HHS Public Access

Author manuscript

Curr Opin Behav Sci. Author manuscript; available in PMC 2018 February 01.

Published in final edited form as:

Curr Opin Behav Sci. 2017 February ; 13: 164–170. doi:10.1016/j.cobeha.2016.12.005.

Adolescence and Drug Use Vulnerability: Findings from Neuroimaging

Lindsay M. Squeglia, Ph.D.[1] and **Anita Cservenka, Ph.D.**[2]

[1]Department of Psychiatry and Behavioral Sciences, Addiction Sciences Division, Medical University of South Carolina, 67 President Street, MSC 861, Charleston, SC, 29425, USA

[2]School of Psychological Science, Oregon State University, 2950 SW Jefferson Way, Corvallis, OR, 97331, USA

Abstract

Adolescence is a period of vulnerability for developing substance use disorder. Recent neuropsychological and neuroimaging studies have elucidated underlying neural vulnerabilities that contribute to initiation of substance use during adolescence. Findings suggest poorer performance on tasks of inhibition and working memory, smaller brain volumes in reward and cognitive control regions, less brain activation during executive functioning tasks, and heightened reward responsivity are predictive of youth initiating substance use during adolescence. In youth who are family history positive (FHP) for substance use disorder, poorer executive functioning, smaller volume of limbic brain regions (e.g., amygdala), sex-specific patterns of hippocampal volume, and a positive association between nucleus accumbens volume and family history density have been reported. Further, reduced white matter integrity, altered brain response during inhibitory control, including both greater and less frontal lobe response, blunted emotional processing, and weaker neural connectivity have also been found in FHP youth. Thus, there is significant overlap among the neural precursors shown to be predictive of alcohol and substance use initiation during adolescence and those that distinguish FHP from youth without a family history of substance use disorder, suggesting common targets for prevention and intervention. Understanding these predictive factors helps identify at-risk youth for prevention efforts, as well as create interventions targeting cognitive weaknesses or brain regions involved in substance use initiation.

Corresponding author: Dr. Lindsay M Squeglia, Medical University of South Carolina, Psychiatry and Behavioral Sciences, 67 President St, MSC861, Charleston, South Carolina 29425, United States, Phone: 8437925451, squegli@musc.edu.

Contributors

Authors Squeglia and Cservenka conducted literature searches and wrote and edited the first draft and revised version of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of Interest

All authors declare that they have no conflicts of interest.

INTRODUCTION

Underage alcohol and drug use is recognized as a leading public health and social problem for adolescents. Alcohol is by far the most commonly used substance among adolescents, with 64% of 18 year olds endorsing lifetime alcohol use, followed by marijuana (45%) and cigarette use (31%) (1). Acute alcohol and drug intoxication is related to a number of adverse outcomes, ranging from poor decision making to substance-related deaths (2). Long-term consequences include poorer academic performance (3), neurocognitive deficits (4), and psychosocial problems (5, 6). Earlier initiation of substance use is related to worse outcomes (7, 8), with youth who begin drinking before age 15 having four to six times the rate of lifetime alcohol dependence than those who do not drink by age 21 (9, 10). However, many of these associations reported in cross-sectional studies do not explain the directionality of alcohol use and these outcomes, thus necessitating longitudinal studies of risk factors for adolescent alcohol use, of which neuroimaging studies are reviewed herein.

One contributing factor to the peak in substance use during adolescence could be the "imbalance" in adolescent brain development, where emotion and reward systems develop before cognitive control systems, leaving youth more vulnerable to engage in risk-taking behaviors like substance use (11–13). Understanding the factors that contribute to initiation of substance use, particularly in regards to adolescent neurodevelopment, are important for developing targeted, effective prevention and intervention efforts to help avoid unwanted negative consequences associated with adolescent substance use.

Over the past decade, researchers have used sophisticated prospective, longitudinal designs to better understand factors that contribute to the initiation of substance use during adolescence. These studies assess youth before they have ever used any alcohol or drugs and continue assessing them over time as a portion naturally transition into substance use. This brief review will cover the existing longitudinal neuroimaging and neurocognitive studies that have identified key features that predate adolescent substance use and make youth more vulnerable to engage in substance use. Further, we review studies examining neurocognitive and neural differences that distinguish youth with a family history of substance use disorder from their peers. The majority of studies reviewed are alcohol-related, as alcohol is the most commonly used substance during adolescence and youth who use other drugs typically are also using alcohol (1).

Neural features related to alcohol and drug use vulnerability

Neuropsychological Precursors—Neurocognitive features, particularly executive functioning performance, may make youth more vulnerable to engage in substance use during adolescence. Executive functioning refers to higher-order cognitive processing skills, including inhibition, attention, working memory, planning, problem solving, and cognitive flexibility. Inhibition, or impulse control, appears to be a key cognitive feature involved in substance use initiation (14, 15). Compromised inhibitory function in substance-naïve 12–14 year olds has been related to greater subsequent alcohol and marijuana use by age 18, even after controlling for common predictors of youth substance use including sex, externalizing behaviors, familial substance use disorder, pubertal development, academic achievement, and age (16); 23% of the total variance in substance use was accounted for by predictors.

Poorer performance on spatial planning and problem solving tasks (17), as well as deficits in working memory (18) have also been linked to escalation of drinking during adolescence. These findings suggest that neuropsychological data, particularly in regards to executive functioning, could be helpful in identifying teens at risk for initiating problematic substance use.

Structural Brain Precursors—Pre-existing structural brain differences may also predispose youth to engage in heavy substance use. Smaller orbitofrontal cortex (a region of the brain involved in reward processing and decision making) volumes at age 12 predicted marijuana use by age 16 (19). Similarly, other studies have found that smaller frontal gray matter volume (20–22) and less cerebellar white matter volume (21) predict initiation of drinking by late adolescence (20). Reward-related subcortical brain structures also appear to be involved in initiation of substance use. In substance-naïve 15–18 year olds, smaller volume of the left nucleus accumbens (NAcc), predicted greater substance use at 2 year follow-up (23). Smaller volumes of the anterior cingulate, a region implicated in affective processes, self-control, and substance use, have also been found to predict later alcohol-related problems (24). White matter integrity, as measured by diffusion tensor imaging, has been examined in relation to development of substance use. In 16 to 19 year old youth, lower white matter integrity in fronto-limbic regions predicted alcohol and marijuana use at an 18 month follow-up (25). Overall, less volume in brain regions involved in impulsivity, reward sensitivity, and decision making and lower white matter integrity appear to influence initiation of alcohol and marijuana use during adolescence.

Functional Brain Precursors—Beyond structural neuroimaging studies, functional magnetic resonance imaging (fMRI) has been used to elucidate brain function precursors of adolescent substance use. Longitudinal fMRI studies of substance-naïve youth have shown that even in the presence of comparable behavioral performance, abnormal brain activation during inhibition tasks, including both less (26, 27) and greater (22) frontal lobe response, predict alcohol use by mid-to-late adolescence. Less frontal activation also predicts future substance use and dependence symptoms (26, 28), while greater frontal response has been shown to predict significant alcohol-related consequences like blackouts (29). On tasks of visual working memory, less brain activation during early adolescence is predictive of greater substance involvement by late adolescence (17, 30). Brain activation during reward processing has also been found to predict future adolescent substance use engagement; reduced resting-state cerebral blood flow within reward and default mode networks has been associated with greater alcohol consumption during mid-to-late adolescence (31). In a large multisite European neuroimaging study, hyperactivity in superior frontal regions during reward processing at age 14 was predictive of initiation of alcohol use by age 16 (22). Greater brain activation while observing alcohol-related pictures predicted larger increases in drinking and more alcohol-related problems, beyond other measured risk factors, at a one year follow-up in a study of first-year college students (32). Increased saliency of alcohol-related cues and overactive reward response appear to make youth more vulnerable to substance use initiation. Overall, findings suggest that less brain activation during tasks of inhibition and working memory, as well as greater brain activation during reward processing and alcohol cue reactivity, could identify youth who are more likely to initiate substance use

during adolescence. Findings suggest that prevention and intervention techniques that either boost executive functioning or dampen reward response could be helpful in delaying or avoiding early adolescent substance use.

Family history of alcohol use disorder

Experimentation with alcohol and drugs is characteristic of adolescence, but vulnerability for developing substance-related problems is especially heightened among individuals with a family history of substance use disorder (SUD) (33). While family history of various SUDs heightens risk for the development of the disorder in offspring (34), family history of alcohol use disorder (AUD) has been more extensively investigated (for detailed review, see (35)). In particular, adolescents with familial AUD (family history positive; FHP) are more likely to transition into hazardous drinking (36) and are 3–5 times more likely to go on to develop an AUD (37) than youth without a family history of alcoholism (FHN). A large portion of this research has aimed to uncover the neurobiological and behavioral markers that may increase risk for AUD in FHP adolescents who are largely alcohol and substance-naïve. Ultimately, the goal is to inform prevention efforts aimed at reducing the incidence of AUD, so that they may target specific behaviors or design interventions that strengthen and/or modify neural networks identified to contribute to the vulnerability for developing AUD in at-risk youth.

Neurocognitive functioning—FHP youth have shown differences in neurocognitive functioning from their FHN peers in various neuropsychological domains, including verbal and language abilities (38), visuospatial functioning (39), planning (40), and executive functioning (41–43). Importantly, studies of executive functioning have found weaknesses in FHP adolescents in different frontal lobe-mediated functions, including working memory (41), set-shifting (42), and response inhibition (43). Since AUD has been characterized by deficits in executive functioning (44), these findings may indicate the presence of early risk markers that may lead FHP adolescents to make poor decisions with regards to alcohol use.

Brain structure—Neuroimaging studies of FHP and FHN youth have contributed greatly to our understanding of the neurobiological underpinnings that may be related to heightened risk for developing AUD. Three important limbic structures involved in addiction have been examined in FHP youth, including the amygdala (45, 46), hippocampus (47), and NAcc (46). A study of FHP youth found smaller amygdalar volumes in FHP vs. FHN youth (45), although family history density (FHD) of AUD was unrelated to amygdalar volume in adolescents with no heavy alcohol or drug use (46). In another study, FHP males had larger left hippocampal volume than FHN males, suggesting that sex-specific patterns of family history risk may be present (47). This was also seen in a study that found FHD was significantly positively associated with left NAcc volume in adolescent girls (46). Future longitudinal studies should investigate how volumes of these subcortical structures may contribute to heavy alcohol use among FHP youth. Furthermore, it will be important to examine whether there are volumetric differences between FHP and FHN youth in other brain areas, such as the prefrontal cortex, since neuropsychological testing has shown executive functioning deficits among FHP adolescents (41–43).

Increases in white matter integrity are related to improvements in cognitive functioning during adolescence (48), but several studies have reported decreased white matter integrity in FHP adolescents (49, 50), with one exception (51). FHP youth have decreased white matter integrity in frontal cortical tracts such as the anterior corona radiata (49, 50), and long-range association tracts, such as the superior longitudinal fasciculus (49, 50), which connects frontal and parietal areas involved in top-down executive functioning. These findings may explain some of the executive functioning deficits reported on neuropsychological tests in FHP youth. Longitudinal studies will be able to elucidate whether these decreases in white matter integrity represent developmental delays in FHP adolescents, and/or contribute to hazardous drinking.

Both macro (45–47) and microstructural (49–51) investigations of brain morphometry in FHP adolescents suggest that gray and white matter development may be altered in youth with familial AUD, warranting further research to understand how brain structural alterations may represent risk factors for heavy alcohol use.

Brain function—FMRI studies of FHP adolescents have focused on brain activity during both task and resting conditions. During inhibitory control, FHP youth have shown less brain response in frontal and parietal cortex (52), which was also seen during cognitive control within emotional contexts (53), despite comparable behavioral performance between the groups. These two studies exemplify that inhibitory control weaknesses may be present in FHP youth, with the latter study highlighting the importance of examining inhibition within emotional contexts as day-to-day decision making may take place in heated situations that could promote risky decisions. However, other analyses found increased frontal brain response during inhibitory control in FHP youth (54) and positive associations between FHD and cognitive control (55), even in the absence of group differences in commission or interference errors. Thus, identifying whether task-related or analytical differences are related to discrepancies among findings is an important step for future studies.

While frontal and cerebellar response is lower in FHP youth during risky decision making relative to their FHN peers (56), studies of reward processing have not found differences in brain activity between FHP and FHN adolescents (57, 58), suggesting that reward salience may not be significantly different between FHP and FHN youth. On the other hand, reduced brain activity in response to emotional faces has been reported in FHP youth in temporal (53) and parietal (59) areas. Blunted emotional reactivity may be a risk factor that drives FHP youth to seek out emotionally arousing experiences, such as risky alcohol use.

Finally it should be noted, that differences in both task-related connectivity (60, 61) and resting state connectivity (53, 62) are present between FHP and FHN youth. Specifically, fronto-cerebellar (60) and fronto-parietal (61) synchrony is reduced in FHP vs. FHN youth. Furthermore, reward and cognitive control brain regions are less segregated in FHP youth compared with their FHN peers (62), which could suggest that miscommunication may occur between regions that process rewards (i.e. NAcc) and areas involved in inhibitory control (i.e. inferior frontal gyrus).

These fMRI investigations highlight that FHP youth consistently show altered brain activity during both executive functioning and emotional processing tasks compared with their FHN peers, and that some of these differences could be explained by neural connectivity of functional brain networks in FHP adolescents. Future longitudinal studies will need to examine if any of these neural markers explain increases in heavy alcohol use in FHP adolescents relative to their low-risk peers.

Neuroimaging data in the context of other important factors

Clearly other factors play an important role in adolescent substance use initiation, including demographic, behavioral, environmental, and personality factors. Two recent neuroimaging studies have attempted to incorporate the multitude of factors that are associated with adolescent substance use initiation (17, 22). In the most recent study, 12 to 14 year old substance-naïve youth underwent extensive clinical interviewing, neuropsychological testing, and neuroimaging (17). Youth were followed annually until age 18 and classified as either continuous non-users or moderate-to-heavy alcohol initiators. Machine learning was used to understand which variables best predict alcohol use outcomes based on demographic, behavioral, neuropsychological, and neuroimaging data. Thirty-four predictors were found to contribute to alcohol use by age 18. Demographic and behavioral factors included being male, coming from more affluent families, dating by age 14, endorsing more externalizing behaviors, and believing alcohol would affect them positively in social settings; neuropsychological factors included poorer executive functioning; and neuroimaging factors included thinner cortices and less brain activation during a visual working memory task in diffusely distributed regions of the brain, consistent with previous findings (7, 21, 26, 29, 30, 63). This study showed that multimodal neuroimaging data, as well as neuropsychological testing, is important in prediction of future behaviors. In a large European multisite neuroimaging study, a mix of history, personality, and brain factors at age 14 were able to predict which youth transitioned into alcohol use by age 16. The results indicated that romantic history (beta = −0.18), 1–2 alcohol use occasions by age 14 (beta = −0.18), reduced temporal and increased frontal response during reward outcome activity (beta = 0.23), greater frontal and sensorimotor response during failed inhibitory control (beta = 0.18), and smaller bilateral superior frontal gyrus and parahippocampal as well as larger premotor and postcentral gyrus gray matter volume (beta = 0.164), were some of the markers most predictive of future binge drinking at age 16 (22). Taken together, these studies suggest that neurocognitive and neuroimaging data can be useful in predicting future substance use behaviors. Future studies incorporating multiple predictors, as opposed to focusing on singular predictors, will be helpful in understanding the complex, multifaceted transition into adolescent substance use.

Conclusion—Neurocognitive aberrations predate initiation of alcohol use and appear to leave youth more vulnerable to engage in risk-taking behaviors like alcohol and drug use. Neuropsychological and neuroimaging studies show poorer performance on tasks of inhibition and working memory, smaller brain volumes in reward and cognitive control regions, less brain activation during executive functioning tasks, and hyperactivation during reward processing is predictive of youth who initiate substance use during adolescence. In FHP youth, poorer executive functioning, smaller amygdalar volume, and sex-specific

patterns of hippocampal and nucleus accumbens volume been reported. Thus, there is significant overlap among the neural precursors shown to be predictive of alcohol and substance use initiation during adolescence and those that distinguish FHP and FHN youth. This suggests that particular attention should be given to at-risk FHP adolescents who may exhibit neurocognitive and neural vulnerabilities for future engagement in heavy alcohol and/or substance use.

To date, most of the reported findings are from high-functioning samples and examine risk factors for initiation into any and up to moderate levels of substance use, as opposed to problematic or severe levels of use. Furthermore, some effect sizes reported in the literature are quite small, potentially reducing their clinical relevance (e.g., (16). Larger sample sizes over multiple years are needed to further clarify the most important predictors of alcohol and drug use initiation versus escalation of problematic use during adolescence. Large-scale multisite studies are already underway, including the National Consortium on Alcohol and Neurodevelopment in Adolescence [NCANDA; (64); following >800 youth for at least 10 years] and the Adolescent Brain Cognitive Development (ABCD; http://abcdstudy.org/); following 11,500 youth for 10 years). These studies will help identify the most important risk factors for substance use along the spectrum of substance use. Understanding these factors may help identify at-risk youth for prevention efforts, as well as create interventions targeting cognitive weaknesses or brain regions involved in substance use initiation. For example, training self-control during childhood in both laboratory-based and ecologically valid (i.e. school, community, family) settings has shown success in improving executive functioning skills, and targeting the structure and/or function of the right inferior frontal gyrus may be one brain region that could support improvements in cognitive control (65). However, adolescents may require more tailored and direct interventions to benefit from self-control training compared with children who may exhibit greater brain plasticity amenable to interventions during earlier development (65). Furthermore, other cognitive control interventions for substance abuse, including mindfulness-based interventions that target the anterior cingulate cortex (66), and physical activity, which may modify prefrontal cortical activity (67) hold promise for improving neurocognitive functioning, and are currently being actively explored.

Acknowledgments

Role of Funding Sources

Funding for this study was provided by NIDA grant K12 DA031794 (Squeglia) and K23 AA025399 (Squeglia). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

References

1. Johnston, LD.; O'Malley, PM.; Miech, RA.; Bachman, JG.; Schulenberg, JE. Monitoring the Future national results on adolescent drug use: Overview of key findings, 2015. Ann Arbor, Michigan: 2016.
2. Centers for Disease Control and Prevention. Alcohol and Public Health: Alcohol-Related Disease Impact (ARDI). 2016

3. Kristjansson AL, Sigfusdottir ID, Allegrante JP. Adolescent substance use and peer use: A multilevel analysis of cross-sectional population data. Substance Abuse Treatment, Prevention, and Policy. 2013:8.

4. Squeglia LM, Gray KM. Alcohol and drug use and the developing brain. Current Psychiatry Reports. 2016; 18:46. [PubMed: 26984684]

5. Rowe CL, Liddle HA, Greenbaum PE, Henderson CE. Impact of psychiatric comorbidity on treatment of adolescent drug abusers. Journal of Substance Abuse Treatment. 2004; 26:129–140. [PubMed: 15050090]

6. Deas D, Thomas S. Comorbid psychiatric factors contributing to adolescent alcohol and other drug use. Alcohol Research & Health. 2002; 26:116–121.

7. Brown SA, McGue M, Maggs J, Schulenberg J, Hingson R, Swartzwelder S, Martin C, Chung T, Tapert SF, Sher K, Winters KC, Lowman C, Murphy S. A developmental perspective on alcohol and youths 16 to 20 years of age. Pediatrics. 2008; 121:S290–310. [PubMed: 18381495]

8. Spear LP. Adolescents and alcohol: Acute sensitivities, enhanced intake, and later consequences. Neurotoxicology and Teratology. 2014; 41

9. Grant BF, Dawson DA. Age at onset of alcohol use and its association with DSM-IV alcohol abuse and dependence: Results from the National Longitudinal Alcohol Epidemiologic Survey. Journal of Substance Abuse. 1997; 9:103–110. [PubMed: 9494942]

10. Substance Abuse and Mental Health Services Administration. Results from the 2013 National Survey on Drug Use and Health: Summary of National Findings [PDF-3.2MB]. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2014. NSDUH Series H-48, HHS Publication No. (SMA) 14-4863

11. Casey BJ, Getz S, Galvan A. The adolescent brain. Developmental Review. 2008; 28:62–77. [PubMed: 18688292]

12*. van Duijvenvoorde AC, Achterberg M, Braams BR, Peters S, Crone EA. Testing a dual-systems model of adolescent brain development using resting-state connectivity analyses. NeuroImage. 2016; 124:409–420. This paper directly tests the dual-systems model of adolescent brain development. Findings from this paper suggest adolescence is associated with strengthening of connectivity between cognitive-control and emotion/reward-related regions of the brain, consistent with the idea of an increase in top-down control during adolescence into young adulthood. The imbalance between cognitive control and reward centers of brain during adolescence are believed to increase the likihood of engaging in risk-taking behaviors like substance use. [PubMed: 25969399]

13. Mills KL, Goddings AL, Clasen LS, Giedd JN, Blakemore SJ. The developmental mismatch in structural brain maturation during adolescence. Developmental Neuroscience. 2014; 36:147–160. [PubMed: 24993606]

14. López-Caneda E, Rodríguez Holguín S, Cadaveira F, Corral M, Doallo S. Impact of alcohol use on inhibitory control (and vice versa) during adolescence and young adulthood: A review. Alcohol and Alcoholism. 2014; 49:173–181. [PubMed: 24243684]

15**. 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; 2:91–103. This reviews recent findings from functional neuroimaging studies in children, adolescents, and emerging adults with a specific focus on inhibitory control and reward circuitry due to their involvement in risk-taking behaviors. [PubMed: 26236575]

16. Squeglia LM, Jacobus J, Nguyen-Louie TT, Tapert SF. Inhibition during early adolescence predicts alcohol and marijuana use by late adolescence. Neuropsychology. 2014; 28:782–790. [PubMed: 24749728]

17**. Squeglia LM, Ball TM, Jacobus J, Brumback T, McKenna BS, Nguyen-Louie TT, Sorg SF, Paulus MP, Tapert SF. Neural predictors of alcohol use initiation during adolescence. The American Journal of Psychiatry. in press. This paper examines a multitude of demographic, environmental, familial, neuropsychological, and neuroimaging factors that affect intiation of alcohol use during adolescence. Several demographic and behavioral factors (being male, higher socioeconomic status, early dating, more externalizing behaviors, positive alcohol expectancies), worse executive functioning, and thinner cortices and less brain activation in diffusely distributed

regions of the brain were related to initaition of alcohol use by age 18. Machine learning scripts are published so other groups can replicate findings.

18. Khurana A, Romer D, Betancourt LM, Brodsky NL, Giannetta JM, Hurt H. Working memory ability predicts trajectories of early alcohol use in adolescents: The mediational role of impulsivity. Addiction. 2013; 108:506–515. [PubMed: 23033972]
19. Cheetham A, Allen NB, Whittle S, Simmons JG, Yücel M, Lubman DI. Orbitofrontal volumes in early adolescence predict initiation of cannabis use: A 4-year longitudinal and prospective study. Biological Psychiatry. 2012; 71:684–692. [PubMed: 22129756]
20. Weiland BJ, Korycinski ST, Soules M, Zubieta JK, Zucker RA, Heitzeg MM. Substance abuse risk in emerging adults associated with smaller frontal gray matter volumes and higher externalizing behaviors. Drug and Alcohol Dependence. 2014; 137:68–75. [PubMed: 24513182]
21. Squeglia LM, Rinker DA, Bartsch H, Castro N, Chung Y, Dale AM, Jernigan TL, Tapert SF. Brain volume reductions in adolescent heavy drinkers. Developmental Cognitive Neuroscience. 2014; 9:117–125. [PubMed: 24632141]
22**. Whelan R, Watts R, Orr CA, Althoff RR, Artiges E, Banaschewski T, Barker GJ, Bokde AL, Büchel C, Carvalho FM, Conrod PJ, Flor H, Fauth-Bühler M, Frouin V, Gallinat J, Gan G, Gowland P, Heinz A, Ittermann B, Lawrence C, Mann K, Martinot JL, Nees F, Ortiz N, Paillère-Martinot ML, Paus T, Pausova Z, Rietschel M, Robbins TW, Smolka MN, Ströhle A, Schumann G, Garavan H, IMAGEN Consortium. Neuropsychosocial profiles of current and future adolescent alcohol misusers. Nature. 2014; 512:185–189. This paper is from a large longitudinal study in Europe (IMAGEN) that aimed to identify predictors of adolescent substance misuse, incorporating brain structure and function, individual personality and cognitive differences, environmental factors, life experiences, and candidate genes. Life experiences, neurobiological differences, and personality were important antecedents of binge drinking by age 16. [PubMed: 25043041]
23. Urošević S, Collins P, Muetzel R, Schissel A, Lim K, Luciana M. Effects of reward sensitivity and regional brain volumes on substance use initiation in adolescence. Social Cognitive and Affective Neuroscience. 2015; 10:106–113. [PubMed: 24526186]
24. Cheetham A, Allen NB, Whittle S, Simmons J, Yücel M, Lubman DI. Volumetric differences in the anterior cingulate cortex prospectively predict alcohol-related problems in adolescence. Psychopharmacology. 2014; 231:1731–1742. [PubMed: 24553579]
25. Jacobus J, Thayer RE, Trim RS, Bava S, Frank LR, Tapert SF. White matter integrity, substance use, and risk taking in adolescence. Psychology of Addictive Behaviors. 2013; 27:431–442. [PubMed: 22564204]
26. Heitzeg MM, Nigg JT, Hardee JE, Soules M, Steinberg D, Zubieta JK, Zucker RA. Left middle frontal gyrus response to inhibitory errors in children prospectively predicts early problem substance use. Drug and Alcohol Dependence. 2014; 141:51–57. [PubMed: 24882366]
27. Norman AL, Pulido C, Squeglia LM, Spadoni AD, Paulus MP, Tapert SF. Neural activation during inhibition predicts initiation of substance use in adolescence. Drug and Alcohol Dependence. 2011; 119:216–223. [PubMed: 21782354]
28. Mahmood OM, Goldenberg D, Thayer R, Migliorini R, Simmons AN, Tapert SF. Adolescents' fMRI activation to a response inhibition task predicts future substance use. Addictive Behaviors. 2013; 38:1435–1441. [PubMed: 23006248]
29. Wetherill RR, Castro N, Squeglia LM, Tapert SF. Atypical neural activity during inhibitory processing in substance-naïve youth who later experience alcohol-induced blackouts. Drug and Alcohol Dependence. 2013; 128:243–249. [PubMed: 23021773]
30. Squeglia LM, Pulido C, Wetherill RR, Jacobus J, Brown GG, Tapert SF. Brain response to working memory over three years of adolescence: Influence of initiating heavy drinking. Journal of Studies on Alcohol and Drugs. 2012; 73:749–760. [PubMed: 22846239]
31. Ramage AE, Lin AL, Olvera RL, Fox PT, Williamson DE. Resting-state regional cerebral blood flow during adolescence: Associations with initiation of substance use and prediction of future use disorders. Drug and Alcohol Dependence. 2015
32. Dager AD, Anderson BM, Rosen R, Khadka S, Sawyer B, Jiantonio-Kelly RE, Austad CS, Raskin SA, Tennen H, Wood RM, Fallahi CR, Pearlson GD. Functional magnetic resonance imaging

(fMRI) response to alcohol pictures predicts subsequent transition to heavy drinking in college students. Addiction. 2014; 109:585–595. [PubMed: 24304235]

33. Cloninger CR, Sigvardsson S, Reich T, Bohman M. Inheritance of risk to develop alcoholism. NIDA Res Monogr. 1986; 66:86–96. [PubMed: 3106820]
34. Merikangas KR, Stolar M, Stevens DE, Goulet J, Preisig MA, Fenton B, Zhang H, O'Malley SS, Rounsaville BJ. Familial transmission of substance use disorders. Archives of general psychiatry. 1998; 55:973–979. [PubMed: 9819065]
35. Cservenka A. Neurobiological phenotypes associated with a family history of alcoholism. Drug and alcohol dependence. 2015
36. Lieb R, Merikangas KR, Hofler M, Pfister H, Isensee B, Wittchen HU. Parental alcohol use disorders and alcohol use and disorders in offspring: a community study. Psychol Med. 2002; 32:63–78. [PubMed: 11883731]
37. Cotton NS. The familial incidence of alcoholism: a review. J Stud Alcohol. 1979; 40:89–116. [PubMed: 376949]
38. Tapert SF, Brown SA. Substance dependence, family history of alcohol dependence and neuropsychological functioning in adolescence. Addiction. 2000; 95:1043–1053. [PubMed: 10962769]
39. Ozkaragoz T, Satz P, Noble EP. Neuropsychological functioning in sons of active alcoholic, recovering alcoholic, and social drinking fathers. Alcohol. 1997; 14:31–37. [PubMed: 9014021]
40. Tarter RE, Jacob T, Bremer DA. Cognitive status of sons of alcoholic men. Alcoholism, clinical and experimental research. 1989; 13:232–235.
41. Harden PW, Pihl RO. Cognitive function, cardiovascular reactivity, and behavior in boys at high risk for alcoholism. J Abnorm Psychol. 1995; 104:94–103. [PubMed: 7897058]
42. Corral M, Holguin SR, Cadaveira F. Neuropsychological characteristics of young children from high-density alcoholism families: A three-year follow-up. J Stud Alcohol Drugs. 2003; 64:195–199.
43. Nigg JT, Glass JM, Wong MM, Poon E, Jester JM, Fitzgerald HE, Puttler LI, Adams KM, Zucker RA. Neuropsychological executive functioning in children at elevated risk for alcoholism: findings in early adolescence. J Abnorm Psychol. 2004; 113:302–314. [PubMed: 15122950]
44. Ratti MT, Bo P, Giardini A, Soragna D. Chronic alcoholism and the frontal lobe: which executive functions are imparied? Acta Neurol Scand. 2002; 105:276–281. [PubMed: 11939939]
45. Hill SY, Wang S, Carter H, McDermott MD, Zezza N, Stiffler S. Amygdala volume in offspring from multiplex for alcohol dependence families: The moderating influence of childhood environment and 5-HTTLPR. J Alcohol Drug Depend. 2013; S1:1–9.
46. Cservenka A, Gillespie AJ, Michael PG, Nagel BJ. Family history density of alcoholism relates to left nucleus accumbens volume in adolescent girls. J Stud Alcohol Drugs. 2015; 76:47–56. [PubMed: 25486393]
47. Hanson KL, Medina KL, Nagel BJ, Spadoni AD, Gorlick A, Tapert SF. Hippocampal volumes in adolescents with and without a family history of alcoholism. Am J Drug Alcohol Abuse. 2010; 36:161–167. [PubMed: 20465374]
48. Treit S, Chen Z, Rasmussen C, Beaulieu C. White matter correlates of cognitive inhibition during development: a diffusion tensor imaging study. Neuroscience. 2014; 276:87–97. [PubMed: 24355493]
49. Herting MM, Schwartz D, Mitchell SH, Nagel BJ. Delay discounting behavior and white matter microstructure abnormalities in youth with a family history of alcoholism. Alcohol Clin Exp Res. 2010; 34:1590–1602. [PubMed: 20586754]
50**. Acheson A, Wijtenburg SA, Rowland LM, Winkler AM, Gaston F, Mathias CW, Fox PT, Lovallo WR, Wright SN, Hong LE, Dougherty DM, Kochunov P. Assessment of whole brain white matter integrity in youths and young adults with a family history of substance-use disorders. Hum Brain Mapp. 2014; 35:5401–5413. This study reported that youth with a family history of substance use disorder have decreased white matter integrity in widespread frontocortical tracts compared with their family history negative peers and that greater presence of substance use disorder in one's family is related to poorer white matter integrity. Thus, both

the presence and degree of familial substance use disorder were important predictors of white matter integrity in at-risk youth. [PubMed: 24867528]

51. Squeglia LM, Jacobus J, Brumback T, Meloy MJ, Tapert SF. White matter integrity in alcohol-naive youth with a family history of alcohol use disorders. Psychol Med. 2014; 44:2775–2786. [PubMed: 25066702]
52. Schweinsburg AD, Paulus MP, Barlett VC, Killeen LA, Caldwell LC, Pulido C, Brown SA, Tapert SF. An FMRI study of response inhibition in youths with a family history of alcoholism. Ann N Y Acad Sci. 2004; 1021:391–394. [PubMed: 15251915]

53**. Cservenka A, Fair DA, Nagel BJ. Emotional processing and brain activity in youth at high risk for alcoholism. Alcohol Clin Exp Res. 2014; 38:1912–1923. This study found that youth with a family history of alcoholism show a) blunted neural response to emotional faces, b) less inhibitory control brain activity within emotional contexts, and c) lower amygdalar connectivity with the superior frontal gyrus compared to youth without a family history of alcoholism. These findings established that emotional processing may impact cognitive control during both task and resting conditions in youth at risk for alcoholism. [PubMed: 24890898]

54. Acheson A, Tagamets MA, Rowland LM, Mathias CW, Wright SN, Hong LE, Kochunov P, Dougherty DM. Increased forebrain activations in youths with family histories of alcohol and other substance use disorders performing a Go/NoGo task. Alcohol Clin Exp Res. 2014; 38:2944–2951. [PubMed: 25406902]
55. Silveri MM, Rogowska J, McCaffrey A, Yurgelun-Todd DA. Adolescents at risk for alcohol abuse demonstrate altered frontal lobe activation during stroop performance. Alcohol Clin Exp Res. 2011; 35:218–228. [PubMed: 21073483]
56. Cservenka A, Nagel BJ. Risky decision-making: An fMRI study of youth at high risk for alcoholism. Alcohol Clin Exp Res. 2012; 36:604–615. [PubMed: 22250647]

57*. Muller KU, Gan G, Banaschewski T, Barker GJ, Bokde AL, Buchel C, Conrod P, Fauth-Buhler M, Flor H, Gallinat J, Garavan H, Gowland P, Heinz A, Ittermann B, Lawrence C, Loth E, Mann K, Martinot JL, Nees F, Paus T, Pausova Z, Rietschel M, Strohle A, Struve M, Schumann G, Smolka MN. No differences in ventral striatum responsivity between adolescents with a positive family history of alcoholism and controls. Addict Biol. 2015; 20:534–545. The authors examined a large sample of adolescents from the IMAGEN study, and found no differences in reward anticipation or reward receipt processing between adolescents with a family history of alcohol use disorder and those without. Importantly, these findings replicated previous work, and suggest that reward processing may not be significantly different in adolescents with familial alcoholism compared with their peers. [PubMed: 24903627]

58. Bjork JM, Knutson B, Hommer DW. Incentive-elicited striatal activation in adolescent children of alcoholics. Addiction. 2008; 103:1308–1319. [PubMed: 18851716]
59. Peraza J, Cservenka A, Herting MM, Nagel BJ. Atypical parietal lobe activity to subliminal faces in youth with a family history of alcoholism. Am J Drug Alcohol Abuse. 2015; 41:139–145. [PubMed: 25268683]
60. Herting MM, Fair D, Nagel BJ. Altered fronto-cerebellar connectivity in alcohol-naive youth with a family history of alcoholism. Neuroimage. 2011; 54:2582–2589. [PubMed: 20970506]
61. Wetherill RR, Bava S, Thompson WK, Boucquey V, Pulido C, Yang TT, Tapert SF. Frontoparietal connectivity in substance-naive youth with and without a family history of alcoholism. Brain Res. 2012; 1432:66–73. [PubMed: 22138427]

62*. Cservenka A, Casimo K, Fair DA, Nagel BJ. Resting state functional connectivity of the nucleus accumbens in youth with a family history of alcoholism. Psychiatry Res. 2014; 221:210–219. This was one of the first studies to report both decreased functional segregation and reduced functional integration of brain regions during resting state functional connectivity in youth with a family history of alcohol use disorder, indicating differences in synchrony between reward processing and cognitive control brain regions in at-risk adolescents compared with their peers. [PubMed: 24440571]

63. 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. 2013

64. Brown SA, Brumback T, Tomlinson K, Cummins K, Thompson WK, Nagel BJ, De Bellis MD, Hooper SR, Clark DB, Chung T, Hasler BP, Colrain IM, Baker FB, Prouty D, Pfefferbaum A, Sullivan EV, Pohl KM, Rohlfing T, Nichols BN, Chu W, Tapert SF. The National Consortium on Alcohol and NeuroDevelopment in Adolescence (NCANDA): A multi-site study of adolescent development and substance use. Journal of Studies on Alcohol and Drugs. 2015; 76:895–908. [PubMed: 26562597]

65. Berkman ET, Graham AM, Fisher PA. Training self-control: A domain-general translational neuroscience approach. Child Development Perspectives. 2012; 6:374–384. [PubMed: 23894251]

66. Tang YY, Yang L, Leve LD, Harold GT. Improving executive function and its neurobiological mechanisms through a mindfulness-based intervention: Advances within the field of developmental neuroscience. Child Development Perspectives. 2012; 6:361–366. [PubMed: 25419230]

67. Hillman CH, Drobes DJ. Physical activity and cognitive control: Implications for drug abuse. Child Development Perspectives. 2012; 6:367–373.

Highlights

- Adolescence is a period of vulnerability for developing substance use disorder.
- Executive functioning deficits are predictive of substance use initiation.
- Reduced brain volume and response are present prior to initiating substance use.
- Youth with familial substance use disorder have altered brain structure/activity.
- These findings may aid prevention studies aimed at reducing youth substance use.