [PubMed: 28499113] One of the largest prospective studies of alcohol-naïve youth, this 3-year study focused on risk factors (including sensation seeking) for alcohol initiation and use.
30**. Quinn PD, Harden KP. Differential changes in impulsivity and sensation seeking and the escalation of substance use from adolescence to early adulthood. Development and psychopathology. 2013;25(1):223–39. doi:10.1017/s0954579412000284. [PubMed: 22824055]
31. Belin D, Mar AC, Dalley JW, Robbins TW, Everitt BJ. High impulsivity predicts the switch to compulsive cocaine-taking. Science. 2008;320(5881):1352–5. doi:10.1126/science.1158136. [PubMed: 18535246]
32. Charles NE, Ryan SR, Bray BC, Mathias CW, Acheson A, Dougherty DM. Altered developmental trajectories for impulsivity and sensation seeking among adolescent substance users. Addictive behaviors. 2016;60:235–41. doi:10.1016/j.addbeh.2016.04.016. [PubMed: 27174219]
33. Kim-Spoon J, Deater-Deckard K, Holmes C, Lee J, Chiu P, King-Casas B. Behavioral and neural inhibitory control moderates the effects of reward sensitivity on adolescent substance use. Neuropsychologia. 2016;91:318–26. doi:10.1016/j.neuropsychologia.2016.08.028. [PubMed: 27580969]
34**. Khurana A, Romer D, Betancourt LM, Brodsky NL, Giannetta JM, Hurt H. Experimentation versus progression in adolescent drug use: A test of an emerging neurobehavioral imbalance model. Development and psychopathology. 2015;27(3):901–13. doi:10.1017/s0954579414000765. [PubMed: 25154377] This paper found that heightened reward seeking balanced by strong executive control was associated with substance use experimentation, whereas heightened reward seeking and weak executive control was associated with progression of substance use. This is important working highlighting the importance of considering the balance between executive and reward systems and stages of substance use.
35. Hussong AM, Jones DJ, Stein GL, Baucom DH, Boeding S. An internalizing pathway to alcohol use and disorder. . Psychology of Addictive Behaviors. 2011;25(3):390–404. [PubMed: 21823762]
36. Price JL, Drevets WC. Neurocircuitry of Mood Disorders. Neuropsychopharmacology. 2010;35(1): 192–216. doi:10.1038/npp.2009.104. [PubMed: 19693001]
37. Heatherton TF, Wagner DD. Cognitive Neuroscience of Self-Regulation Failure. Trends in cognitive sciences. 2011;15(3):132–9. doi:10.1016/j.tics.2010.12.005. [PubMed: 21273114]
38. Ernst M, Korelitz KE. Cerebral maturation in adolescence: behavioral vulnerability. L'Encephale. 2009;35 Suppl 6:S182–9. doi:10.1016/s0013-7006(09)73469-4.
39. Somerville LH, Jones RM, Casey BJ. A time of change: behavioral and neural correlates of adolescent sensitivity to appetitive and aversive environmental cues. Brain and cognition. 2010;72(1):124–33. doi:10.1016/j.bandc.2009.07.003. [PubMed: 19695759]
40. Hill SY, De Bellis MD, Keshavan MS, Lowers L, Shen S, Hall J et al. Right amygdala volume in adolescent and young adult offspring from families at high risk for developing alcoholism. Biological psychiatry. 2001;49(11):894–905. [PubMed: 11377407]

41. Glahn DC, Lovallo WR, Fox PT. Reduced Amygdala Activation in Young Adults at High Risk of Alcoholism: Studies from the Oklahoma Family Health Patterns Project. Biological psychiatry. 2007;61(11):1306–9. doi:10.1016/j.biopsych.2006.09.041. [PubMed: 17306772]

42. Peraza J, Cservenka A, Herting MM, Nagel BJ. Atypical parietal lobe activity to subliminal faces in youth with a family history of alcoholism. The American journal of drug and alcohol abuse. 2015;41(2):139–45. doi:10.3109/00952990.2014.953251. [PubMed: 25268683]

43. Cservenka A, Fair DA, Nagel BJ. Emotional Processing and Brain Activity in Youth at High Risk for Alcoholism. Alcoholism, clinical and experimental research. 2014;38(7):1912–23. doi: 10.1111/acer.12435.

44. Kuntsche E, Muller S. Why do young people start drinking? Motives for first-time alcohol consumption and links to risky drinking in early adolescence. European addiction research. 2012;18(1):34–9. doi:10.1159/000333036. [PubMed: 22142752]

45. Kuhn C Emergence of sex differences in the development of substance use and abuse during adolescence. Pharmacology & therapeutics. 2015;153:55–78. doi:10.1016/j.pharmthera. 2015.06.003. [PubMed: 26049025]

46. Heitzeg MM, Hardee JE, Beltz AM. Sex Differences in the Developmental Neuroscience of Adolescent Substance Use Risk. Curr Opin Behav Sci. 2018;23:21–6. doi:10.1016/j.cobeha. 2018.01.020. [PubMed: 29977984]

47*. Hardee JE, Cope LM, Munier EC, Welsh RC, Zucker RA, Heitzeg MM. Sex differences in the development of emotion circuitry in adolescents at risk for substance abuse: a longitudinal fMRI study. Social cognitive and affective neuroscience. 2017;12(6):965–75. doi:10.1093/scan/nsx021. [PubMed: 28338724] A unique longitudinal study examining sex differences in emotion processing neurocircuitry and one of the few studies to directly examine internalizing symptomatology in at-risk adolescents.

48. Edwards AC, Latendresse SJ, Heron J, Cho SB, Hickman M, Lewis G et al. Childhood internalizing symptoms are negatively associated with early adolescent alcohol use. Alcoholism, clinical and experimental research. 2014;38(6):1680–8. doi:10.1111/acer.12402.

49. Cerda M, Bordelois PM, Keyes KM, Galea S, Koenen KC, Pardini D. Cumulative and recent psychiatric symptoms as predictors of substance use onset: does timing matter? Addiction. 2013;108(12):2119–28. doi:10.1111/add.12323. [PubMed: 23941263]

50*. Hussong AM, Ennett ST, Cox MJ, Haroon M. A systematic review of the unique prospective association of negative affect symptoms and adolescent substance use controlling for externalizing symptoms. Psychology of addictive behaviors : journal of the Society of Psychologists in Addictive Behaviors. 2017;31(2):137–47. doi:10.1037/adb0000247. [PubMed: 28134539] An important review paper that demonstrates the importance of controlling for externalizing symptoms, and attending to subtypes of internalizing problems and specific substance use outcomes in studies investigating associations between negative affect and addiction risk.

51**. Nikolova YS, Knodt AR, Radtke SR, Hariri AR. Divergent responses of the amygdala and ventral striatum predict stress-related problem drinking in young adults: Possible differential markers of affective and impulsive pathways of risk for alcohol use disorder. Molecular psychiatry. 2016;21:348–56. doi:10.1016/j.cogdev.2010.08.003.Personal. [PubMed: 26122584] This study is the first to identify distinct internalizing and externalizing pathways to problem drinking and how these risk phenotypes are associated with recent life stress. It is an important large cross-sectional study of older adolescents and young adults examining how stress and drinking affect two neural pathways associated with AUD risk: a positive emotion enhancement and behavioral impulsivity pathway, and a negative emotion relief and coping pathway.

52. Hulvershorn LA, Finn P, Hummer TA, Leibenluft E, Ball B, Gichina V et al. Cortical Activation Deficits During Facial Emotion Processing in Youth at High Risk for the Development of Substance Use Disorders. Drug and alcohol dependence. 2013;131(3):230–7. doi:10.1016/ j.drugalcdep.2013.05.015. [PubMed: 23768841]

53. Agrawal A, Verweij KJ, Gillespie NA, Heath AC, Lessov-Schlaggar CN, Martin NG et al. The genetics of addiction-a translational perspective. Transl Psychiatry. 2012;2:e140. doi:10.1038/tp. 2012.54. [PubMed: 22806211]

54. Schulenberg JE, Maslowsky J, Patrick ME, Martz ME. Substance use in the context of adolescent development In: Brown SA, Zucker RA, editors. The Oxford Handbook of Adolescent Substance Abuse. New York, NY: Oxford University Press; 2016.
55. Enoch MA. The role of early life stress as a predictor for alcohol and drug dependence. Psychopharmacology (Berl). 2011;214(1):17–31. doi:10.1007/s00213-010-1916-6. [PubMed: 20596857]
56. Novick AM, Levandowski ML, Laumann LE, Philip NS, Price LH, Tyrka AR. The effects of early life stress on reward processing. J Psychiatr Res. 2018;101:80–103. doi:10.1016/j.jpsychires.2018.02.002. [PubMed: 29567510]
57. Teicher MH, Samson JA, Anderson CM, Ohashi K. The effects of childhood maltreatment on brain structure, function and connectivity. Nature reviews Neuroscience. 2016;17(10):652–66. doi:10.1038/nrn.2016.111. [PubMed: 27640984]
58. Fava NM, Trucco EM, Martz ME, Cope LM, Jester JM, Zucker RA et al. Childhood adversity, externalizing behavior, and substance use in adolescence: Mediating effects of anterior cingulate cortex activation during inhibitory errors. Development and Psychopathology. In press.
59. Casement MD, Shaw DS, Sitnick SL, Musselman SC, Forbes EE. Life stress in adolescence predicts early adult reward-related brain function and alcohol dependence. Social cognitive and affective neuroscience. 2015;10(3):416–23. doi:10.1093/scan/nsu061. [PubMed: 24795442]
60. Keren H, O'Callaghan G, Vidal-Ribas P, Buzzell GA, Brotman MA, Leibenluft E et al. Reward Processing in Depression: A Conceptual and Meta-Analytic Review Across fMRI and EEG Studies. Am J Psychiatry. 2018:appiajp201817101124. doi:10.1176/appi.ajp.2018.17101124.
61. Tarokh L, Saletin JM, Carskadon MA. Sleep in adolescence: physiology, cognition and mental health. Neuroscience and biobehavioral reviews. 2016;70:182–8. doi:10.1016/j.neubiorev.2016.08.008. [PubMed: 27531236]
62. Logan RW, Hasler BP, Forbes EE, Franzen PL, Torregrossa MM, Huang YH et al. Impact of Sleep and Circadian Rhythms on Addiction Vulnerability in Adolescents. Biological psychiatry. 2018;83(12):987–96. doi:10.1016/j.biopsych.2017.11.035. [PubMed: 29373120]
63. Kelly RJ, El-Sheikh M. Parental Problem Drinking and Children's Sleep: The Role of Ethnicity and Socioeconomic Status. Journal of family psychology : JFP : journal of the Division of Family Psychology of the American Psychological Association (Division 43). 2016;30(6):708–19. doi:10.1037/fam0000209.
64. Hairston IS, Conroy DA, Heitzeg MM, Akbar NZ, Brower KJ, Zucker RA. Sleep mediates the link between resiliency and behavioural problems in children at high and low risk for alcoholism. Journal of sleep research. 2016;25(3):341–9. doi:10.1111/jsr.12382. [PubMed: 26853891]
65. Conroy DA, Hairston IS, Zucker RA, Heitzeg MM. Sleep Patterns in Children of Alcoholics and the Relationship with Parental Reports. Austin Journal of Sleep Disorders. 2015;2(1):1009.
66. Telzer EH, Fuligni A, Lieberman MD, Galvan A. The effects of poor sleep quality on brain function and risk taking in adolescence. Neuroimage. 2013;71:275–83. doi:10.1111/j.1743-6109.2008.01122.x.Endothelial. [PubMed: 23376698]
67. Hasler BP, Casement MD, Sitnick SL, Shaw DS, Forbes EE. Eveningness among late adolescent males predicts neural reactivity to reward and alcohol dependence 2 years later. Behav Brain Res. 2017;327:112–20. doi:10.1016/j.bbr.2017.02.024. [PubMed: 28254633]
68. Roberts RE, Duong HT. The prospective association between sleep deprivation and depression among adolescents. Sleep. 2014;37(2):239–44. doi:10.5665/sleep.3388. [PubMed: 24497652]
69. Prather AA, Bogdan R, Hariri AR. Impact of sleep quality on amygdala reactivity, negative affect, and perceived stress. Psychosomatic medicine. 2013;75(4):350–8. doi:10.1097/PSY.0b013e31828ef15b. [PubMed: 23592753]
70. Killgore WDS. Self-Reported Sleep Correlates with Prefrontal-Amygdala Functional Connectivity and Emotional Functioning. Sleep. 2013;36(11):1597–608. doi:10.5665/sleep.3106. [PubMed: 24179291]

Table 1.

Summary of recent studies in the externalizing domain.

Study	Design	Participants	Behavioral/ Imaging Measures of Interest	Alcohol-Related Measures of Interest	Main Findings	Gender-Related Differences
Neuroimaging Studies of Inhibitory Control						
Heitzeg et al., 2014a	Prospective; Baseline fMRI and substance use follow-up 4 yrs later	*N*=45; Reference group=19 (*M*=10.9 yrs, *SD*=1.1); Non-users=13 (*M*=10.9 yrs, *SD*=0.9); Problematic users=13 (*M*=11.0 yrs, *SD*=1.0)	Go/No-Go task	Heavy drinking; alcohol problems	Lower baseline activation in left middle frontal gyrus during failed inhibition vs. correct inhibition trials, controlling for behavioral task performance and externalizing behavior problems, was prospectively associated with heavy drinking and alcohol-use problems at follow-up	22.2% female; Exploratory analyses showed that findings remained in the same direction for males and females
Mahmood et al., 2013	Prospective; Baseline fMRI and substance use follow-up 18 mos later	*N*=80; Low frequency substance users=71 (*M*=17.6 yrs, *SD*=1.0); High frequency substance users=39 (*M*=17.4 yrs, *SD*=0.9)	Go/No-Go task	Heavy drinking; alcohol problems	Lower activation in ventromedial prefrontal cortex and greater activation in left angular gyrus during response inhibition was prospectively associated with a greater extent of substance use and dependence symptoms at follow-up in youth who were high-frequency substance users at baseline	High frequency substance users: 31% female; low frequency substance users: 27% female; No gender-related differences examined
Wetherill et al., 2013	Prospective; Baseline fMRI and substance use follow-up 3–4 yrs later	*N*=40; Control subjects=20 (*M*=14.1 yrs, *SD*=1.2); Heavy drinkers=20 (*M*=14.7 yrs, *SD*=1.1)	Go/No-Go task	Heavy drinking	Future heavy drinkers showed preexisting differences in brain function associated with response inhibition, with less activation in inhibitory circuitry prior to initiating heavy drinking and greater activation in these regions at follow-up as drinking escalated	45% female; Gender included as a covariate
Whelan et al., 2014	Prospective; Baseline fMRI and substance use follow-up 2 yrs later	*N*=692; Control subjects=150 (*M*=14.53 yrs, *SD*=0.43); Current binge drinkers=115 (*M*=14.62 yrs, *SD*=0.39); Future binge drinkers=121 (*M*=14.45 yrs, *SD*=0.40); External validation sample=306	Stop Signal Task	Binge drinking	Future binge drinkers: greater activation in right middle, medial, and precentral gyri and in left postcentral and middle frontal gyri during inhibitory errors	Controls: 60% female; future binge drinkers: 46% female; No gender-related differences tested
Neuroimaging Studies of Reward Responsivity						
Heitzeg et al., 2014b	Prospective; Baseline fMRI with up to 3 follow-up scans and substance use follow-up 3–6 yrs after baseline scan	*N*=175; Adolescent=76 (*M*=10.8 yrs, *SD*=1.2) or Young adult=99 (*M*=20.3 yrs, *SD*=1.4)	Monetary Incentive Delay Task	Alcohol problems	NAcc activation during reward anticipation mediated association between GABRA2 genotype and number of alcohol-use problems	30.5% female; Exploratory analyses indicated no gender-related differences

Study	Design	Participants	Behavioral/ Imaging Measures of Interest	Alcohol-Related Measures of Interest	Main Findings	Gender-Related Differences
					reported over at least 3 yrs following baseline	
Stice & Yokum, 2014	Substance naïve FH+ and FH− comparison	*N*=52: FH+ =26 (*M*=14.7 yrs, *SD*=0.9); FH− =26 (*M*=14.9 yrs, *SD*=1.0)	Monetary Incentive Delay Task; Food Reward Paradigm	Family history of substance use	FH+ adolescents had greater activation in reward circuitry, which may be a risk factor for later substance use	FH+: 46.2% female; FH−: 50.0% female; No gender-related differences examined
Waller et al., 2018	Mediation	*N*=139; Substance use: 11, 12, 15, 17 yrs, fMRI scan: 20 yrs, AUD symptoms: 22 yrs (no *M* or *SD*)	Card-Guessing Game	AUD symptoms	Accelerated alcohol use from ages 11 to 17 yrs old was associated with greater VS reactivity during reward anticipation at age 20. Greater VS reactivity was associated with a greater extent of AUD symptoms at age 22 yrs, even after accounting for comorbid psychopathology and marijuana and tobacco use	0% female
Whelan et al., 2014	Prospective; Baseline fMRI and substance use follow-up 2 yrs later	*N*=692; Controls=150 (*M*=14.53 yrs, *SD*=0.43); Current binge drinkers=115 (*M*=14.62 yrs, *SD*=0.39); Future binge drinkers=121 (*M*=14.45 yrs, *SD*=0.40); External validation sample=306	Monetary Incentive Delay Task	Binge drinking	Future binge drinkers: lower activation in occipito-temporal and posterior cingulate during reward anticipation. During reward outcome, future binge drinkers had lower activation in left temporal pole and greater activation in bilateral superior frontal gyrus	Controls: 60% female; Future binge drinkers: 46% female; No gender-related differences tested
The Externalizing Pathway and Stages of AUD Risk						
Charles et al., 2016	Prospective; Assessment every 6 mos (max follow-up 54 mos, median 36 mos)	T1: *N*=386 (*M*=11.9 yrs; no *SD*); Use=117; No use=269	Impulsivity and sensation-seeking	Substance use and breath/urine testing (used to categorize Use and No Use groups)	At baseline: Use group more impulsive than No use group; Use group marginally higher on sensation-seeking than No use group. Greater decrease in impulsivity in No use vs. Use group, and greater increase in sensation-seeking in Use vs. No use group	51.6% female; Use and No use groups did not differ on gender; No gender-related differences examined
Khurana et al., 2015	Prospective; 4 annual assessments	T1: *N*=382 (*M*=12.4 yrs, *SD*=0.87)	Working memory, sensation-seeking, acting without thinking, delay discounting	Recent substance use	Acting without thinking and delay discounting fully mediated the association between weak working memory and progression of substance use; sensation-seeking was marginally associated with experimentation but was not related to class membership after controlling for acting without thinking and delay discounting	52% female; Gender was included in the model
Kim-Spoon et al., 2016	Cross-sectional	*N*=157 (*M*=14.13 yrs, *SD*=0.54)	Behavioral inhibition and approach systems,	Age of initiation and frequency of substance use	High reward sensitivity was associated with earlier onset of substance use among those with low,	48% female; Gender was not associated with any of the

Study	Design	Participants	Behavioral/ Imaging Measures of Interest	Alcohol-Related Measures of Interest	Main Findings	Gender-Related Differences
			inhibitory control		but not high, inhibitory control	outcome variables
Lopez-Vergara et al., 2017	Prospective; Assessment over 3 yrs with 6 waves	Wave 1: *N*=944 (*M*=12.16 yrs, *SD*=0.96) (alcohol-naïve); Wave 6: 17% attrition (*M*=15.14 yrs, *SD*=0.95)	Sensation-seeking, other individual and social levels of influence	Alcohol initiation and level of drinking	Parental conflict, perceived prevalence of peer drinking, and sensation-seeking was prospectively associated with alcohol-use initiation. Grades and perceived descriptive norms of peer drinking were prospectively associated with level of drinking	52% female; Being female was associated with initiation
Quinn & Harden, 2013	Prospective; Biennial assessment between ages 15 and 26	*N*=5,632 (no *M* or *SD*)	Impulsivity and sensation-seeking	Frequency of past-year alcohol use	Slower decreases in impulsivity, but not sensation-seeking, were associated with greater increases in alcohol use	
Environmental Influences on Externalizing Pathways for AUD						
Fava et al., in press	Mediation	Model 1: *N*=465 (adverse childhood experiences: ages 3–11 yrs, externalizing: *M*=13 yrs, *SD*=1.21, substance use: *M*=16.55 yrs, *SD*=0.94); Model 2: *N*=92 (fMRI scan: *M*=12 yrs, *SD*=1.59)	Go/No-Go Task	Problematic alcohol use	ACEs prior to age 11 associated with externalizing at 12–14 yrs, which in turn was associated with problematic alcohol use at 15–17 yrs. Greater ACEs associated with reduced ACC activity, which in turn was associated with higher externalizing	Model 1: 26% female; Model 2: 34.8% female; Controlled for gender, no gender-related differences examined
Hasler et al., 2017	Prospective cross-lagged; fMRI and behavioral assessments at ages 20 and 22 yrs	*N*=93 males, ages 20 and 22 yrs (no *M* or *SD*)	Card-Guessing Game	Alcohol-use frequency and problems	Later sleep-wake timing at age 20 was prospectively associated with increased mPFC and VS activation during reward responsivity and greater alcohol dependence at age 22	0% female
Nikolova et al., 2016	Prospective; Baseline fMRI and substance use follow-up 3 mos later	*N*=759; *M*=19.65 yrs, *SD*=1.24	Stressful life events; Number Guessing Reward Task	Alcohol problems	Stress was associated with AUD diagnosed at scan time and problem drinking reported 3 mos later among young adults with low reward-related VS reactivity and high threat-related amygdala reactivity	56% female; Males showed greater activation in the amygdala and VS and higher AUDIT scores
Telzer et al., 2013	Psychophysiological interaction analysis; mediation	*N*=46; *M*=15.23 yrs, no *SD*	Go/No-Go Task/Balloon Analogue Risk Task	General risk-taking	Poor sleep disrupted balance between affective and cognitive control systems. Adolescents showed reduced activation in dlPFC during response inhibition, greater activation in insula during increasing reward salience, and lower functional coupling between dlPFC and affective brain regions	59% female; Controlled for gender, no gender-related differences examined

Note. *yrs* years, *M* mean age, *SD* standard deviation, *mos* months, *NAcc* nucleus accumbens, *GABRA* gamma-aminobutyric acid A receptor, *FH+* family history positive, *FH−* family history negative, *AUD* alcohol use disorder, *T* time, *VS* ventral striatum, *fMRI* functional magnetic resonance imaging, *ACEs* adverse childhood experiences, *ACC* anterior cingulate cortex, *mPFC* medial prefrontal cortex, *AUDIT* Alcohol Use Disorders Identification Test, *dlPFC* dorsolateral prefrontal cortex

Table 2.

Summary of recent studies in the internalizing domain.

Study	Design	Participants	Behavioral/ Imaging Measures of Interest	Alcohol-Related Measures of Interest	Main Findings	Gender-Related Differences
Neuroimaging Studies of Emotional Control						
Peraza et al., 2015	Cross-sectional	*N*=29; FH+ =14, (*M*=13.73 yrs, *SD*=1.49), FH− =15 (*M*=13.67 yrs, *SD*=1.60)	Adapted Masked Faces Task	FH+ vs. FH−	FH−: deactivated to both masked fearful and neutral faces in the left superior parietal lobule. FH+: only deactivated to masked fearful faces	41% female; Gender-related differences not assessed
Cservenka et al., 2014	Cross-sectional	*N*=36; FH+ =19 (*M*=14.92 yrs, *SD* 1.34), FH+ =17 (*M*=14.69 yrs, *SD*=1.10)	Emotional Go/No-Go Task; Resting state	FH+ vs. FH−	FH+: reduced activation during positive emotional contexts in left superior temporal cortex, reduced activation in frontal and striatal regions during emotionally-valenced inhibitory control trials; greater negative connectivity between left amygdala and left superior frontal gyrus	47% female; Gender-related differences not assessed
Hardee et al., 2017	Longitudinal; 3–4 fMRI scans per participant, 1–2 yrs between scans	*N*=36; age range 8.5–17.6 yrs (*M*=12.8 yrs, *SD*=2.3)	Emotional Word Task; Internalizing/ externalizing	Family history of AUD	Males: internalizing symptoms significantly decreased with age; fMRI activation for negative vs. neutral words significantly decreased with age in right amygdala, right precentral gyrus. Females: internalizing symptoms significantly increased with age. No significant change for fMRI activation in two ROIs, but activation was sustained across age in both regions	50% female; Primary aim of study was gender-related differences
Considerations in Internalizing Research						
Edwards et al., 2014	Longitudinal; Baseline internalizing then follow-up every 1.5–2 yrs	*N*=11,157; baseline internalizing *M*=3.9 yrs; T1=6.8 yrs; T2=8.1 yrs; T3=9.5 yrs; T4=11.7 yrs (no *SD*); alcohol use *M*=13.8 yrs *SD*=2.5 mos	Internalizing (maternal report)	Alcohol use; maternal depression	Children with elevated internalizing symptoms: less likely to use alcohol in early adolescence, both for those who displayed increasing levels of internalizing symptoms over time and those who had desisting symptoms over time	50% female; Gender used as a covariate in follow-up analyses
Cerda et al., 2013	Longitudinal; Baseline substance use and psychiatric disorder measures, then follow-up annually	*N*=460 (alcohol follow-up sample); baseline *M*=6.7 yrs (no *SD*); assessed annually until age 19	Depression, anxiety, conduct disorder symptoms	Alcohol and marijuana use	Recent anxiety and conduct disorder symptoms (year prior to measurement), as well as cumulative conduct disorder and depression symptoms (up to two years prior to measurement), were associated with earlier alcohol use onset	0% female
Hulvershorn et al., 2013	Cross-sectional	*N*=37; high risk=19 (*M*=12.2 yrs, *SD* 1.4), healthy	Facial Emotion Matching Task; Emotional traits	FH+ & high externalizing (high risk) vs.	High risk group: greater activation in right medial prefrontal cortex, left precuneus, right and left	32% female; Groups matched on gender but

Study	Design	Participants	Behavioral/ Imaging Measures of Interest	Alcohol-Related Measures of Interest	Main Findings	Gender-Related Differences
		controls=18 (*M*=11.9 yrs, *SD*=1.4)		FH− & no externalizing	occipital cortex; occipital activation positively correlated with parent-report of emotional lability/negativity and emotional flatness	gender-related differences were not assessed
Environmental Influences on Internalizing Pathways for AUD						
Casement et al., 2015	Mediation	*N*=153; Stressful life events: 15–18 yrs, fMRI scan: 20 yrs (*M*=19.52, *SD*=0.51), alcohol dependence: 20 yrs	Reward Guessing Task; Stressful life events	Alcohol problems	Greater number of cumulative life stressors during adolescence associated with lower brain activation in mPFC during both reward anticipation and receipt. mPFC response to rewards significant mediator between adolescent life stress and symptoms of alcohol dependence measured at age 20	0% female
Nikolova et al., 2016	Prospective; Baseline fMRI and substance use follow-up 3 mos later	*N*=759; *M*=19.65 yrs, *SD*=1.24	Stressful life events; Number Guessing Reward Task	Alcohol problems	Positive correlation between stress and problem drinking; moderated by threat-related amygdala in individuals with high amygdala but low VS activation	56% female; Males showed greater activation in the amygdala and VS and higher AUDIT scores

Note. *M* mean age, *SD* standard deviation, *FH+* family history positive, *FH−* family history negative, *yrs* years, *AUD* alcohol use disorder, *fMRI* functional magnetic resonance imaging, *ROIs* regions of interest, *T* time, *mos* months, *mPFC* medial prefrontal cortex, *VS* ventral striatum, *AUDIT* Alcohol Use Disorders Identification Test